Pathogenesis and Prevention of Bone Loss in Patients Who Have Kidney Disease and Receive Long-Term Immunosuppression

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The coexistence of kidney disease with a need for immunosuppressive therapy leads to the convergence of several threats to bone. These comprise general effects of the primary disease, *e.g.*, inflammatory state, more specific effects of acute renal failure or chronic kidney disease, and effects of therapies. Multisystem inflammatory disease that requires immunosuppression is associated frequently with kidney damage, and any reduction of kidney function that takes the patient into or beyond chronic kidney disease stage 2 for more than a short time is likely to have a negative impact on bone health. Bone mineral density frequently is low and fracture rates are high, although correlations often are poor. Chronic inflammation leads to local and systemic imbalance between bone formation and resorption. Upregulation of NF-$\kappa\beta$ ligand (RANKL) and variable down-regulation of osteoprotegerin are implicated, and bone health may improve in response to treatment of the inflammatory state. Certain immunosuppressive agents, especially glucocorticoids and calcineurin inhibitors, contribute further to bone loss. Antiresorptive agents such as bisphosphonates are used widely and, although able to prevent loss of bone mineral density, have uncertain effects on fracture rates. Augmentation of anabolic activity is desirable but elusive. Synthetic parathyroid hormone is untested but has potential. Manipulation of the RANKL/osteoprotegerin system now is feasible using antibodies to RANKL or synthetic osteoprotegerin. In the future, manipulation of the calcium-sensing receptor using calcimimetic or calcilytic agents may allow the anabolic effects of parathyroid hormone to be harnessed to good effect. With all of these therapies, it will be important to assess response in relation to important clinical end points such as fracture.

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Patients who receive long-term treatment with immunosuppressive agents are, self-evidently, likely to manifest underlying chronic disease. The spectrum of such diseases that are treated in this way is broad, both in the context of severity and in the range of pathologies that merit such treatment. Attention to the skeletal consequences of these management programs has been scant and until recent years essentially was nonexistent. This lack of attention reflects the priorities that exist in clinicians' minds with focus mainly on the primary disease process and its early and potentially life-threatening consequences. These are serious diseases, and it is hard to envisage, for example, a lupus specialist giving serious thought to long-term skeletal issues as a patient presents with severe cerebral lupus and renal failure.

Nevertheless, as management regimens are refined and the level of understanding and predictability of the treatment modified natural history of many of these diseases becomes clearer and the relevance of longer term causes of morbidity increases. For example, posttransplantation bone disease now is a widely recognized clinical entity that is known to affect a high proportion of recipients and to carry substantial morbidity and mortality. Bone health is very much "on the radar" in most transplant centers, even though the evidence base is fairly thin and management protocols often are empirical. In the case of long-term immune suppression for multisystem inflammatory disease, data are more sparse. The available information is limited to a few observational studies, and there is little in the way of randomized or other controlled intervention studies. Clinical practice is haphazard, and the likelihood of bone health being recognized as a significant issue for these patients depends largely on the clinical expertise and interest of the clinical group providing care. Patients who are treated in departments of rheumatology are probably more likely to receive attention to bone issues than are patients who are treated, for example, by ophthalmologists or dermatologists. No data exist as to the diligence with which nephrologists address this problem. Personal experience suggests that it is patchy.

Scope of the Clinical Problem

Three broad categories of patient are likely to require long-term immunosuppressive treatment: (*1*) Those with inflammatory diseases, especially if multisystem, with or without kidney involvement; (*2*) organ transplant recipients; and (*3*) those with malignant disease, including hematologic malignancy. The areas of particular interest to nephrologists are renal transplantation and multisystem inflammatory disease with involvement of the kidneys. Patients who have malignancy and receive

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cytotoxic chemotherapy are not discussed further. Although clearly immunosuppressive, these therapies are exhibited principally for their cytotoxic effects rather than for immune suppression, and their skeletal toxicity generally is low. Also not discussed is nonrenal solid-organ transplantation; this has been the subject of comprehensive reviews (1–5).

Bone formation driven by osteoblasts and resorption driven by osteoclasts are, in healthy young adults at least, in a state of approximate balance such that the net movement of mineral in and out of the skeleton is close to zero. Disease and medications may disturb this balance, by decreasing formation, increasing resorption, or both. Imbalance in favor of resorption exists from age 30 and increases in the postmenopausal setting. Much faster rates of bone loss frequently are documented in pathologic conditions, however, suggesting very substantial acceleration of bone resorption, sometimes in combination with impaired formation as well (6). Bone loss rates may be extraordinarily high and potentially catastrophic if not self-limiting or limited by appropriate therapies.

