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Related Disorders of Bone

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Abstract

Renal osteodystrophy includes a broad spectrum of abnormalities in bone and mineral metabolism. This review article discusses related bone disorders, including calcific uremic arteriolopathy, "osteoporosis" and compromised bone strength, and dialysis-related amyloidosis, as well as the contributing roles of glucocorticoids and metabolic acidosis. Bone disorders in the setting of renal transplantation, including osteoporosis, osteonecrosis, and presistent hyperparathyroidism, are also reviewed.

Key Words: Renal osteodystrophy, calcific uremic arteriolopathy, osteoporosis, dialysis-related amyloidosis, hyper parathyroidism.

Introduction

In patients with chronic kidney disease (CKD), the term "renal osteodystrophy" describes a broad spectrum of abnormalities in bone and mineral metabolism *(1)*. Traditionally, renal osteodystrophy referred only to abnormalities of bone turnover. Nowadays, however, renal osteodystrophy also encompasses abnormalities in vascular calcification, such as calcific uremic arteriolopathy (calciphylaxis), changes in bone density and bone architecture, and dialysis-related amyloidosis (DRA). Changes in bone turnover, density, and architecture can cause decreased bone strength and lead to increased fracture rates. In the non-CKD population, these changes are often referred to as "osteoporosis," but "renal osteodystrophy" may be the preferred term in the CKD population *(1,2)*. Glucocorticoid treatment, renal transplantation, and metabolic acidosis are other circumstances that result in abnormal bone and mineral metabolism. These related disorders of renal osteodystrophy will be discussed under the appropriate headings in this review article.

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Calcific Uremic Arteriolopathy (Calciphylaxis)

Calcific uremic arteriolopathy (CUA) is a syndrome characterized by medial arteriolar calcification of the dermis and by local tissue ischemia of dermis, subcutaneous fat, and even muscle. In the past, CUA was often termed as "calciphylaxis," owing to CUA's similarity to an animal model of ectopic systemic calcification first described by Selye *(3)*. The lesions seen in CUA, however, differ from the lesions described by Selye, so CUA is the preferred and more accurate term to describe the syndrome *(4,5)*. The history and evolution of the terminology of CUA and "calciphylaxis" have been described

elsewhere *(6–9)*. CUA usually occurs in persons with renal failure and in recipients of renal transplants *(10,11)*, although there are reported cases in persons without kidney disease *(12)*. The incidence of calciphylaxis among persons with renal failure appears to be increasing *(13)*, although broad, population-based estimates are lacking. In one study, the incidence of CUA was 4.5/100 patient-years *(13)*, a figure mirrored by a recent cross-sectional study in which 4.1% of patients in a hemodialysis unit were diagnosed with CUA *(14)*.

Clinically, CUA usually presents as painful cutaneous and subcutaneous lesions. Violaceous mottling similar to livedo reticularis and painful plaque-like nodules or panniculitis are common, initial presentations of CUA *(8)*. These lesions may be located distal to the knees and elbows (e.g., on toes, fingers, or ankles) or more proximally (e.g., on thighs, buttocks, abdominal wall, or breasts) *(8)*. As CUA worsens, these lesions may progress into nonhealing ulcers and eschars and become sources of infection and sepsis *(7,15)*. These lesions often cause intense cutaneous pain *(6)*. The diagnosis of CUA confers a grim prognosis, and patients have an eightfold increased risk of mortality *(16)*. Patients with proximal lesions appear to have a worse prognosis than patients with distal lesions *(6)*.

The precise pathophysiology and pathogenesis of CUA remain unclear, but CUA is likely a dramatic manifestation of vascular calcification *(17–19)*. Although intravascular precipitation of amorphous calcium–phosphorus contributes to vascular calcification and CUA, vascular calcification and CUA are complex syndromes that probably involve other mechanisms. These other mechanisms may include (1) loss of tissue-derived and circulatory inhibitors of mineralization, such as matrix Gla protein and fetuin-A (α2-Heremens-Schmid glycoprotein); (2) induction of bone formation from altered differentiation of vascular smooth muscle or stem cells; (3) circulating complexes released from actively remodeling bone, which serve as crystal nucleation sites; and (4) cell death leading to release of apoptotic bodies and/or necrotic debris that can nucleate calcium–phosphorus complexes *(18)*. In CUA, mineralization of arterioles leads to ischemia and necrosis of skin and adipose tissue.

