

Renal Osteodystrophy

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Abstract

The incidence of chronic renal disease is increasing, and the pattern of renal osteodystrophy seems to be shifting from the classic hyperparathyroid presentation to one of low bone turnover. Patients with persistent disease also live longer than previously and are more physically active. Thus, patients may experience trauma as a direct result of increased physical activity in a setting of weakened pathologic bone. Patient quality of life is primarily limited by musculoskeletal problems, such as bone pain, muscle weakness, growth retardation, and skeletal deformity. Chronic renal disease also increases the risk of comorbidity, such as infection, bleeding, and anesthesia-related problems. Current treatment strategies include dietary changes, plate-and-screw fixation, and open reduction and internal fixation.

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None of the following authors or the departments with which they are affiliated has received anything of value from or owns stock in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Tejwani, Dr. Schachter, Mr. Immerman, and Dr. Achan.

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J Am Acad Orthop Surg 2006;14:303-311

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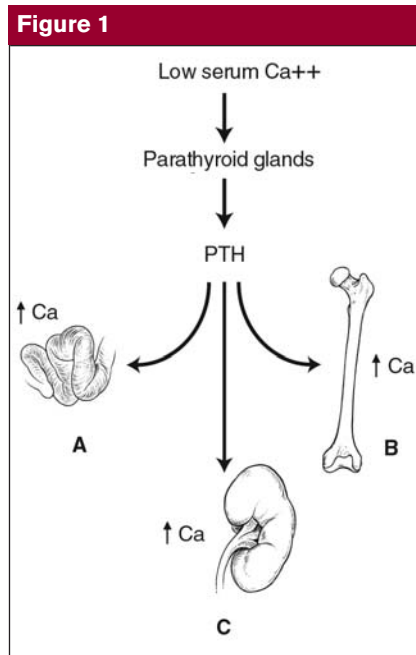
Renal osteodystrophy refers to pathologic bone conditions in patients with known kidney disease. The kidneys monitor the physiologic homeostasis of mineral metabolism; thus, any deficiency in their operation directly affects bone mineralization because of the consequent negative effect on calcium and phosphate regulation. This is noteworthy because the rising incidence of chronic renal disease translates into more patients with bone pathology presenting to orthopaedic surgeons for elective surgery and to emergency trauma units because of pathologic fractures.

Musculoskeletal problems significantly limit quality of life in patients with renal failure.¹ According to the Health Care Financing Administration, each year 325,000 Americans are treated for end-stage renal disease, and more than 1.2 million patients worldwide receive dialysis.² These figures were growing by about 8% annually, although the incidence seems to be leveling out. The United States Renal Data Sys-

tem reports an incidence of 338 per million of population in 2003, with the largest proportion in patients aged 45 to 64 years.³

Patient Demographics

According to the US Renal Data System 2003 Annual Report, in 2001 the median age of patients with end-stage renal disease was 64.5 years.² Caucasians had the highest median age (67.1 years) and Hispanics, the lowest (60.6 years). Overall incidence in the US population is 334 cases per million. In 2001, the incidence of end-stage renal disease was highest in African-Americans (988 cases per million) and lowest in Caucasians (254 cases per million), adjusted for age and sex. Patients aged 45 to 64 years represented the largest proportion of new cases in 2001 (36%), with an incidence of 625 per million, adjusted for sex and race. However, the incidence was much higher in patients aged 65 to 74 years (1,402 per million) and in those age 75 years and older (1,542 per mil-



Normal calcium homeostasis. In response to low serum calcium, the parathyroid gland secretes parathyroid hormone (PTH). This hormone acts indirectly at the gut (A) with vitamin D to increase dietary calcium absorption, at the kidney (C) within the distal renal tubules by increasing calcium reabsorption, and at the bone by increasing osteoclastic resorption (B). All of these mechanisms result in net increase in serum calcium.

lion). Males are more likely than females to be diagnosed with end-stage renal disease. In 2001, the incidence rate adjusted by age and race was 404 per million in males compared with 280 per million in females.