Relevant Terminology

The importance of consistency of terminology is emphasized by the current efforts of the Kidney Disease Improving Global Outcomes (KDIGO), acting through its Global Bone and Mineral Initiative, to reach consensus on the terminology and classification of skeletal disorders as seen in chronic kidney disease (CKD) (7). The descriptive terms that are applied widely to the general osteoporosis population are likely to be inappropriate in the groups of patients discussed here. The World Health Organization (WHO) definitions of osteopenia and osteoporosis are based purely on measurements of bone mineral density (BMD), usually made by dual-energy x-ray absorptiometry (DXA) (8). A white postmenopausal population was used to define the WHO criteria, this having limited applicability to immunosuppressed patients, among whom many will experience conditions that can cause secondary osteoporosis. Furthermore, they are considerably more heterogeneous, being of both genders, mixed ethnicity, and variable age and carrying a wide spectrum of primary pathologies. Nevertheless, with these provisos, it is helpful to keep in mind the WHO definitions, if only because they are so widely quoted in the literature (Table 1).

The National Institutes of Health issued a consensus statement on osteoporosis that has more relevance to patients with secondary forms of the disease (9). The National Institutes of Health defined osteoporosis as "a skeletal disease characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features—bone density and bone quality" (Figure 1). This suggests that bone strength and fracture risk, which are the key clinical end points of this type of bone disease, are determined by a combination of BMD (easily measured by DXA) and bone quality (more difficult to measure).

There is an understandable tendency for inappropriate weight to be given to BMD measurements even though there are arguments in favor of moving the emphasis away from DXA and toward the other determinants of bone strength, including microarchitecture, turnover, damage accumulation/repair, macroarchitecture (geometry), and the properties of the physical composition of bone. The importance of the last is illustrated by the experience with fluoride therapy in which increases of BMD in the order of 35% were not matched by significant reduction of fracture rate (10,11). Geometry is not assessed by DXA, although it is by quantitative computed tomography, yet powerfully influences strength that increases as the fourth power of the distribution of bone mass from the central axis of the bone (12). Nevertheless, it is clear that measurements of area BMD using DXA technology or quantitative computed tomography scanning yield data that, at least in the postmenopausal osteoporosis population, predict fracture risk reasonably well. The extent to which these measurements predict fracture risk in the secondary forms of osteoporosis that are considered here is much less certain. In CKD and patients who have received a transplant, correlations between BMD and fracture rates are poor (13). What really matters to the patient is the strength of their bones; assigning the term osteoporosis implies that a diagnosis has been made and to do this from just a BMD measurement is clearly a leap of faith that is unlikely to be justifiable without additional information to complete the overall bone data set.

Biomarkers of bone metabolism have been explored, but evidence of satisfactory prediction of fracture risk by this means is unimpressive, especially in the CKD population (14–17). More direct assessment of bone quality may be undertaken by examination of bone biopsy specimens, but this requires an invasive procedure of sample acquisition and challenging sample handling and assessment skills that often are not available. A new and simplified histologic classification for renal osteodystrophy has been advanced recently and should be appli-

Table 1. World Health Organization definition of osteoporosis (8)[a]

Classification	Definition	Fracture Risk
Normal	BMD no more than 1 SD below the young adult mean	Very low
Osteopenia	BMD is 1 to 2.5 SD below the young adult mean (T score −1 to −2.5)	4×
Osteoporosis	BMD >2.5 SD below the young adult mean (T score >−2.5)	8×
Severe osteoporosis	BMD >2.5 SD below the young adult mean plus history of one or more fragility fractures	20×

[a]BMD, bone mineral density.

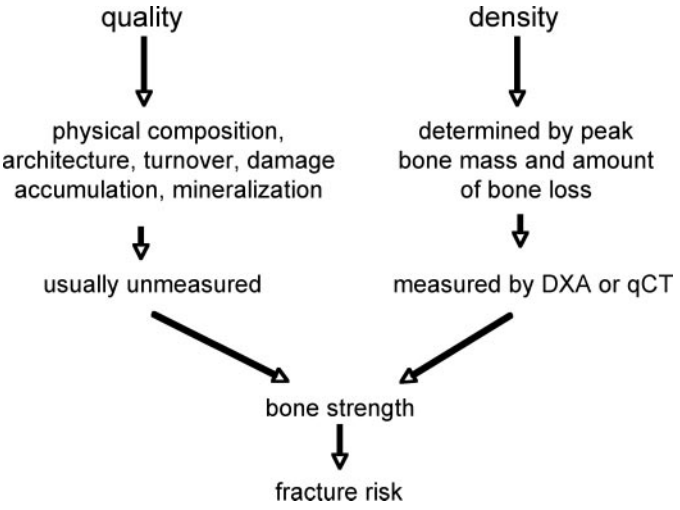

Figure 1. Determinants and measurement of bone strength.

cable to other skeletal disorders in which structural and ultrastructural bone changes are prominent (7). Three elements of bone structure and function, turnover, mineralization, and volume (TMV system) are reported in a semiquantitative manner (Table 2).

Mechanisms of Bone Loss

Mechanisms of bone loss can be ascribed to various combinations of (*1*) general effects of the primary disease (*e.g.*, immobility, nutritional insufficiency, inflammatory state), (*2*) more specific effects of underlying organ dysfunction (*e.g.*, acute renal failure, CKD), and (*3*) effects of therapies.