Epidemiologic studies have identified several risk factors for CUA. Not surprisingly, hyperphosphatemia *(13,16,20)*, elevated calcium–phosphorus products *(13,20)*, elevated parathyroid hormone (PTH) concentrations *(15,21)*, and administration of active vitamin D *(13)* are associated with CUA. Of note, however, some studies have failed to link elevated parathyroid hormone (PTH) with CUA *(16,20)*, and CUA may occur in patients with adynamic bone disease *(22)*. Obesity *(20,23)*, anticoagulation with coumadin *(4)*, malnutrition-inflammation *(4,16,20)*, and female sex *(16)* have also been reported as contributing factors in the pathogenesis of CUA.

The diagnosis of CUA may be difficult and requires a skin biopsy of the area surrounding the skin lesions. The differential diagnosis of CUA includes vasculitis, panniculitis, atherosclerotic peripheral vascular disease, atheroembolic disease, cryoprecipitate disorders, scleroderma, and porphyria cutanea tarda *(6,24)*. Physical examination can assist in the diagnosis of CUA. In particular, with distal lesions, the absence of peripheral pulses suggests peripheral vascular disease rather than CUA, although CUA and vascular disease often coexist. In CUA, the skin biopsy displays vascular calcification of the medial layer of the arterioles, without vasculitic changes. Performance of a skin biopsy incurs the risk of further lesions at the biopsy site, so biopsies are not always performed in suspected cases of CUA.

Currently available diagnostic tests that are less invasive than skin biopsy are unproven. Laboratory tests, such as elevated PTH, phosphorus, and calcium–phosphorus product levels, are suggestive but not diagnostic of CUA. In one study of 36 patients with CUA, 97% of patients had abnormal uptake, usually subcutaneous, on bone scans performed using ^{99}Tc-MDP *(13)*. Another noninvasive test for CUA is measurement of the transcutaneous oxygen tension ($TCPO_2$), which is often low in CUA, even at areas free of skin lesions *(25)*. The diagnostic utility of bone scans and $TCPO_2$ remains uncertain.

No cure for CUA exists, so treatment is largely supportive. To our knowledge, no randomized, controlled trials of therapies for CUA have been published. Instead, the CUA literature mainly consists of case reports, case series, and retrospective cohort and case–control studies. Consensus opinion endorses tight control of serum calcium and phosphorus concentrations and of the calcium–phosphorus product *(7,26)*. Control of these mineral parameters may require use of noncalcium-based phosphorus

binders, use of low-calcium dialysate, longer or more frequent dialysis sessions, and decrease or discontinuation of active vitamin D administration. Of note, some authors have advocated cautious use of vitamin D analogues in order to lower elevated PTH levels *(27)*. Aggressive pain control and wound care, including avoidance of additional skin and tissue trauma, are also suggested. Surgical debridement of necrotic tissue and administration of antibiotics may be helpful *(15)*.

The role of parathyroidectomy in the treatment of CUA is unclear, given the absence of any supporting randomized trials. When PTH levels are frankly elevated, parathyroidectomy may have a role in the management of CUA, by helping to control calcium and phosphorus levels *(7,8,27,28)*. Parathyroidectomy may also be useful in persons with particularly painful skin lesions *(28)*. In a review of prior cases of CUA, parathyroidectomy (versus no parathyroidectomy) was associated with increased patient survival *(21)*. Other surgical series have also reported a benefit from parathyroidectomy *(29)*. These results may be attributable to selection bias, since critically ill patients with CUA may be less likely to be offered the operation *(28)*. Furthermore, patients with good outcomes after parathyroidectomy may be more likely to be reported in the literature (publication bias) *(28)*. The optimal type of parathyroidectomy operation (subtotal, total with autotransplantation, or total without autotransplantation) remains unknown *(14,28)*. Proof of the effectiveness of parathyroidectomy in the treatment of CUA will require a randomized, controlled trial, but given the rarity of CUA, such a trial is highly unlikely. At this time, consensus opinion appears to endorse parathyroidectomy in selected cases when PTH concentrations are very elevated *(7–9,28)*.

Case series and case reports have reported successful treatment of CUA using other therapies, but the effectiveness of these therapies remains unproven and unknown. For example, hyperbaric oxygen therapy may assist in the healing of the skin lesions of CUA *(30–32)*. Patients may require treatments five times per week for 5–8 wk, however, and resolution of skin lesions does not occur in all CUA patients who receive the treatments *(30,31)*. Other therapies that have anecdotally helped to treat CUA include intravenous sodium thiosulfate, given three times weekly for a total of 8 mo *(33)*; intravenous pamidronate, given five times over 4 wk *(34)*; oral prednisone for nonulcerating CUA, given as 30–50 mg every other day for 3–8 wk *(13)*; and low-dose tissue plasminogen activator, given daily for 10 d and followed by warfarin and low-dose aspirin anticoagulation *(35)*; and ozonated autohemotherapy over 3 wk *(36)*. Some of these therapies may actually be harmful in CUA and should be used with caution. For example, warfarin anticoagulation has been suggested as a risk factor for calcification and CUA *(4)*. Definitive proof of the effectiveness of any of these interventions will require randomized clinical trials.