Disease Pathophysiology

The kidneys are responsible for monitoring and regulating calcium homeostasis as well as for controlling levels of phosphate, magnesium, and other minerals (Figure 1). The kidneys act both as target organs for parathyroid hormone (PTH) and for excreting it. The proximal convoluted tubules of the kidneys

are the site of production of 1,25-dihydroxycholecalciferol (the active form of vitamin D following hydroxylation of 25-hydroxycholecalciferol catalyzed by 1α -hydroxylase), the foremost regulator of intestinal calcium absorption. This hormone also promotes osteoclastic resorption of bone and the feedback inhibition of PTH synthesis. The kidneys serve as the primary route for the excretion of metals, such as aluminum. Modest changes in the efficacy of renal excretion dramatically alter the body's ability to maintain mineral homeostasis.

The bony manifestations of renal compromise are subdivided into high turnover, caused by persistently elevated levels of PTH (secondary hyperparathyroidism), and low turnover, seen with either excess aluminum deposition in bone or normal or reduced PTH levels. Cannata Andia⁴ described the increasing prevalence of low-turnover renal osteodystrophy. Sherrard et al⁵ distinguished between peritoneal dialysis patients with the low-turnover form, compared with hemodialysis patients with high-turnover lesions. Bushinsky⁶ emphasized the presence of two distinct histologic entities presenting with a common clinical picture.

High-dose corticosteroids used therapeutically for chronic renal disease play a role in osteopenia and—more significantly—in osteonecrosis. Approximately 15% of patients with renal transplantation develop osteonecrosis within 3 years of surgery.^{7,8}

High-Turnover Renal Osteodystrophy

High-turnover renal osteodystrophy is the classic form of this disease. PTH secretion is increased and, in the absence of medical intervention, leads to parathyroid gland hyperplasia. This hyperplasia is associated with loss of feedback inhibition in normal regulation of PTH secretion; consequently, even after correction of the renal disease, the

kidneys continue to secrete excessive levels of PTH. This condition is called secondary hyperparathyroidism. The sustained increase in PTH secretion may be caused by hypocalcemia, hyperphosphatemia, impaired renal production of 1,25-dihydroxycholecalciferol, alteration in the skeletal response to PTH, or alteration in the control of PTH gene transcription. Serum levels of PTH may be 5 to 10 times above the upper level of normal in patients with secondary hyperparathyroidism; in patients with severe end-stage renal disease, the upper level may be exceeded by 20 to 40 times. In the presence of excessive PTH levels, bone turnover remains high because of increased activity of both osteoblasts and osteoclasts. If unchecked, this process can lead to the development of osteitis fibrosa cystica (Figure 2).

Low-Turnover Renal Osteodystrophy (Adynamic Lesions)

Before the advent of modern medical treatment of renal disease, secondary hyperparathyroidism was an almost inevitable consequence of chronic renal failure. With the efficient management of this condition, including early diagnosis and instigation of appropriate dialysis, patients with renal disease and secondary bone pathology without abnormal levels of PTH are presenting with low-turnover (adynamic) bone. According to Sherrard et al,⁹ the aplastic lesion has low bone formation without an increase in unmineralized osteoid. With continued early detection and management of renal disease, more adynamic bone lesions will be encountered. Unlike osteomalacia, the bone does not have defective osteoid (unmineralized collagen). It was believed that the failure of the kidney to excrete aluminum led to overload and secondary bone deposition. In bone, aluminum impairs both proliferation of osteoblasts as well as differentiation from precursors to mature osteo-

blasts. However, these lesions are noted even after managing the aluminum overload.

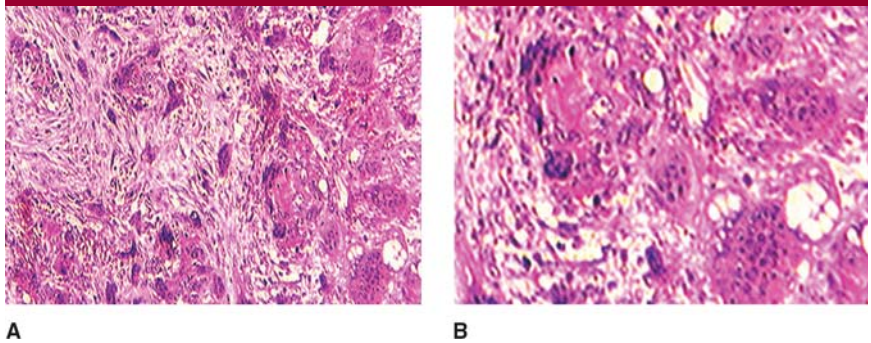
Histologic Features of Bone in Renal Disease