General Effects of Primary Disease

Immobility. Adverse skeletal effects of these processes are likely to be compounded by relative immobility in many cases (18,19). The importance of appropriate mobility and weight bearing to skeletal health has been studied extensively, as have the consequences of relative or complete immobility. Prolonged bed rest in the context of any serious disease has a powerful negative impact on skeletal health.

Nutritional Deficiency. The association between chronic disease and vitamin D deficiency is established clearly in the cases of CKD, chronic liver disease, and diseases of the large and small intestines (20–22). In patients with systemic lupus erythematosus (SLE), for example, nearly half of a group of 57 consecutive patients assessed had 25-hydroxyvitamin D concentration below the seasonally adjusted normal range, with approximately one fifth manifesting severe vitamin D deficiency (25-hydroxyvitamin D <5 ng/ml). Low 25-hydroxyvitamin D concentration was associated significantly with high disease activity but not with BMD (23,24). In addition, protein malnutrition and low body weight both predispose to low bone density. The role of obesity is unclear, although there is some indirect evidence that leptin, the levels of which are increased in renal failure, might be implicated by augmenting maturation of osteoblasts and inhibiting osteoclastogenesis (25).

Table 2. Renal osteodystrophy revised classification

Turnover	Mineralization	Volume
High	Normal	High
Normal	Defective	Normal
Low		Low

Inflammation. An important issue is whether treatments that control disease activity by lessening the intensity of the inflammatory processes and acute-phase response can be expected to have beneficial effects on bone. If true, this would strengthen the view that treatment of bone abnormalities in these patients should start with treatment of the primary disease.

Much information supports an important role for disturbances of the balance between the receptor activator of NF-$\kappa\beta$ ligand (RANKL) and its soluble decoy receptor, osteoprotegerin, in the control of osteoclastogenesis in chronic inflammatory states (Figure 2). This is particularly so in inflammatory arthritis, which is associated with striking local bone demineralization as well generalized skeletal effects. Evidence exists also for involvement of the RANKL/osteoprotegerin system in systemic effects on the skeleton during chronic inflammation. Accelerated osteoclastogenesis is driven by RANKL and the balance of RANKL with osteoprotegerin is central to this. In addition, various inflammatory cytokines are likely to be involved directly and indirectly. For example, IL-6 is a potent stimulator of osteoclast differentiation (26). IL-1 upregulates the differentiation and activation of osteoclast-like cells (27), and both IL-1β and TNF-α stimulate RANKL gene expression in human osteoblastic cells (28).

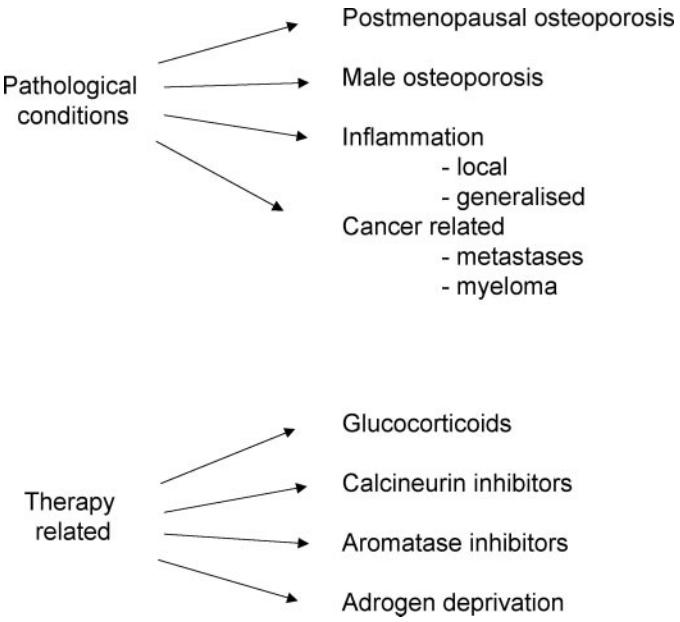

Figure 2. Causes of bone loss that are thought to act *via* disturbance of the balance between the receptor activator of NF-$\kappa\beta$ ligand (RANKL) and its soluble decoy receptor, osteoprotegerin, in the control of osteoclastogenesis.

More Specific Effects of Underlying Organ Dysfunction

Glomerulopathy. There is little information concerning patients who are given glucocorticoids specifically for treatment of glomerulopathy. An observational study evaluated 72 patients (25 men and 47 premenopausal women) who had primary or secondary glomerular diseases and normal renal function and were taking glucocorticoids. The findings suggested a high frequency of osteopenia among young and premenopausal patients who had glomerular diseases and were given corticosteroid therapy, with low body weight, low calcium intake, and furosemide therapy also identified as risk factors (29). Patients who had nephrotic syndrome and were treated with prednisolone or deflazacort and followed for 6 to 12 mo experienced significant loss of bone in all parts of the skeleton (30). The position in children may be different. Patients with glucocorticoid-sensitive nephrotic syndrome did not experience bone loss, possibly benefiting from intermittent exposure and high-turnover growing bone (31). The applicability of these data to adults with CKD is probably limited.