Osteoporosis and Compromised Bone Strength in Renal Osteodystrophy

Persons with renal osteodystrophy are at increased risk for osteoporosis and bone fractures *(37)*. "Osteoporosis," defined by a recent NIH Consensus Statement as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture" *(38)*, is one component of renal osteodystrophy. The remainder of this section will discuss "osteoporosis" and bone strength in patients with CKD, including patients requiring maintenance dialysis. Renal osteodystrophy and osteoporosis in persons treated with glucocorticoids and recipients of renal transplants are discussed separately, in their own sections below.

Despite the increased fracture rates in CKD, a recent Working Group discouraged use of the term "osteoporosis" in CKD *(1,2)*. "Osteoporosis" is defined by bone strength, which is determined by both bone density and bone quality. Since neither bone strength nor bone quality is directly measurable, osteoporosis is typically diagnosed by measuring bone mineral density (BMD), using dual X-ray absorptiometry (DEXA). As a result, osteoporosis is often (and erroneously) considered synonymous with suboptimal BMD. In postmenopausal women, BMD measurements accurately reflect fracture risk *(39)*; a BMD more than 2.5 standard deviations below the young adult normal value defines osteoporosis and confers an 8× increased risk of fracture *(2)*.

In CKD patients, however, DEXA BMD measurements correlate inconsistently with fracture risk *(40–42)*. This inconsistency partly stems from the complexity of renal osteodystrophy, because the

bone turnover, which does not correlate with BMD, also contributes to bone strength. Low BMD and normal–high BMD can each coexist with low, normal, or high bone-turnover disease. Furthermore, the optimal site for BMD measurement—spine, hip, radius, or other—remains unknown *(2)*. Finally, PTH excess is associated with loss of cortical bone but gain of trabecular bone *(43)*. DEXA fails to differentiate these effects and unfortunately integrates these changes into one BMD measurement. Thus, renal osteodystrophy and secondary hyperparathyroidism may plausibly result in increased, decreased, or normal BMD. Many studies have used BMD as a surrogate for fracture risk *(44–49)*, but these studies should be interpreted with caution, given the limitations of BMD and DEXA in renal osteodystrophy. Recent guidelines from the National Kidney Foundation recommend use of DEXA to measure BMD in patients with fractures or known risk factors for osteoporosis *(50)*, but a more recent Working Group has advocated caution in the use and interpretation of BMD in CKD *(2)*. Quantitative computed tomography (QCT) may be a more accurate method than DEXA for assessing BMD, as it can distinguish cortical from trabecular bone *(51)*. The clinical relevance of both QCT and DEXA, however, remains unproven in CKD.

Several studies have reported that the risk of bone fracture appears increased in persons with CKD. In a large study of Caucasian hemodialysis patients, the relative risk for hip fracture was increased more than fourfold, compared to a reference population *(37)*. The fracture risk increased as time on dialysis increased *(37)*. It remains unclear whether this increased risk extends to non-Caucasians, to patients on peritoneal dialysis, or to those with other types of fractures (e.g., vertebral). A single-center study also reported increased rates of hip fracture among hemodialysis patients, compared to a standard reference population *(52)*. Few data exist regarding fracture risk among patients with CKD who do not require maintenance dialysis. Prospective studies of fracture rates in nondialysis CKD patients are needed.

Multiple factors probably contribute to increased fracture risk in CKD *(53)*. Demographic factors associated with fracture include increased age, female gender, and nonblack race *(52,53)*. Lower body mass index and the presence of peripheral vascular disease are also associated with fracture risk *(53)*. Gonadal dysfunction, especially decreased estrogen and testosterone levels, and decreased physical activity may also contribute to impaired bone strength in CKD *(54)*. These risk factors are similar to the risk factors for osteoporosis in the non-CKD population. Several studies have correlated potential risk factors with BMD *(48,49)*, but the usefulness of these studies is unclear, given the uncertain correlation of BMD with fracture risk in CKD.

The association between circulating PTH concentrations and fracture risk remains unclear. In a large cohort of hemodialysis patients, Stehman-Breen et al. reported that intact PTH levels were not associated with the risk of hip fracture *(53)*. In contrast, single-center studies have associated low intact PTH with both hip fractures *(52)* and vertebral fractures *(40)*. Low PTH levels are often, but not always, associated with adynamic bone disease. Pathophysiologically, adynamic bone disease may hamper repair of microfractures and maintenance of skeletal integrity, leading to osteoporosis and clinically apparent fractures *(55)*. Although intriguing, this hypothesis remains unproven. At present, the target PTH range at which fracture risk is lowest remains unknown.

