Invited Comment

New concepts in renal osteodystrophy

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Introduction

Renal osteodystrophy is the term used to describe the skeletal complications of end-stage renal disease. It is a multifactorial disorder of bone remodelling. Some of the factors contributing to the disorder, are known substances whose actions are well defined, and strategies have been developed to treat these abnormalities in end-stage renal disease. As a result, the nature of renal osteodystrophy has changed in the last two decades. For instance, the identification of secondary hyperparathyroidism and 1,25-dihydroxycholecalciferol (calcitriol) deficiency as major contributors to renal osteodystrophy has led to the development of treatment regimens which maintain normal serum calcium and phosphate concentrations, reduced parathyroid hormone secretion, and correct low calcitriol levels. These improvements in the treatment of renal osteodystrophy have resulted in a decrease in the frequency and severity of osteitis fibrosa, the most common and important type of renal osteodystrophy. The removal of aluminium from both water used for dialysis and aluminium phosphate binders has tremendously diminished the incidence of osteomalacia and aluminium intoxication as a cause of the adynamic bone disorder. The frequency of aluminium-related bone disease has waned only to be replaced by increasing prevalence of the adynamic bone disorder. As a result of these developments new hypotheses related to the pathogenesis of renal osteodystrophy have been generated and tested, at least on a preliminary basis. This review will discuss these new hypotheses and suggest future directions for study and treatment.

Pathogenesis of osteitis fibrosa

The histological features of osteitis fibrosa cystica include a proliferation of osteoblasts leading to an increase in bone surfaces covered by osteoblast and an increase in osteoblastic cells with a cuboidal type of cellular morphology. There is an increase in osteoclast number, and an increase in the number of osteoclastic resorption bays demonstrating the increased rates of bone resorption in osteitis fibrosa.

In addition, osteitis fibrosa is characterized by a prominent accumulation of fibroblastic cells around the trabecular surfaces in the bone-marrow cavity. These cells produce a peritrabecular fibrosis which is a hallmark of osteitis fibrosis cystica. The pathogenesis and nature of the fibroblastic cells and their extracellular matrix has not been defined.

From the histological features of osteitis fibrosa, the conclusion that bone remodelling is increased in this form of renal osteodystrophy is straightforward. Bone remodelling consists of the selection of site for remodelling activity followed by the activation of the process. Remodelling activation consists of a complex stimulation of two differentiation programmes, one of the osteoblast differentiation programme and one of the osteoclast differentiation programme (Figure 1). Osteoclastic differentiation proceeds and concludes more rapidly resulting in the stimulation of bone resorption. Parathyroid hormone and locally produced or systemic activating factors including interleukin-1 and tumour necrosis factor stimulate release of soluble factors from stromal cells and the haematopoietic tissue which induce the proliferation and differentiation of osteoclast precursors. As a result, there is an activation of osteoclastic bone resorption by an elevated number of multinucleated highly polarized osteoclasts. The soluble factors involved in the development of osteoclasts are many, including macrophage colony-stimulating factor (m-CSF), granulocyte–macrophage colony-stimulating factor (g-CSF), interleukin-6, interleukin-11, leukaemia induction factor (LIF) and others. Parathyroid hormone, tumour necrosis factor, and interleukin-1 stimulate production of osteoclasts at different stages of cell differentiation, leading to synergism when the concentrations of cytokines and parathyroid hormone are both elevated, as in chronic renal failure [1]. The actions of parathyroid hormone, and calcitriol on osteoclast differentiation occur late in the programme. Recent studies suggest the calcitriol may be a factor regulating substances that function at the multinucleation stage. In addition, new information demonstrates that a soluble circulating molecule of the TNF receptor family, named osteoprotegerin, inhibits...
the late stages of osteoclast development [2]. Since this substance is made in the kidney besides the lung and heart, its deficiency in chronic renal disease would promote osteoclastogenesis independent of PTH or calcitriol.