Bone biopsies provide information on the quality of osteoid, number of osteoblasts and osteoclasts, the extent of areas of resorption, and evidence of fibrosis within the marrow. Ho and Sprague¹⁰ stated that bone biopsy is "an essential tool in the understanding of underlying bone pathology and in directing therapeutic intervention." Bone formation rate can be assessed via tetracycline labeling. After a preload of tetracycline, bone turnover is assessed under fluorescent microscopy after a defined period of time.¹¹⁻¹³

Osteitis fibrosa lesion, which is the response to prolonged elevation of PTH levels, is seen in high-turnover disease. Osteoclasts are numerous and enlarged, with an increased number of Howship's lacunae. Fibrous tissue is seen adjacent to trabecular bone or within the marrow. The increased number of osteoblasts is caused by the action of PTH on cell receptor osteoblasts, which causes increased osteoclastic activity via PTH receptor 1 (PTHR1), resulting in newly formed osteoid with disordered collagen. Hoyland and Picton¹⁴ showed downregulation of PTHR1 mRNA by osteoblasts in renal bone compared with normal, fractured, or pagetoid bone.

In low-turnover disease, the histologic appearance is that of osteomalacia. Excess osteoid accumulates in bone because of abnormal mineralization, and wide osteoid seams with reduced osteoblastic activity secondary to poor bone turnover are seen on tetracycline labeling studies. The histologic finding of increased aluminum deposition is no longer as consistent because this condition is now identified and managed earlier.

Figure 2



A, Histopathologic hematoxylin-eosin stain demonstrating extensive osteoclast proliferation, bone resorption, and hypervascularity caused by high levels of parathyroid hormone. Note the increased presence of multinucleated giant cells and marrow stroma. **B**, High-power view of the multinucleated osteoclasts found in high-turnover renal osteodystrophy. Note the paucity of osteoid with numerous, interspersed Howship's lacunae.

Clinical Manifestations

In renal osteodystrophy, bone pain is diffuse and nonspecific and may be associated with weight bearing. Whether this pain is a consequence of microfractures within the structurally weaker bone remains unconfirmed. Occasionally, the initial manifestation of pain is periarticular, akin to an exacerbation of an arthritic condition. The pain is more severe in aluminum-related bone disease.¹⁵

Muscle weakness is commonly associated with renal disease, usually with a proximal myopathic distribution. The physiologic basis for this weakness is not clear.^{16,17} Such weakness may have an adverse impact on the patient's ability to rehabilitate adequately after surgery. In some patients, clinical weakness resolves with treatment of the renal disease.

Growth retardation, seen in children with chronic renal failure, is a result of renal bone disease, malnutrition, and chronic acidosis.¹⁸ The pediatric orthopaedic surgeon may encounter a child with both growth retardation and progressive skeletal deformity. Treatment requires correcting the angular deformity as well as selective limb lengthening.

Skeletal deformity is the most significant clinical manifestation of renal osteodystrophy. It may affect the appendicular as well as the axial skeleton and is often more pronounced in children. Radiographically, the deformity resembles that seen in vitamin D-deficient rickets, with rachitic rosary, enlargement of the metaphyses (eg, thickened wrists and ankles), bowing of long bones (most classically, genu varum), frontal bossing, and ulnar deviation at the wrists. Slipped capital femoral epiphysis is seen in adolescents with renal disease,^{19,20} although the physis has been shown to be more nearly vertical in these children, it has not been shown to be weaker.²¹ Adults tend to have less appendicular involvement.¹⁶

The clinical manifestations of renal osteodystrophy are diverse and show poor specificity. They also show a poor correlation with the severity of the disease, biochemical markers, or radiologic appearance. Bone density is reduced in patients with renal osteodystrophy, but Lima et al²² showed the value of peripheral quantitative computed tomography in distinguishing between cortical bone density (CBD) and trabecular bone density (TBD). In patients with renal osteodystrophy, TBD values