Pharmacologic therapies for osteoporosis in the general population are often used, possibly mistakenly, to treat decreased bone strength in CKD *(2,54)*. Therapies that increase BMD in non-CKD patients include bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), calcitonin, calcium, and active analogs of vitamin D *(2,54)*. Some of these agents, notably the bisphosphonates, have not been evaluated in CKD, so their effects on bone turnover and bone quality in renal osteodystrophy are unknown. These agents have been more extensively evaluated in the renal transplant population (see sections on renal transplantation below) than in the dialysis or predialysis population. At the present time, although CKD patients have an increased risk of fracture, use of these agents to treat or prevent osteoporosis in CKD cannot be recommended *(2)*. In particular, the bisphosphonates may theoretically exacerbate adynamic bone disease, and some authorities recommend bone biopsy to exclude adynamic bone disease prior to initiation of bisphosphonate therapy *(2)*. Of course, calcium supplements and active vitamin D analogs may be used to treat other aspects of renal osteodystrophy that are unrelated to

osteoporosis. A recent Working Group noted that since "more data exist on the diagnosis and treatment of abnormalities of bone turnover in CKD, clinicians are encouraged to focus first on correction of this component of renal osteodystrophy [than on BMD abnormalities]" *(2)*.

Glucocorticoids

Perhaps the most important interaction between glucocorticoid therapy and renal osteodystrophy is found in the role glucocorticoids play in the pathophysiology of posttransplant bone loss *(56)*. A number of studies *(57,58)* describe the rapid and rather profound bone loss in renal transplant recipients early after transplantation. The major factor in posttransplant bone loss is glucocorticoid administration, although other agents such as cyclosporine (CsA) may also contribute though inducing hypercalciuria. In studies in which no specific therapy is used to prevent the bone loss posttransplantation, the median decline in the lumbar bone mineral density was –13.2%/yr in the first 6 mo *(59)*. Although there is not always a direct correlation between the dosage of glucocorticoids administered and the severity of bone loss, many studies support the idea that glucocorticoid use is the major cause of bone demineralization both early and late after renal transplantation *(60,61)*. The issue of posttransplantation bone disease will be extensively discussed below, in the sections on transplantation.

DRA

DRA is a serious complication of end-stage renal disease (ESRD) caused by deposition of β2-microglobulin fibrils in bones, joints, and periarticular structures *(62–67)*. The prevalence of DRA, which is also known as β2-microglobulin amyloidosis, increases as the duration of dialysis increases *(64,68,69)*. Although its prevalence has decreased since the 1980s *(70)*, DRA continues to cause substantial musculoskeletal and rheumatic morbidity in ESRD patients.

The amyloid deposits in DRA are primarily composed of β2-microglobulin, an 11.8 kilodalton protein that is metabolized and excreted by the kidney. Amyloid deposits in DRA also contain other proteins, such as amyloid P component, proteoglycans, antiproteases *(71)*, and immunoglobulin light chains *(72)*, but β2-microglobulin appears to the most important constituent protein *(66,73,74)*. In persons with preserved renal function, plasma concentrations of β2-microglobulin vary between 1 and 3 mg/mL *(66)*. In ESRD, however, decreased metabolism and excretion cause circulating levels of β2-microglobulin to increase up to 60-fold *(64)*. ESRD may also be associated with increased production of β2-microglobulin owing to release of inflammatory mediators stemming from the hemodialysis procedure *(64)*.

The pathophysiology of DRA remains unclear. Elevated serum concentrations of β2-microglobulin predispose to DRA but do not inevitably lead to the formation and deposition of amyloid fibrils. β2-microglobulin may need to undergo biochemical modifications that render it more amyloidgenic *(67)*. Some postulated modifications include oxidative stress, advanced glycation end product (AGE) formation, conformation changes in the three-dimensional structure of the β2-microglobulin molecule, and limited proteolysis (the latter remains controversial) *(66,67)*. Amyloid formation and deposition may also require the actions of local factors, such as extracellular matrix (e.g., proteoglycans) and inflammatory markers *(66)*.

The clinical manifestations of DRA stem from deposition of β2-microglobulin-containing amyloid fibrils in the musculoskeletal system. These symptoms usually occur after many years of renal failure. The most common manifestations of DRA are carpal tunnel syndrome (CTS); amyloid arthropathy, whose spectrum of symptoms ranges from limited joint mobility to severe joint pain, sometimes with effusions; and bone cysts and articular erosions, which can lead to pathologic fractures and destructive spondyloarthropathy. Less commonly, manifestations of DRA may arise from deposition of β2-microglobulin in visceral tissues, such as the cardiovascular and gastrointestinal systems.