SLE. Disease severity is a predictor of bone loss in SLE. In a cross-sectional study of 307 women with SLE (32), high cumulative disease damage index was associated with significant reduction of BMD at the hip and lumbar spine, independent of glucocorticoid use. In studies of a murine SLE model, two strains of mice were examined, the strains manifesting a mild or a severe form of the disease (33). In the severely affected animals, bone mass, calcium content, and protein content all were significantly reduced. The more severely affected animals had marked reduction of trabecular bone volume and reduced cortical and femoral areas at the midshaft site.

Fracture rates in SLE are increased by approximately fivefold compared with age-matched women in the United States (34). Almost half of these fractures occurred in patients who were younger than 50 yr. An adverse effect of glucocorticoids was noted in these studies with duration of use being a significant predictor of the time from diagnosis to fracture. Yee *et al.* (35) examined 242 patients with SLE, 51% of whom had reduced BMD; 22 (9.1%) patients had a history of fragility fracture, and of these, 32% fell in the osteoporotic range. Glucocorticoid use was associated with reduction of BMD but not directly with fracture. Examination of the possible influence of glucocorticoid use in patients with SLE conducted in longitudinal manner during a period of approximately 2 yr showed significant loss of bone at the lumbar spine but not at the hip, with greater bone loss in those who took prednisolone at a mean dosage of 7.5 mg/d or greater (36). A cohort of premenopausal women showed an inverse correlation between BMD and both duration of treatment and cumulative dosage of prednisolone (37). Low body mass index and prolonged disease also predicted low BMD. Disease severity is likely to correlate with glucocorticoid exposure, and the difficulty in separating these influences may explain the inconsistent picture that emerges from the literature.

Vasculitis. Bone status in patients with ANCA-associated vasculitis has been assessed in relation to therapy with glucocorticoids and cyclophosphamide (38). This was a cross-sectional study in which 99 consecutive patients, with the genders equally distributed, were studied 15 mo after a diagnosis of ANCA-associated vasculitis. A total of 57% of the patients had WHO-defined osteopenia (T score −1.0 to −2.5), and 21% had osteoporosis at at least one site. Cumulative glucocorticoid dosage was associated inversely with *Z* scores at the lumbar spine and proximal femur. Cyclophosphamide exposure did not correlate with *Z* scores.

Rheumatoid Arthritis. Systemic bone loss occurs early in the natural history of rheumatoid arthritis (RA) and is related to disease activity (39). Studies using bone biopsies in patients with RA point to a dominant influence of decreased bone formation in the genesis of low bone mass in these patients (40), although biochemical markers of bone metabolism have pointed to accelerated resorption as the dominant abnormality, especially in corticosteroid-treated patients (41,42).

The effect of disease-modifying agents (DMARDS) on bone density and biochemical markers of resorption was measured in a group of patients who were starting treatment (43). None of these patients received glucocorticoids, and none received prophylaxis against the development of bone loss. Of 40 patients, initial elevation of deoxypyridinoline correlated with erythrocyte sedimentation rate (ESR) and the disease activity score (DAS). Treatment led to significant reduction of both ESR and DAS. There was a parallel reduction of deoxypyridinoline, with a reasonable correlation between ESR and deoxypyridinoline during a 1-yr period. Bone density measurement in 21 of the patients showed no significant change during the 2-yr period of the study, whereas the change in DAS was inversely correlated with that of lumbar spine BMD. These results are important because, although the study was of modest size, the data suggest that effective disease activity reduction may have beneficial outcomes for bone as well. Simonini *et al.* (44) used broadband ultrasound attenuation to evaluate the evolution of bone status in a group of patients who had juvenile RA and were treated for 1 yr with the TNF soluble receptor etanercept. Control of underlying disease activity in this way was associated with a significant improvement.

CKD. The coexistence of kidney disease, especially if chronic, with a need for immunosuppressive therapy leads to the convergence of several threats to bone and raises the skeletal stakes considerably. Multisystem inflammatory disease is frequently associated with loss of renal function, and any reduction of kidney function that takes the patient into or beyond CKD stage 2 for more than a short time is likely to have a negative impact on bone health. This usually takes the form of hyperparathyroidism with associated skeletal changes. Low-turnover bone disease is extremely uncommon in this group. The magnitude of this depends loosely on the severity of kidney dysfunction and its duration. Studies of bone histology in advanced CKD have shown consistently that, depending on definitions, few patients could be described as normal. The changes fall into a wide spectrum ranging from severe adynamic bone disease to uncontrolled hyperparathyroidism with a variable loss of BMD and increase of fracture risk at the clinically important sites (vertebrae and hip) (45,46). Morbidity and mortality from fracture is high in these comorbid patients (47). Increased variability of bone quality probably serves to

diminish the association between bone density and bone strength.