Following remodelling activation, bone is resorbed by multinucleated osteoclasts. When a quantity of bone has been resorbed, increased local concentrations of calcium [3] or activation of latent factors in the bone matrix (e.g., transforming growth factor β) leads to diminished osteoclast activity, separation of osteoclasts from the bone surfaces, and apoptosis. Some of the same signals that decrease resorptive activity, (transforming growth factor β, heparin bound growth factors—i.e. fibroblast growth factors and bone morphogenetic proteins) bring osteoprogenitors or osteoblasts into the resorption lacunae and activate them [4,5] (Figure 2). This process initiates bone formation from osteoblasts and osteoblast precursors which have differentiated from the activation of the osteoblast differentiation programme at the onset of remodelling activation (Figure 1). Bone formation includes the proliferation and differentiation of osteoblast precursors, matrix (osteoid) synthesis, mineralization, resorption of woven bone and its replacement with lamellar nutrient shaped supplied bone. At the end of the remodelling cycle in chronic renal diseases, the amount of bone formed is smaller than that which was resorbed. This difference increases with age, so that older patients with end-stage renal disease may have osteopenia in addition to renal osteodystrophy.

One of the major difficulties in our current understanding of bone formation is stimulation of bone anabolism by substances that regulate activation of the remodelling cycle. For instance, parathyroid hormone, tumour necrosis factor α, and interleukin-1 stimulate the production of an osteoblastic phenotype consistent with the resorptive process. That is, parathyroid hormone stimulates osteoblastic cells to secrete collagenase [6], tissue plasminogen activator [7] and inhibits the synthesis of collagen [8] and inhibits progression of the osteoblastic cell cycle [9,10]. One question that becomes immediately apparent then is how parathyroid hormone induces its anabolic actions. The current theory is that parathyroid hormone is not a mitogenic factor. We and others have provided evidence clearly supporting this concept of parathyroid hormone action on cells in the osteoblast differentiation programme [9,11–13]. In addition, Dobnick and Turner [14] have demonstrated that parathyroid hormone may increase osteoblast number by causing dedifferentiation of the lining cells to assume an osteoblast phenotype. This has become the current concept of how parathyroid hormone induces an increase in osteoblast number during bone remodelling. However, it ignores the accumulation of peritrabecular fibroblastic-like cells in osteitis fibrosa cystica. We have shown that parathyroid hormone is indeed mitogenic for cells very early in the osteoblast differentiation programme [15,16]. We have recently demonstrated that parathyroid hormone is mitogenic for a stromal cell isolated from human bone marrow which we have characterized as a non-committed osteoprogenitor [15] (and Onishi et al., unpublished). (Figure 3). As a result of this data we have postulated that parathyroid hormone stimulates proliferation of an osteoprogenitor leading
Fig. 2. Activation of bone resorption in ROD. Following remodelling activation and osteoclast differentiation, bone is resorbed by highly polarized multinucleated osteoclasts (left). Osteoclasts form a tight seal with the bone matrix in a process involving adhesion through the $\alpha_v\beta_3$ integrin in the osteoclast clear zone. The seal is sufficient to allow acidification of the resorption space by secretion of $H^+$ through the activity of a vacuolar H-ATPase inserted into the ruffled border. Acidification dissolves bone mineral and the matrix is degraded by a cathepsin active at acid pH. As resorption proceeds (right), release of the products of resorption into the resorption bay, including Ca, decrease osteoclast adherence leading to apoptosis. Other products of resorption including heparin-bound growth factors (TGF$\beta$ and BMPs) stimulate preosteoblasts and osteoblasts to move into the resorption bay and begin bone formation.

Fig. 3. Effects of CRD on the osteoblast differentiation programme. New preliminary data indicate that PTH, elevated by secondary hyperparathyroidism, stimulates proliferation of uncommitted osteoprogenitors. However, these accumulate because of failure to move along the differentiation programme. Factors contributing to deficiency in osteoblast differentiation in CRD include low calcitriol levels, hypogonadism (possibly leading to reduced BMP-6) and others such as BMP-7. In addition there is a mineralization defect in CRD leading to increased unmineralized matrix (osteoid) and formation of woven bone.

to accumulation of fibroblastic cells producing marrow fibrosis in the osteitis fibrosa osteodystrophy. These observations raise the question of why these cells do not move further along the osteoblast differentiation programme. We have begun to address this question as discussed below in our considerations of the adynamic bone disorder.