CTS may be the most common clinical manifestation of DRA. The prevalence of CTS appears to increase with time spent on maintenance dialysis *(75)*. Clinically, symptoms of CTS arise from entrapment of the median nerve. These symptoms include pain and paresthesias in the thumb, first two fingers, and the radial-half of the ring finger *(76)*. The palm and dorsum of the hand are usually spared *(76)*. The

findings that best correlate with nerve conduction electrodiagnosis of CTS include hand symptoms diagrams, hypalgesia, and weak thumb abduction strength testing *(76)*. The traditional Tinel and Phalen signs have limited ability to predict the electrodiagnosis of CTS *(76)*. Treatment of CTS is initially conservative, involving pain relief and splinting of the wrist. DRA-related CTS is progressive, however, so surgical carpal tunnel release is often required.

Amyloid arthropathy includes both pain and swelling of the joints. Symptoms of amyloid arthropathy are typically bilateral and tend to worsen over time *(63)*. Arthralgias typically involve large- and medium-sized joints, such as the shoulders, knees, and hips *(64,77)*. The shoulder joints are the most classically affected; ESRD patients with scapulohumeral periarthritis typically have amyloid infiltration of the synovium and subacromial bursa *(65)*. Joint swelling and effusions can affect smaller joints (e.g., wrists, fingers, and ankles) as well as the larger, more proximal joints that develop arthralgias. The effusion is usually serous and noninflammatory, although exceptions occur *(65)*.

Bony involvement by DRA manifests as cystic lesions, typically at the ends of long bones and near synovial joints. These cystic lesions contain amyloid and enlarge over time *(65)*. These cysts can lead to pathologic fractures, classically at the femoral and humeral heads *(77)*. β2-microglobulin amyloid cysts must be distinguished from brown tumors of secondary hyperparathyroidism.

Destructive spondyloarthropathy results from the development of erosive vertebral lesions, typically on the cervical spine *(78–81)*. Some observers classify spondyloarthropathy either as a type of amyloid arthropathy or as a bony consequence of DRA. Clinically, symptoms are sometimes absent but often range from pain and stiffness, typically in the neck, to nerve compression syndromes and even paralysis *(63,79,82)*. Radiographically, DRA-associated spondyloarthropathy can manifest as narrowing of the intervertebral spaces, erosions, and cysts of the vertebral plates *(63)*. Deposition of β2-microglobulin contributes to destructive spondyloarthropathy, but other factors, such as secondary hyperparathyroidism, also play a role *(79)*.

Although clinical features are often suggestive, definitive diagnosis of DRA requires histologic confirmation of β2-microglobulin amyloid deposition *(63,66,83)*. Deposition of amyloid fibrils is classically confirmed by positive Congo red staining; fibrils display green-yellow birefringence under polarized light. Congo red-positive tissues may be immunostained with a labeled anti-β2-microglobulin antibody to confirm that the amyloid contains β2-microglobulin *(84)*. Alternatively, electron microscopy of tissue specimens may demonstrate characteristics of amyloid fibrils. Specimens of synovial membranes or bone are the most useful in the diagnosis of DRA, whereas rectal and fat pad specimens are not useful.

Noninvasive imaging studies are also used to diagnose DRA. For example, ultrasonography of capsules and tendons can detect thickening of the synovial membranes because of amyloid deposition *(85)*. The disadvantages of ultrasonography include inter-observer variability and its limited applicability to selected joints *(66)*. Cystic involvement of the bones may be detected radiographically by plain X-rays. Radiographs may show bone cysts that enlarge over time and fat pad displacement because of soft tissue swelling *(63)*. When strict criteria are used to classify radiograph cysts as a result of DRA, then radiographs may be specific for DRA, albeit insensitive. Scintigraphy with radiolabelled β2-microglobulin may also assist the diagnosis of DRA *(86)*. In particular, use of ^{111}In-labeled recombinant human β2-microglobulin appears to provide safer and better quality imaging *(86)*, but it may not be widely available.

Treatment of DRA includes medical and surgical interventions. Medical therapy includes analgesics, heat, and physical therapy to decrease the discomfort from carpal tunnel syndrome, amyloid arthropathy, and other joint and bone manifestations of DRA *(87)*. Corticosteroids, given either orally in low doses or via intra-articular injection, have also been used *(87)* but are not currently recommended *(50)*. Surgical therapy includes carpal tunnel release for carpal tunnel syndrome; arthroscopic synovectomy, typically of the shoulders, to remove amyloid deposits *(88)*; and curettage and bone grafting of amyloid cysts in weight-bearing long bones *(63)*. These therapies treat the symptoms of DRA but fail to correct the underlying pathophysiology of DRA.