Effects of Immune Suppressive Therapies

In addition to the adverse endogenous factors described, the patient who is treated with immunosuppressive agents finds himself or herself on the receiving end of a range of potentially deleterious exogenous factors as well. The drugs that exhibit the most dangerous general toxicity are relatively benign as far as the skeleton is concerned. Immunosuppressive agents of the cytotoxic group, including azathioprine, cyclophosphamide, chlorambucil, and mycophenolate mofetil, have not been demonstrated as causing abnormal bone loss (48,49). This probably is because the toxicity of these agents is determined largely by rates of cell turnover—even in areas of high bone turnover, the mitotic rate in bone cells is relatively low.

In contrast, glucocorticoids and the calcineurin inhibitors are much more problematic (50). Glucocorticoid skeletal toxicity is well documented and severe. The bone toxicity of glucocorticoids has been reviewed extensively elsewhere, and the reader is referred to these discussions (51,52); only a brief review of the issue is offered here. Glucocorticoid toxicity is powerful, even in previously healthy individuals. When given on a background of preexisting bone disease or other skeletal morbidity, the effects are often dramatic. Even small dosages of prednisolone (as low as 5 to 7.5 mg/d) have been associated with significant reduction of bone density and increase in fracture rate (53). Both local and systemic effects operate, with local ones dominant. There is downregulation of various osteoblast gene products, in particular type 1 collagen, bone morphogenic protein, TGF-β, and osteocalcin. There also is a reduction of osteoblast proliferative activity and acceleration of apoptosis, resulting in a substantial reduction in osteoblast numbers (52,54). Bone resorption is accelerated; these patients manifest a decrease in osteoprotegerin and increase in RANKL (55). Osteoclastogenesis increases, and osteoclastic apoptotic rate decreases. This effect is potentiated modestly by the development of mild secondary hyperparathyroidism in glucocorticoid-treated patients; reductions of intestinal calcium absorption and increased calciuria drive this. Finally, hypogonadotropic hypogonadism induced by glucocorticoids reduces overall anabolic input to the skeleton as well as increasing the vulnerability of bone to resorptive activity in females.

The action of the calcineurin inhibitors on the skeleton has been the subject of a considerable research effort in the past 15 yr (50). Much experimental evidence points to adverse effects on osteoblasts and osteoclasts (56,57), although the picture is not entirely consistent. Experimentally, cyclosporine first was shown to accelerate bone resorption *in vivo* using rats and to lead to a very severe high-turnover osteopenic state with increased levels of osteocalcin and calcitriol. Antiresorptive therapies, including estrogen, raloxifene, and bisphosphonates, attenuate the bone loss in this model, and this led to the hope that bisphosphonates would also prove effective in the clinical arena (58,59). Testosterone did not retard the changes significantly (59). Effects of tacrolimus in the same rat model are broadly similar to those of cyclosporine (60). Clinically, there is more uncertainty. Both cyclosporine and tacrolimus have been associated with bone loss in the posttransplantation setting, although nearly always with concomitant glucocorticoids (61). On the plus side, there is no doubt that in some conditions, particularly certain dermatoses and glomerulopathies, cyclosporine and tacrolimus have proved highly effective and therefore have greatly lessened the need for high-dosage glucocorticoid therapy. To a certain extent, this is the case in the posttransplantation setting as well. After kidney transplantation, BMD falls rapidly in most patients, with bone loss rates as high as 20% per annum documented (62,63), although fortunately this high attritional rate rarely is sustained beyond 6 mo. Nevertheless, there is a very substantial increase in fracture risk (64). The development of steroid-free immunosuppressive regimens in patients who receive a transplant has allowed evaluation of the effect of steroids in this patient group. Bone loss in transplant recipients who are treated with little or no glucocorticoid and with calcineurin inhibitors as the backbone therapy has been very low. In one study, 364 renal transplant recipients were randomly assigned to a steroid-free regimen that was based on daclizumab, tacrolimus, and mycophenolate, with prednisolone given for the first 3 days only (65). The comparator group received prednisolone 0.3 mg/kg daily tapered to zero by 16 wk, also in combination with tacrolimus and mycophenolate. Bone loss was similar in the two groups at 4% in the steroid-free and 4.2% in the prednisolone-treated patients. These reductions were seen at 3 mo and had recovered by 12 mo and are considerably less than those that are seen in association with regimens that use larger dosages of glucocorticoids. The effect of early glucocorticoid withdrawal was examined further by Vanrenterghem *et al.* (66). Minimum steroid exposure followed by complete withdrawal at 3 mo was compared with a control group that received a standard prednisolone protocol without withdrawal. Lumbar spine bone density was greater in the patients with minimum steroid exposure at 12 mo, but a worrying trade-off was a significantly increased number of rejection episodes in that group. There was no difference in 12-mo graft loss between the two groups.

Studies in rats using a combination of cyclosporine and sirolimus, as well as each agent singly, showed dose-dependent bone loss when using cyclosporine with none seen either with low-dose sirolimus or with combined low-dose sirolimus and cyclosporine (67). Studies by the same group, also conducted in rats, have shown that cyclosporine, but not tacrolimus, lowered testosterone in male animals, whereas both led to similar high-turnover osteopenia. Testosterone replacement failed to prevent this bone loss (59). Sirolimus, therefore, seems to be more benign than are cyclosporine and tacrolimus, at least in experimental settings (68), and in the clinical arena, there also is some evidence that abnormally high bone turnover is less likely during treatment with sirolimus than with cyclosporine (69).