Pathophysiology of adynamic bone disorder

The pathogenesis of adynamic bone disorder is poorly understood. The disorder is most common in patients with end-stage renal disease who do not have secondary hyperparathyroidism (e.g. after parathyroidectomy), or following treatment with calcium and calcitriol.
addition, diabetes mellitus and/or aluminium intoxication are associated with the adynamic bone disorder. Continuous ambulatory peritoneal dialysis has also been associated with adynamic bone disorder. This may be due to greater transfer of calcium from the dialysate, and suppression of parathyroid hormone secretion with this form of dialysis as compared to haemodialysis [17]. From these data, one may consider that hypersecretion of parathyroid hormone is required to maintain normal rates of bone formation in patients with end-stage renal disease [18–20]. This would suggest that the need to maintain bone remodelling at a normal level may be an inherent stimulus for hyperparathyroidism in chronic renal diseases. Recent clinical studies support this conclusion [18,21]. The presence of adynamic bone disorder in patients with end-stage renal disease who have normal parathyroid function suggest that the production of one or more suppressors of bone formation is increased or that other promoters of bone formation (growth differentiation factors) are not produced (Figure 3). Either mechanism could contribute to the need for increased parathyroid hormone secretion. Recent reports that therapy for end-stage renal disease activates the immune system suggest that there are numerous candidates for suppression factors including interleukin-11 which may inhibit osteoblastic bone formation [22] and interleukin-4 [23]. Deficiency of a factor involved in bone formation or growth may contribute to adynamic bone disorder. Osteogenic protein-1 (also called bone morphogenetic protein-7), a potent activator of the osteoblast differentiation programme, is produced by normal renal tubular cells [24,25]. In the adult there is some evidence to suggest that OP-1 is a systemic factor that derives from renal tubular cells. Thus, one possibility regarding the inability of cells proliferating in response to PTH to transit through the osteoblast differentiation programme is that its capacity is decreased in chronic renal disease.

Another important factor contributing to osteopenia in patients with end-stage renal disease is hypogonadism [26]. In both women and men with end-stage renal disease, serum concentrations of gonadal steroids tend to be low as a result of a complex set of endocrine and non-endocrine factors. As a result, anovulation, amenorrhoea or oligomenorrhoea, infertility, impotence, loss of libido, oligospermia, are common in chronic renal disease. Recent studies in animals [27], demonstrate that oestrogen deficiency produces a decrease in bone morphogenetic protein-6. Thus hypogonadism may contribute further to the pathogenesis of adynamic bone disorder in the absence of parathyroid hormone.

Although initial reports suggested that adynamic bone disease does not cause symptoms [18,28] subsequent follow up has not resolved the issue. The importance of adynamic bone disorder may be the long-term risks of osteopenia and its provision of new insights into the pathogenesis of renal osteodystrophy.

Another factor, calcitriol, used in the treatment of secondary hyperparathyroidism may also be important in the pathogenesis of the adynamic bone disorder. Calcitriol may stimulate the expression of the differentiated osteoblast phenotype which involves inhibition of cell proliferation and expression of the markers of the osteoblast phenotype including osteocalcin, osteonectin, bone sialoprotein, and matrix mineralization. The mechanisms by which calcitriol regulates matrix mineralization are unknown. However, it may affect osteoblastic calcium and phosphate transport or regulate the phosphorylation of matrix proteins which could serve as nidii for formation of calcium phosphate crystals leading to the growth of apatite.