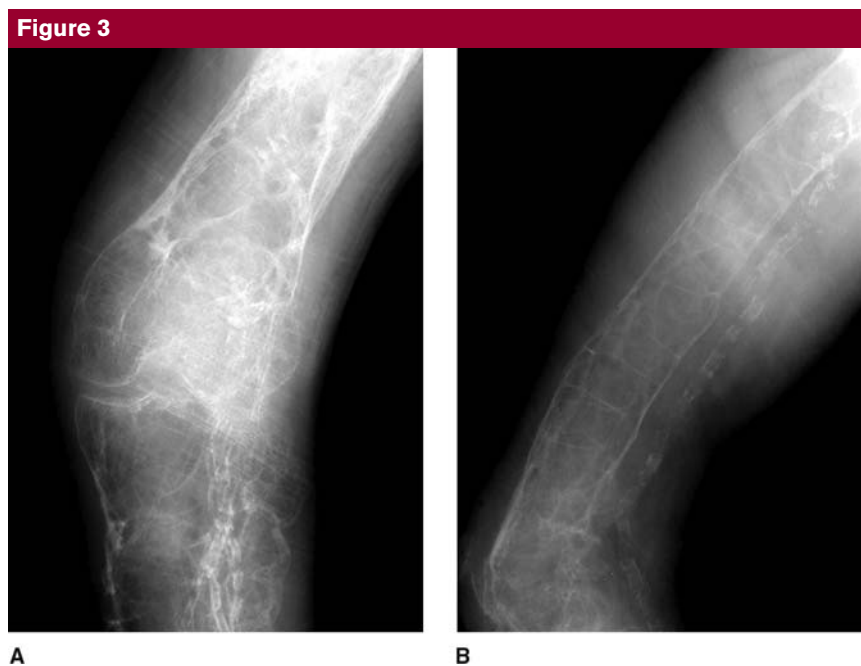


Figure 3
A, Anteroposterior radiograph of the knee demonstrating severe osteopenia, advanced cystic resorption, joint deformity, and arthritic changes in a patient with advanced renal failure. Note the presence of severe atherosclerosis and large vessel calcification. **B**, Lateral radiograph of the femur demonstrating marked osteopenia, femoral bowing, and calcification of the femoral artery.

were higher than in control subjects, but the CBD values were lower. The authors also reported that TBD was lower in low-turnover disease than in high-turnover lesions; conversely, the CBD was lower in high-turnover than in low-turnover lesions. The most striking manifestation in children is growth retardation. In adults, renal osteodystrophy manifests primarily as pain, weakness, skeletal deformity, and heterotopic calcification.

The extraskeletal manifestations of renal osteodystrophy include periarticular calcification that simulates inflammatory arthritides; vascular calcification of medium and small arteries (Mönckeberg's sclerosis), making peripheral vascular status difficult to interpret; and visceral calcification affecting the lungs, heart, kidneys, and skeletal muscle. The patient may develop restrictive lung disease, which has associated anesthetic implications. The patient

with extremely severe renal osteodystrophy may present with calchylaxis, a rare clinical condition in which the patient suffers ischemic necrosis of the skin, subcutaneous tissues, and skeletal muscle with catastrophic consequences. The consequences are especially dire with surgical wounds.²³

Radiologic Manifestations

Radiologically, renal osteodystrophy may present as osteomalacia, osteosclerosis, fracture, amyloid deposition, and soft-tissue calcification and bone resorption. Osteomalacia may be evident as osteopenia only when significant amounts of bone loss have occurred; in extreme circumstances, however, its presentation is dramatic (Figure 3). Osteopenia is particularly common following renal transplantation; evidence of decreased bone mass is present in near-

ly all patients within 5 years of surgery.²⁴ Large immunosuppressive doses of corticosteroids also may significantly contribute to osteopenia. Sclerosis may appear as patchy and nonspecific or, as in the spine, show concentrated end plate involvement. Chondrocalcinosis may be seen in the hyaline or fibrocartilage around the knee, at the pubic symphysis, or in the triangular fibrocartilaginous complex at the wrist.²⁵⁻²⁹ Looser's zones—microfracture lines or complete fractures following an osteoporotic insufficiency pattern—may be noted.

Bone resorption may be subchondral, endosteal, subperiosteal, or subligamentous. The classic sites of subchondral resorption are the distal clavicle, sacroiliac joints, and pubic symphysis.²⁵⁻²⁹ Endosteal resorption is evident in the long bone diaphysis. Subperiosteal resorption occurs at the joint margins, giving the appearance of rheumatoid marginal erosions; the hands and feet demonstrate subperiosteal erosion along the radial border of the middle phalanges and at the tufts of the distal phalanges. Subligamentous or subtendinous erosions can be seen at the calcaneal insertion of the plantar fascia, the triceps insertion on the olecranon, and the hamstring attachment at the ischial tuberosities.³⁰

In children with renal osteodystrophy, the radiographic appearance is that of osteomalacia with rachitic changes, including widening and elongation of the growth plates and cupping of the metaphyses.³¹

Management

The orthopaedic surgeon will encounter patients with bone pathology secondary to chronic renal disease and the consequences of associated medical therapy. These consequences include corticosteroid-induced osteonecrosis as well as immunologic compromise leading to increased risk of infection and significant anesthetic risk.