It is likely that these effects of the calcineurin inhibitors are mediated by alterations of the balance between RANKL and osteoprotegerin; there is abundant evidence that these drugs increase RANKL and decrease osteoprotegerin in cultured stromal cells. Sirolimus also has this effect *in vitro*, although differ-

ent effects in more mature bone cells in which sirolimus increased osteoprotegerin message and protein synthesis (70).

Preventive Strategies

Conceptually and also practically, it is helpful to distinguish between bone pathology that results from the underlying disease or that results from immunosuppressive therapies. Interesting studies that have examined the prevention and reversal of systemic bone loss have been conducted in human TNF transgenic mice, which develop erosive arthritis and systemic bone loss. Treatment was evaluated using parathyroid hormone (PTH), osteoprotegerin, and also anti-TNF antibody (infliximab) alone and in combination. Systemic bone loss was completely reversed after combination treatment with osteoprotegerin and infliximab, with partial reversal seen with osteoprotegerin alone (71). These studies illustrate the potential benefits of effectively tackling the primary inflammatory process while simultaneously modifying the deranged bone metabolism with a directly targeted therapy.

Studies that specifically address the issue of glucocorticoid-induced bone loss in the context of renal insufficiency are, with the exception of transplantation, few. Patients with impaired renal function, including most transplants and many others with renal involvement in multisystem diseases, are likely to manifest adaptive responses such as secondary hyperparathyroidism. It is logical to optimize the management of hyperparathyroidism and other components of the CKD that are relevant to bone health before or at least in parallel with exhibiting therapies that are directed at the bone itself.

It also is reasonable to separate acute rapid bone loss that occurs early after the initiation of the skeletal insult from the long-term skeletal attrition that accompanies protracted immunosuppressive therapy (6). Accelerated resorption dominates most of the former cases, whereas impaired bone formation often becomes increasingly relevant later. A logical approach dictates that management should augment bone formation rate when it is inappropriately low, while also retarding accelerated bone resorption when excessively high. Because the time course of bone loss after the initiation of the skeletal insult is one of very rapid early attrition, dominated by accelerated resorptive activity, the effect of antiresorptive agents that are given at this time has been studied in detail.

Bisphosphonates, whether given intravenously or orally, have been evaluated extensively in glucocorticoid-induced bone loss and also after solid-organ transplantation. Early bone loss rate in glucocorticoid-treated patients can be attenuated substantially using oral or intravenous bisphosphonates. The first convincing illustration of this was by Reid *et al.* (72), who demonstrated effective prevention of glucocorticoid-induced bone loss in patients with normal or near normal renal function who were given pamidronate. Subsequent studies used etidronate (73) and more recently alendronate (74) and risedronate (75–77). Some of these studies showed a reduction of fracture risk in addition to protection of BMD in treated patients. A range of underlying diseases (excluding transplantation) were included in these studies, in some of which a significant proportion of patients had underlying impairment of renal function. Certain bisphosphonates also may be capable of achieving very long-term inhibition of resorptive activity: Single intravenous injections of zoledronate have achieved progressive increase in BMD and reduction of bone resorption markers for periods of up to 1 yr (78), and work showing an effective role for zoledronate as protection against local and systemic bone loss in TNF-mediated arthritis now has been completed (71).

There are several reports of preventive strategies in patients who had inflammatory disease and were treated with glucocorticoids. Clearly, these patients are at substantial risk for loss of bone and also of fracture. In these patients, the well-documented early phase of rapid bone loss again is evident (36). There also are encouraging pointers to fracture reduction in association with risedronate use in glucocorticoid-treated patients with early RA (79).

After organ transplantation, bone loss in patients who are treated with a combination of glucocorticoids and calcineurin inhibitors is retarded by bisphosphonates such as pamidronate (80,81) and ibandronate (82). Although none of these studies was powered to examine the question of fracture convincingly, the ibandronate-based study by Grotz *et al.* (82) hinted at a reduction in vertebral fractures in the ibandronate-treated group. Coco *et al.* (83) conducted one of the few good studies of bisphosphonate intervention after transplantation in which histologic examination was undertaken. Patients received vitamin D and calcium as background therapy, with randomization to pamidronate or no pamidronate at the beginning of a 12-mo follow-up. At baseline, 50% of the patients manifested low-turnover bone disease. As had been shown previously, bone mass fell less in pamidronate-treated patients than in control subjects. By 6 mo, all of the pamidronate-treated patients had developed adynamic bone disease, whereas in control subjects, 50% continued to have or had developed decreased bone turnover. These observations are very important, raising the question of whether preservation of BMD, possibly in the face of deteriorating adynamic bone histology, is a reasonable objective in its own right. The overall balance in terms of achieved bone health remains uncertain.