The flux and biocompatibility of hemodialyzer membranes may influence the development and treatment of DRA *(50,89)*. Low-flux membranes are relatively impermeable to β2-microglobulin,

whereas high-flux membranes permit removal of some β2-microglobulin during hemodialysis sessions *(62)*. Most studies have compared low-flux, cellulose membranes versus high-flux, biocompatible (noncellulosic) membranes, making it difficult to distinguish the effects of flux and biocompatibility. As recently summarized in the K/DOQI guidelines *(50)*, several studies have demonstrated a benefit of noncellulosic, high-flux membranes on clinical or radiographic symptoms of DRA *(90–92)*. These studies have their limitations, including small sample sizes and retrospective or nonrandomized study designs. Nevertheless, current K/DOQI guidelines recommend use of noncellulosic, high-flux dialyzers in patients with evidence of, or at risk for, DRA *(50)*.

Other dialytic and extracorporeal therapies have been used to treat or prevent DRA *(87,93)*. Compared to hemodialysis, peritoneal dialysis is similarly unable to remove β2-microglobulin from the blood *(62,87)*. Patients receiving hemodialysis and patients receiving continuous ambulatory peritoneal dialysis have a similar prevalence of histological β2-microglobulin amyloidosis *(94)* and CTS *(95)*. Removal of β2-microglobulin from the blood may be accomplished using either nonspecific or specific adsorption modalities, although most of these techniques remain experimental *(93,96,97)*. Other alternatives to traditional hemodialysis include convective treatments, such as hemofiltration and hemodiafiltration, and nocturnal hemodialysis. One study of registry data reported that convective renal replacement therapies were associated with a significant delay in the need for CTS surgery *(98)*. Current K/DOQI guidelines do not recommend any of these therapies for the treatment or prevention of DRA *(50)*.

Renal transplantation is the only therapy that appears to stop progression of DRA and provide symptomatic relief *(50)*. Return of renal function after successful transplantation permits urinary excretion of β2-microglobulin and normalization of serum β2-microglobulin concentrations. After transplantation, many symptoms of DRA, such as shoulder stiffness, disappear, often rapidly *(99,100)*. This improvement is partly attributable to the anti-inflammatory effects of corticosteroids but persists even after reduction or withdrawal of corticosteroids *(101)*. After renal allograft failure and return to dialysis, symptoms of DRA reappear rapidly *(99)*. Radiographic signs of DRA, such as bone cysts, appear to neither improve nor worsen after transplantation *(99,102,103)*. Although some researchers contend that amyloid deposits regress after transplantation *(101)*, most studies suggest that DRA fails to regress *(99,100,104,105)*.

Renal osteodystrophy after renal transplantation

For patients with ESRD, renal transplantation is the preferred treatment option *(106)*. Although successful transplantation restores renal function, there are several reasons why disorders of bone and mineral metabolism continue to afflict renal transplant recipients. First, renal osteodystrophy is already well established in most patients at the time of transplantation; most transplant recipients have suffered from years of CKD prior to receipt of their transplant *(107–109)*. In transplant recipients, the spectrum of pre-existing bone disease (detailed elsewhere in this issue) ranges from high to low turnover disease and includes other conditions such as DRA *(109)*. Second, many, if not most, transplant recipients have impaired renal function despite "successful" transplants *(110)*. Among transplant recipients with allograft survival of at least 2 yr, the mean glomerular filtration rate at 6 mo posttransplant is less than 50 mL/min *(110)*, which corresponds to stage 3 CKD. The continuation of CKD, even after transplantation, exacerbates pre-existing renal bone disease. Finally, the immunosuppressive medications used in transplantation, notably corticosteroids, can affect bone strength and metabolism and increase the risk of fracture.

Osteoporosis after renal transplantation

Like other patients with CKD, renal transplant recipients are at-risk for osteoporosis and bone fractures. Compared to the general population, transplant recipients have increased risk of fractures, particularly of the vertebra and feet *(111)*. More importantly, compared to dialysis patients on the transplant waiting list, renal transplant recipients have a 34% increased risk of hip fracture during the

posttransplant period *(112)*. This increase in fracture risk wanes over time, however, and by approx 630 days posttransplant, the fracture risk is equal among transplant recipients and dialysis patients, at least in one large study *(112)*.