Nonsurgical Treatment

The main objectives of medical management in patients with renal osteodystrophy are maintaining mineral homeostasis (especially calcium and phosphorus), avoiding aluminum and iron toxicity, and preventing extraskeletal calcification. Dietary restriction of phosphorus can help regulate serum phosphate levels.^{32,33} This is important in preventing soft-tissue calcification and controlling secondary hyperparathyroidism. Such diets are often unpalatable,³⁴ however, and patients may prefer regular ingestion of phosphate-binding antacids, which reduce intestinal phosphate absorption by forming complexes with dietary phosphorus.

Even with dietary phosphate restriction, adequate calcium intake, and use of phosphate-binding agents, a substantial number of patients will develop secondary hyperparathyroidism. These patients are treated with active vitamin D sterols, most commonly calcitriol (in the United States) or 1α -hydroxylase (in Europe and Japan).³⁵ These sterols have been shown to be effective in reducing bone pain as well as improving muscle strength and efficiency of gait.³⁶⁻³⁸

Aluminum intoxication can be effectively treated with deferoxamine (a chelating agent) during hemodialysis or peritoneal dialysis. There is an associated risk of serious and potentially lethal infection, however, particularly with *Yersinia* species.^{39,40}

Surgical Treatment

The patient with renal osteodystrophy generally presents in one of four distinct settings: (1) the pediatric patient with growth disturbance and skeletal deformity; (2) the adult patient presenting for elective surgery; (3) the adult patient with pathologic fracture; and (4) the infected adult patient with osteomyelitis, either in isolation or around a joint or fracture implant.

Pediatric Osteodystrophy

In the pediatric patient with growth disturbance and skeletal deformity, the principles of deformity correction are similar to strategies for managing rickets; the surgeon makes careful use of the child's remodeling potential as well as remaining growth to allow correction. Presurgical planning is crucial in order to assess the exact extent of deformity in all three planes. Depending on the extent of deformity, angular and rotational deformity may be managed with corrective osteotomies or with gradual correction through a corticotomy site. Osteotomies and fractures tend to heal faster in children than in adults; however, there is no evidence that they heal at a different rate in children with skeletal deformity than in children with normal bone. Commonly used implants include plates and screws, intramedullary devices (avoiding the growth plates in the younger patient), and external fixators (monoaxial or Ilizarov). Numerous authors have examined the characteristics of implant failure in adult osteoporotic bone,⁴¹⁻⁴⁶ but there are no reports in the literature on the rates of implant cutout in children with osteopenic bone. Parents and older children need to be warned that, despite the success of initial realignment procedures, future corrective procedures may be required.

In the patient with a slipped capital femoral epiphysis, prophylactic pinning on the contralateral side is advocated.^{47,48} Standard screw fixation seems to be adequate, although the literature regarding outcomes is limited.

Adult Osteodystrophy

Hip Arthroplasty The adult patient presenting for elective surgery likely requires joint arthroplasty to address corticosteroid-induced hip osteonecrosis or osteoarthritis (Figure 4). Osteoarthritis may be a primary deformity or may be secondary

Figure 4



Anteroposterior radiograph taken 2 years after total hip arthroplasty using cemented acetabular and femoral components. Note the heterotopic bone at the calcar and greater trochanter.