Treatments that use calcium and vitamin D analogues generally have yielded much less impressive results, perhaps not surprising given the lack of efficacy of this approach in post menopausal women who took part in a Women's Health Initiative study (84). Nevertheless, many postmenopausal patients clearly maintain oral calcium intake well below the current recommendation of 1.5 g/d elemental calcium (85,86). Largely for this reason, supplemental vitamin D and calcium are part of the glucocorticoid osteoporosis preventive strategies that are recommended in many sets of guidelines. Vitamin D deficiency is common in patients with CKD (20–22) and with SLE (23,24), but despite this, studies of calcium and vitamin D therapy in SLE and after solid-organ transplantation generally have been disappointing, particularly so in the case of calcium and native vitamin D. There is no evidence that these treatments reduce fracture rate in immunocompromised patients. A review of interventions for preventing bone disease in kidney transplant recipients, based on the Cochrane central registry, Medline, and Embase, concluded that bisphosphonates and active analogues

of vitamin D that were given after kidney transplantation had a beneficial effect on BMD at both the lumbar spine and the femoral neck. None of the studies reviewed was powered sufficiently to show a beneficial effect on fracture rate (87).

Recommendations that are used widely for elderly patients with osteopenia, including those who are treated with corticosteroids, may not have the same applicability in premenopausal women. This is important because people who develop inflammatory disease that requires immunosuppressive treatment are often young. Some reassurance comes from three large intervention studies that examined etidronate, alendronate, or risedronate as prevention of corticosteroid-induced bone loss. All have shown efficacy in premenopausal women that is similar to that seen in the whole population studied (73–75). Less clear, however, is whether bisphosphonate treatment has a significant effect on fracture rate in premenopausal women. Additional concerns relate to safety. Bisphosphonates are not metabolized and ultimately are eliminated from the body *via* the kidneys. Initial plasma clearance is rapid, with much of the drug dose being taken up by bone, where it may remain for many years (88). This very long potential duration of action, coupled with the known and largely intended effect of bisphosphonates to reduce bone turnover, raises the possibility of a dissociation between beneficial effects on bone density and those on bone quality (89). Microdamage accumulation and repair certainly are impaired by bisphosphonates in some animal models (90). On a reassuring note, Miller *et al.* (91) found no evidence of heightened risk in subsets of patients who had early CKD and were given risedronate. This analysis examined nine randomized trials with approximately 9000 patients assigned to groups with mild (creatinine clearance [CrCl] $\geq$50 to $<$80 ml/min), moderate (CrCl $\geq$30 to $<$50 ml/min), or severe (CrCl $<$30 ml/min) renal impairment.

Hormone replacement therapy may alleviate bone loss in glucocorticoid-treated patients. For example, in patients with RA, hormone replacement that was given to control disease activity also was found to attenuate bone loss (92). Nevertheless, hormone replacement therapy is logical given the frequent existence of low testosterone and estrogen found after transplantation and also in a variety of chronic diseases that are treated with immunosuppressive agents. The balance of potential benefit and risk is difficult to evaluate, and this approach currently finds relatively little use with the present uncertainty as to efficacy. Conversely, testosterone therapy may have a more convincing place, particularly in men with demonstrable hypogonadism. Evidence exists for protection of BMD in glucocorticoid-treated men who are given testosterone but not for reduction of fracture (93).

In the setting of long-term maintenance therapy with immunosuppressive agents, failure of bone anabolic function is likely to contribute importantly and perhaps to dominate the pathologic picture. Here, the therapeutic approach is much more problematic, there having been a lack of anabolic options with which to counter these unwanted developments. The most potent bone anabolic agents that currently are available are sodium fluoride and recombinant human PTH. Sodium fluoride is highly effective in augmenting bone formation, increasing bone density, and in some studies reducing fracture rates (94,95). These studies were conducted in patients with uncomplicated osteoporosis. Unfortunately, sodium fluoride has a narrow therapeutic window and the potential for unwanted effects is high, including a paradoxic increase in fracture rate occurring in parallel with increases of BMD (10,11). Its use in complex patients with multisystem disease is not appealing, although there is limited evidence of its utility in patients who received a cardiac transplant and received cyclosporine and prednisolone (96). PTH given as a low-dosage daily injection that is sufficient to elevate the plasma PTH concentration to two to three times the upper limit of normal (transiently) clearly is a potent anabolic agent (97) that is capable of increasing BMD and reducing fracture risk in patients with osteoporosis (98). PTH use in glucocorticoid-treated patients has led to increase of BMD (99) and probably to increases of bone turnover (100), but the effect of this therapy on fracture rate is unknown at present.

Who Should Be Screened, and Who Should Be Treated?

Correlations between BMD, strength, and fracture risk are poor in the CKD and renal transplantation populations, with little information available in the group of patients with multisystem inflammatory diseases. BMD measurements are relatively easy and frequently undertaken but may lead to a false sense of security or to inappropriate levels of concern. In the CKD population, there may be benefits to be extracted from looking at other more peripheral cortical sites. We badly need better means of estimating bone strength than are currently available, and until we can do this, it is inevitable that our therapeutic approach will remain relatively crude with undertreatment of some and overtreatment of others.