Instead of examining actual fracture rates, most studies of posttransplant bone disease have used BMD, measured by DEXA, as a surrogate for fracture risk. As noted earlier, BMD is an imperfect surrogate for fracture risk in patients with renal osteodystrophy. Nevertheless, BMD appears to decline rapidly during the first 6–12 mo after renal transplantation *(109)*. For example, in a prospective cohort study of 20 recipients of living donor transplants, Julian et al. found that vertebral BMD decreased 6.8 ± 5.6% 6 mo posttransplant and 8.8 ± 7.0% 18 mo posttransplant *(113)*. Similar reductions in BMD occur at the femoral neck *(109)*. Different studies using different study designs (cross-sectional versus cohort studies) have reported conflicting results regarding BMD after the initial 1–2 yr posttransplant. Several studies report that BMD stabilizes and even increases after the first posttransplant year *(59,114)*, but other studies report that BMD continues to decrease *(115)*.

The increased risk for osteoporosis and bone fractures among renal transplant recipients is mainly attributable to the use of glucocorticoids after transplantation. Glucocorticoids can lead to osteoporosis via several mechanisms *(116)*, such as inhibition of osteoblast activity, increase in bone resorption, and increase in osteoblast and osteocyte apoptosis. The correlation, however, between the amount of posttransplant bone loss, as measured by BMD, and the use of glucocorticoids appears to be imperfect *(109)*. The lack of a clear-cut correlation may be because of the limitations of DEXA and BMD in the assessment of bone strength in patients with renal disease. Because glucocorticoids have harmful effects on bone strength (as well as on blood pressure, weight, and lipids), many transplant centers now use immunosuppressive protocols that almost completely avoid use of glucocorticoids *(117,118)*. It remains unclear whether glucocorticoid avoidance will lead to a decrease in actual fractures.

Calcineurin inhibitors have also been associated with deleterious effects on bone strength and metabolism, but these effects may be minor *(109)*. Clinical evaluation of the direct causative effects of calcineurin inhibitors is difficult, largely because of concomitant use of glucocorticoids *(119)*. Furthermore, the in vitro and in vivo effects may differ and may not correlate with clinical outcomes. In vitro studies suggest that CsA inhibits bone resorption *(120,121)*. In vivo studies, however, suggest that CsA increases bone resorption *(122,123)*. Tacrolimus may act similarly to CsA and decrease bone mass, at least in animal experiments *(124,125)*. The clinical significance of changes in bone metabolism because of calcineurin inhibitors remains unclear.

Treatment and prevention of osteoporosis after renal transplantation, such as treatment and prevention of osteoporosis associated with renal osteodystrophy, has utilized therapies originally devised for patients without renal disease. Weight-bearing exercise and enrollment in organized rehabilitation programs posttransplant may help prevent bone loss *(126)*. Pharmacologically, several studies have evaluated the use of antiresorptive therapy with bisphosphonates after renal transplantation, using BMD as a surrogate for fracture risk *(127–132)*. In these studies, bisphosphonates attenuated or eliminated the usual decrease in BMD seen after transplantation *(127–131)*. Owing to their small size, however, no differences in the number of fractures could be shown. As stated earlier, in the transplant population, therapies that prevent loss of BMD do not necessarily produce parallel reductions in fracture risk *(108)*. In one randomized clinical trial that used periodic doses of intravenous pamidronate as the intervention, all the renal transplant recipients who were given pamidronate developed adynamic bone disease, as shown on bone histomorphometry *(133)*. The potential, albeit unproven, benefits of preserving BMD in patients with renal transplants must be weighed against the potential harms and unknowns of bisphosphonate use *(134)*, such as adynamic bone disease.

Minimization of glucocorticoids should theoretically minimize posttransplant bone loss. The apparently rapid loss of bone mass posttransplant, however, means that even relatively rapid tapering of glucorticoids to low maintenance doses (e.g., 5 or 7.5 mg per day) may still result in significant bone loss. Complete (or almost complete) avoidance of glucocorticoids posttransplant may help preserve

bone mass. Published studies have mainly evaluated the safety of glucocorticoid-free immunosuppression and not reported (or evaluated) fracture rates *(117,118,135)*.

Prescription of calcium with active vitamin D (e.g., calcitriol) may also help prevent posttransplant bone loss *(132)*. Most studies have shown that in its inactive form, vitamin D fails to prevent posttransplant bone loss *(126)*. In several randomized trials, calcium with active vitamin D appears effective in preventing bone loss, as measured by BMD *(136–138)*. This prevention of bone loss may be mediated, in part, by reductions in PTH concentrations in patients randomized to receive active vitamin D. Treatment of calcium with active vitamin D may require intensive monitoring, given the risk of hypercalcemia with these therapies.