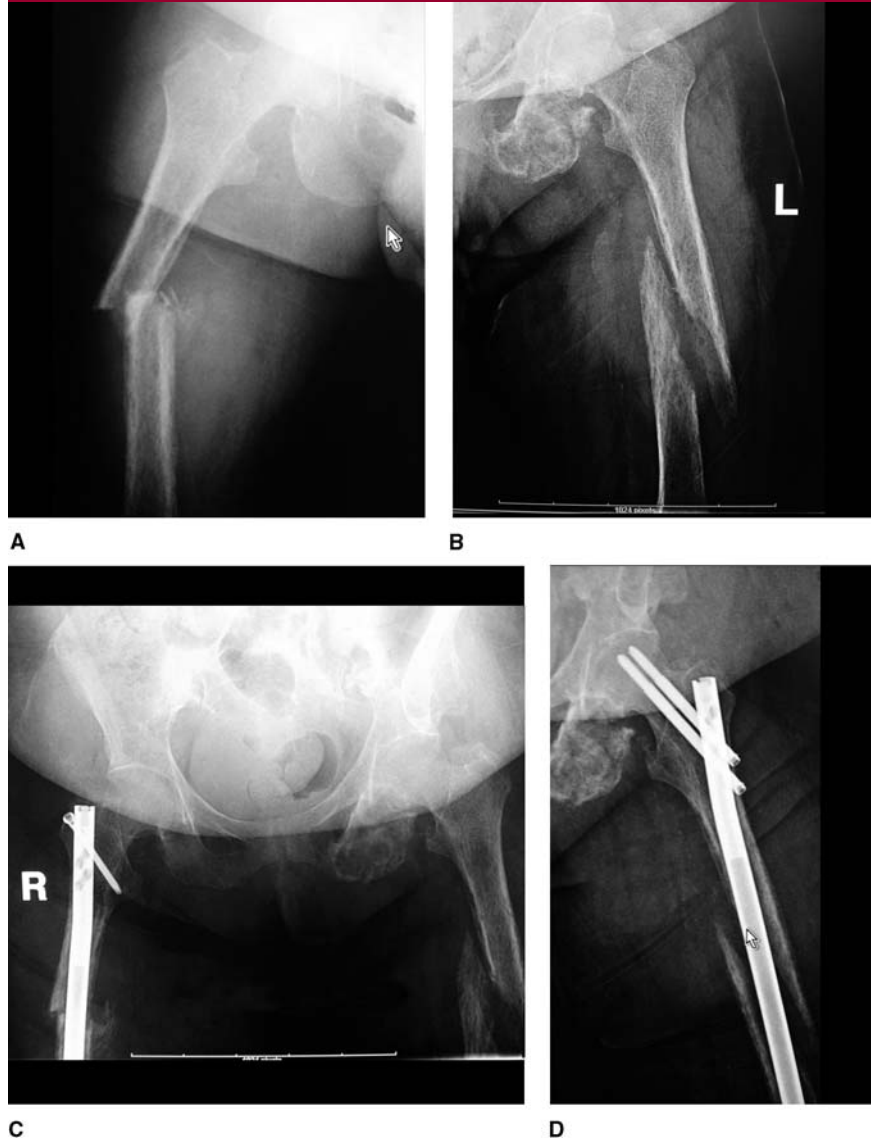
to periarticular erosion and osteopenia. Renal transplant recipients have a cumulative incidence of total hip arthroplasty (THA) of 5.1 episodes per 1,000 person-years—five to eight times higher than in the general population.⁴⁹ Osteonecrosis of the hip was the most frequent primary diagnosis requiring THA in this population (72% of cases).⁴⁹ When aseptic necrosis occurs in transplant patients, it usually does so within the first 7 to 15 months after surgery.⁵⁰⁻⁵² Although clinical symptoms of pain and disability fulfill the criteria for surgery, the radiographic appearance of sparse bone make it a daunting prospect. Careful preoperative planning is crucial to account for angular deformity affecting mechanical axes of the involved limb. Long bone radiographs may reveal the need for

Figure 5

Anteroposterior radiograph of the humerus in a patient with renal osteodystrophy with pathologic fracture of the humeral shaft. Note the cystic changes and profound cortical thinning.

custom-built implants. The absence of significant bone stock may predispose the surgeon to using cemented implants for both the femoral and acetabular components. Immune-compromised patients require the usual antibiotic prophylaxis but also may need careful screening for infective foci before surgery is considered.

Cheng et al⁵³ examined the long-term results of THA using bone cement after renal transplantation and concluded that the results were satisfactory and comparable with those of age-matched patients without a renal transplant. They reported a low infection rate (early [3 weeks], 1.3%) but a high dislocation rate (16%).⁵³ In an earlier study, Murzic and McCollum⁵⁴ reported a 46% rate of loosening in 32 cemented hips at a mean of 8 years after THA. In their retrospective study of 15 patients (24 hips), Toomey and Toomey⁵⁵ reported a 58% failure rate, requiring revision at a mean of 8 years.