The pattern of bone loss in these patient groups means that there is little time for procrastination. Most bone is lost early, and no effective means of predicting who is most likely to lose bone has yet emerged. Therefore, a "wait and see" policy is not logical. If therapies that are effective and safe can be identified, there is a case for treating all patients who are judged to be at risk and in whom no obvious contraindication exists. In practice, this is likely to include most or all patients with active inflammation that is severe enough to merit any form of immunosuppression, all patients who receive glucocorticoids, and all recipients of kidney transplants who are treated with glucocorticoids and calcineurin inhibitors. An important practical issue is whether bisphosphonates satisfy this requirement for safety and efficacy. Available evidence suggests that in transplantation (83) and possibly in CKD 5 as well, the risk of harming bone quality is too high to justify blanket treatment of all patients, at least until such time as fracture reduction is established. In patients with CKD 1 and 2, it is reasonable to extrapolate from the positive results of the studies in "non-CKD" patients (72–76,91).

Future Prospects

The development of an antagonist to RANKL opens interesting possibilities. Potent and longstanding inhibition of bone resorption may be achievable by directly interfering with the

RANKL/osteoprotegerin system. Bone loss in glucocorticoid-induced osteoporosis seems to be related to an increase in the ratio of RANKL to osteoprotegerin, leading to accelerated osteoclastogenesis and bone resorption. Two approaches to inhibition of RANKL effects have been explored. Early studies that examined the effect of an antibody to RANKL have shown that a single dose is associated with substantial reduction of bone resorption markers that extends for a period of 6 mo or more. Infusions of this antibody in postmenopausal women led to brisk and striking (80%) reduction of N-telopeptide/creatinine ratio, with a delayed reduction of bone-specific alkaline phosphatase, suggesting potent inhibition of bone resorption (101). Recombinant osteoprotegerin is emerging as a potentially useful therapy in conditions that are associated with accelerated resorption (102,103), although a possible association between osteoprotegerin in serum and certain cardiovascular risk factors merits a note of caution. Nevertheless, the therapeutic possibilities are considerable and extend to other areas, including periarticular osteoporosis in which increased RANK ligand has been shown to be an important pathogenic factor. Effects on fracture remain to be determined.

An attractive alternative to synthetic recombinant PTH as an anabolic therapy is to use drugs that are capable of manipulating the extracellular calcium-sensing receptor (CaR) on parathyroid cells to reduce or augment endogenous PTH secretion. This might allow induction of PTH cycling—yet to be tested but certainly feasible. Calcimimetics allosterically modify the CaR to increase its sensitivity to calcium. An abrupt fall of PTH ensues in patients with primary hyperparathyroidism as well as in those with secondary hyperparathyroidism and CKD. Calcilytics have a contrary effect on the CaR by decreasing sensitivity to calcium (104). When given to experimental animals or humans, these agents are associated with an abrupt increase in endogenous PTH secretion with augmentation of bone formation, thus mimicking the effect of intermittent daily injections of synthetic PTH. The potential for exploiting these cyclical changes is clear.

Conclusion

Patients who receive immunosuppressive drugs frequently experience very rapid and clinically deleterious bone loss. In most cases, it is likely that this attrition involves deterioration of bone mass and bone quality. Morbidity is substantial. The pathogenesis is driven by a combination of preexisting bone disease, bone disease that is associated with the underlying condition requiring treatment, and skeletal toxicity from medication. Better control of underlying inflammatory diseases using new therapies may well lead to an amelioration of these adverse skeletal developments. The many patients with coexistent impairment of renal function are likely to manifest predictable disturbances of bone and mineral metabolism, including hyperparathyroidism. Attention to the bone and mineral disease of CKD, therefore, is an important parallel part of the therapeutic approach.

Among the drugs that are used widely, corticosteroids clearly represent the greatest source of morbidity, with calcineurin inhibitors also contributing significantly. Moves to reduce overall exposure to these agents, in particular glucocorticoids, are likely to be associated with a reduction of skeletal toxicity. The arrival of the calcineurin inhibitors, even while bringing direct skeletal toxicity in their own right, almost certainly has served to reduce overall skeletal morbidity by virtue of diminishing the reliance on glucocorticoids.

An important deficiency in the present armamentarium continues to be our relative inability to introduce potent anabolic inputs to the skeleton under these circumstances. The most promising of the currently available therapies is synthetic PTH, although its efficacy in the setting of secondary osteoporosis is uncertain. As powerful inhibitors of bone resorption, the bisphosphonates have been used widely in the settings of transplantation immunosuppression, albeit with a fairly weak evidence base. There is no doubt that these agents can effectively retard the loss of BMD in most patients who are threatened by accelerated bone loss. The extent to which this translates to a reduction in fracture risk is uncertain, and long-term concern regarding bone quality in bisphosphonate-treated patients remains.

The pipeline is encouraging. Agents are looming that should allow us to control pathologic resorptive activity with less risk for excessive reduction of bone turnover, whereas others may allow safe augmentation of skeletal anabolic activity.

Disclosures

None.

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