Osteonecrosis After Renal Transplantation

Osteonecrosis, also known as avascular necrosis or ischemic necrosis, is a potentially debilitating complication of glucocorticoid use *(109,139)*. Osteonecrosis most commonly affects the femoral head but can also affect the knee and weight-bearing long bones. The incidence of osteonecrosis was higher in the past, like with the use of higher doses of glucocorticoids *(140)*. Depending on the study, the incidence ranges from 3% to 16% *(109)*; use of lower doses of glucocorticoids has presumably decreased the incidence of most centers to the lower end of this range. Osteonecrosis typically manifests as persistent pain in the affected bone. The diagnosis is best made by radiography, bone scans, and magnetic resonance imaging *(139)*. Therapy is often surgical and includes decompression and hip replacement (for osteonecrosis of the femoral head) *(109,139)*.

Hyperparathyroidism After Renal Transplantation

Persistent hyperparathyroidism after renal transplantation can lead to hypercalcemia and hypophosphatemia *(141–143)*. Persistent hyperparathyroidism is common but usually resolves during the first year posttransplant *(141)*. Continued hypersecretion of PTH can lead to increased bone turnover and resorption, as in the pretransplant setting. Clinically, posttransplant hyperparathyroidism mainly manifests as hypercalcemia that is usually mild and transient *(142)*. In one study of 129 transplant recipients who received prednisone and CsA immunosuppression, 52% of the patients had hypercalcemia at 6 mo posttransplant *(144)*. By 24 mo posttransplant, only 10% of patients were hypercalcemic *(144)*. Curiously, in this study, there was no correlation between calcium and PTH levels, and serum phosphorus levels remained in the low-normal range *(144)*. Most other studies cite the severity of pretransplant hyperparathyroidism as the main risk factor for posttransplant hyperparathyroidism *(145)*. As PTH slowly decreases posttransplant *(146)*, hypercalcemia also resolves.

Management of posttransplant hyperparathyroidism and hypercalcemia depends on the severity of the hypercalcemia. Since the hypercalcemia is usually mild, conservative medical management usually suffices. These measures include volume repletion and avoidance of medications that can worsen hypercalcemia, such as vitamin D and calcium *(141)*. If severe or persistent, hyperparathyroidism and hypercalcemia can lead to decreased renal function and may require parathyroidectomy. In one large case series of 227 transplant recipients with posttransplant hypercalcemia, only 15 patients (6.6%) ultimately required parathyroidectomy, for hypercalcemia that was either symptomatic or persistent *(147)*. The conclusion from surgical series is that parathyroidectomy should be reserved for symptomatic hypercalcemia, acute hypercalcemia in the immediate postoperative period, or asymptomatic hypercalcemia (serum calcium greater than 12.0 mg/dL or 12.5 mg/dL) that persists for over one yr posttransplant *(147,148)*.

Metabolic acidosis

Metabolic acidosis has a rather profound effect on bone structure and function. For example, in a study designed to compare bone changes in children with diabetic ketoacidosis or acute metabolic acidosis as a result of dehydration before and after the correction of acidosis and also compare results to a group of 18 age- and sex-matched healthy children as the control group, severe negative calcium balance occurred during acidosis *(149)*. Plasma ionized calcium levels were increased in both groups, significantly more

so in diabetic ketoacidosis. Although osteoblastic markers, osteocalcin and alkaline phosphatase, were depressed to a comparable degree in both groups, urinary calcium/creatinine ratio and hydroxyproline excretion were significantly greater in diabetic ketoacidosis. No significant changes in calcitrophic hormone (intact PTH, calcitonin, 25-hydroxy vitamin D3) levels were observed. These suggest that, in diabetic ketoacidosis, the observed severe negative calcium balance occurred through diminished bone formation mediated by metabolic acidosis per se and increased bone mineral dissolution and bone resorption because of severe insulin deficiency and secondarily via metabolic acidosis.

Many studies suggest that bone mineral serves as a proton buffer. In in vitro bone organ culture systems, bone carbonate and phosphate content falls when exposed to extracellular acidosis *(150)*. At first, metabolic acidosis stimulates mineral dissolution through a physical–chemical reaction and subsequently induces cellular events, which lead to bone resorption. Acidosis suppresses the activity of bone-resorbing cells, osteoblasts, and decreases gene expression of specific matrix proteins and alkaline phosphatase activity. There is concomitant acid stimulation of prostaglandin production by osteoblasts, which acting in a paracrine manner increases synthesis of the osteoblastic receptor activator of nuclear factor kappa B ligand (RANKL). The acid induction of RANKL then stimulates osteoclastic activity and recruitment of new osteoclasts to promote bone resorption and buffering of the proton load. Both the regulation of RANKL and acid-induced calcium efflux from bone are mediated by prostaglandins *(150)*. Hence metabolic acidosis associated with renal failure or renal tubular acidosis results in an increase in urine calcium excretion. The apparent protective function of bone to help buffer systemic pH comes partly at the expense of its mineral stores *(150)*.

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