Diagnosis

The recognition that renal osteodystrophy encompasses a spectrum of disorders leads to a current controversy in the practice of nephrology. The question is how to make the diagnosis of renal osteodystrophy in the absence of bone biopsy. Standard clinical practice in treating patients with end-stage renal disease and renal osteodystrophy has evolved away from the performance of diagnostic bone biopsies before the initiation of therapy. Thus, characterization of patient profiles have been assigned to certain forms of renal osteodystrophy. Osteitis fibrosa will be associated with high levels of parathyroid hormone, alkaline phosphatase, and other evidences of increased bone resorption. On the other hand, patients with adynamic bone disorder tend to have normal or reduced bone density, only slightly elevated serum alkaline phosphatase concentrations, relatively normal serum parathyroid hormone concentrations, and absence of aluminium, and an increased frequency of hypercalcemia. In population studies, parathyroid hormone measurements have been used to differentiate osteitis fibrosa from adynamic bone disorder, but are not sufficient to establish the type of osteodystrophy in an individual patient [21,29–31]. This is especially the case if calcitriol has been administered [21]. Current recommendations for the maintenance of parathyroid hormone levels take into consideration the necessity of sufficient parathyroid hormone to maintain bone remodelling and prevent the development of the adynamic bone disorder. This has been difficult to attain at set levels of parathyroid hormone. Current recommendations suggest that maintenance of parathyroid hormone levels two to three times the normal range may be sufficient for maintaining bone remodelling in patients with end-stage renal disease. However, there are numerous exceptions to this [21].

Current management recommendations

The current management of renal osteodystrophy is the control of serum phosphate and calcium along with the use of Vitamin D analogues.
Phosphate

A low-phosphate diet is integral to the management of end-stage renal disease. It is necessary to prevent secondary hyperparathyroidism and can be produced by dietary phosphate restriction and the use of phosphate binders. Phosphate binders are either calcium carbonate, calcium acetate, and new compounds in clinical trial [32–34].

Control of serum calcium

Calcium malabsorption is common in end-stage renal diseases because of deficiency in calcitriol. Serum calcium concentrations need to be maintained at the high end of the normal range in order to suppress parathyroid hormone secretion [35]. Dialysate calcium concentrations of 3–3.5 mmol/l provide an influx of calcium during treatment [36]. The positive calcium balance is greater in patients treated with continuous ambulatory peritoneal dialysis than in those treated with haemodialysis. Because calcium salts are generally used to control hyperphosphataemia, the increased dialysate concentration may cause hypercalcaemia. Dialysate calcium concentrations may be reduced to 2–2.5 mmol/l, which will not provide a calcium infusion during treatment, but will allow for sufficient oral intake of calcium salts to use as phosphate binders [37]. The timing of oral calcium intake is important: calcium taken between meals is more of a calcium supplement than a phosphate binder. Use of vitamin D analogues, calcitriol, and other vitamin D preparations (vitamin D, alfacalcidol, dihydrotachysterol, and calcifediol) have been used to treat secondary hyperparathyroidism as well as to correct deficient and endogenous production of 1, 25-dihydroxycholecalciferol. These agents lessen bone pain, improve bone histological characteristics and suppress parathyroid hormone secretion by raising serum calcium concentrations and inhibiting parathyroid hormone gene transcription [38]. Calcitriol is the most potent agent in suppressing parathyroid hormone secretion, but it and other vitamin D preparations cause hypercalcaemia. None of these agents should be used in the presence of hyperphosphataemia, to avoid high concentrations of serum calcium–phosphorus products and extraskeletal calcification. Intermittent intravenous administration of calcitriol is widely used to suppress parathyroid hormone secretion [39,40]. Since vitamin D preparations suppress parathyroid hormone secretion, and decrease the proliferation of osteoblasts, their use has been limited in patients with, or prone to develop, adynamic bone disorder. Because of the difficulty in assessing adynamic bone disorder this has led to a difficult area in the management of patients with end-stage renal disease. The future development of a treatment which would be successful in suppressing secondary hyperparathyroidism but maintaining bone remodelling at a normal rate would be a useful development.

Conclusions

The recognition that there are new concepts regarding the development of renal osteodystrophy comes at a time when new opportunities for its treatment are on the horizon. The possible discovery of additional substances with important pathophysiological roles in osteitis fibrosa and adynamic bone disease may lead to improved approaches to the prevention and treatment of renal osteodystrophy.

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References

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Note added in proof While this manuscript was in publication the discovery of the osteoprotegerin ligand (OPGL) was reported [41,42]. OPGL is also referred to as ‘osteoclast differentiation factor’ and it is regulated by parathyroid hormone. It should be added to the list of local cytokines in Figure 1 affecting osteoclast differentiation.
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