Figure 6

A 42-year-old woman with end-stage renal disease sustained bilateral femur fractures after a fall from standing height (right femur) and, 2 days after the first fracture was fixed, by turning in bed (left femur). **A**, Posteroanterior view of the right femur demonstrating significant comminution and displacement. **B**, Posteroanterior view of the left femur demonstrating a long spiral fracture. **C**, The right femur was fixed with an antegrade femoral nail 2 days after the fracture. **D**, The left femur was also treated 2 days after fracture with an antegrade intramedullary nail.

Pathologic Fracture In the patient with a pathologic fracture (Figure 5), the weakened bone is prone to failure under physiologic loads. Injury patterns are similar to osteoporotic fractures in the elderly.⁵⁶⁻⁶⁰ Within the first 3 years after renal transplant, recipients have a greater incidence of

fracture than the general population and a decreased rate of patient survival.⁶⁰ These fractures are often comminuted and, as with most insufficiency fractures, occur at the distal radius, proximal femur, vertebrae, and ankles (Figure 6, A). The surgeon will encounter problems associated

with both internal fixation of fractures in weak and fragmented bone as well as the extent of preinjury deformity. Any modification to these contours compromises the strength of the implant and, with the locking plate, distorts the shape of the hole, thereby preventing the screw from locking into the plate.

Careful presurgical planning and consideration is vital to a successful outcome; structural augmentation with implants, bone cement, or bone graft may be required. Postoperative rehabilitation should be less aggressive in terms of load bearing. Early mobilization of the joints is crucial, however, because of the risk of periprosthetic fracture at the implant tip when mobilization is begun in a stiff joint. In the advanced stages of the disease, in the presence of marked bony deformity, loss of bony cortices, and limited ambulation, nonsurgical management may be the best option.

Sepsis The infected patient may present with osteomyelitis either in isolation or around a joint or fracture implant. The patient with chronic renal disease is immunologically compromised because of disease as well as corticosteroid therapy. This compromised immunologic state, along with regular renal dialysis sessions (hemodialysis or peritoneal dialysis), leaves the patient with a constantly high circulatory microbiologic load.^{39,61-65} Hematogenous infection is a common consequence. Managing chronic bone infection remains difficult; the acute infective episode requires incision, bone and soft-tissue treatment, and packing of the resulting bone defect with antibiotic beads. Secondary wound closure is performed later. Complete eradication of the infection may not be possible.

The situation becomes more complex with the total joint implant left in situ. Two-stage revision is ideal for managing infected joint arthroplasty. However, with weak fragile bone and lack of bone stock, the surgeon may

prefer débridement with washout, liner exchange, and retention of the total joint despite the presence of deep-seated infection. Resection procedures (eg, Girdlestone excision arthroplasty) may have to be considered despite the associated morbidity. Achieving anatomic reduction and stable fixation will eventually lead to fracture union, even in the presence of infection. In these instances, the infection is managed with antimicrobial drugs until union is achieved, after which the hardware is removed in an attempt to eradicate the infection. The literature contains sparse information regarding the best course of treatment in this subset of patients.

Summary

Chronic renal disease is marked by potentially life-altering manifestations of musculoskeletal disease. Mild forms of musculoskeletal disease should improve with management of the underlying renal disease. In children and adolescents, the advanced sequelae may be categorized as deformity. In the adult, advanced sequelae include secondary osteoarthritis, pathologic fracture, and chronic infection in the presence of immunosuppression. All of these entities require orthopaedic intervention.

Management of pediatric deformity involves extensive preoperative planning and the application of orthopaedic devices that enable deformity correction in three planes. Adequate planning and correct application of devices are required to restore proper mechanical alignment. Counseling for the child and parents is vital, particularly when further surgery may be required to correct secondary deformity. Pinning of slipped epiphyses as well as prophylactic pinning of the contralateral side are recommended.

In adults, degenerative joint disease is often present, the result of osteonecrosis. Additionally, the patient is often younger than the typical ar-

throplasty patient. Thus, specific attention should be paid to variables such as the existence of deformity, absence of bone stock, and chronologic age. A modular joint arthroplasty system that allows offsetting of correction may be useful. Open reduction and internal fixation of pathologic fracture allows early mobilization of joints after surgery and may help reduce associated morbidity. Infection remains a difficult problem in the patient with renal osteodystrophy. The principles governing care of the immunologically compromised patient are the same as those for the management of all patients with osteomyelitis. The orthopaedic surgeon should work with the involved endocrinologist and/or nephrologist to provide optimal care for the patient with renal osteodystrophy.

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Citation numbers printed in **bold type** indicate references published within the past 5 years.

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