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Clinical Forum

Osteoporosis in renal failure: How accurate is the diagnosis and is there any role for bisphosphonates?

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Abstract

Patients with chronic renal failure (CRF) may be at a particularly increased risk for osteoporosis and its related fractures given the high prevalence of some of the known risk factors for osteoporosis. The challenge is how to accurately make the diagnosis of osteoporosis in subjects with CRF since low bone mineral density and fractures could result from secondary hyperparathyroidism, adynamic bone disease, osteomalacia, as well as osteoporosis. Helpful tests include bone turnover markers and double tetracycline-labeled bone biopsy. In patients with confirmed osteoporosis, preliminary data suggest that bisphosphonates seem to be safe and effective down to glomerular filtration rates of 15 mL/min. Low to moderate doses of vitamin D analogues are also helpful in such patients.

Keywords: *biphosphonates, osteoporosis, renal failure*

Introduction

Osteoporosis is a complex multifactorial disease that remains asymptomatic until a fracture occurs, and strategies need to be developed to accurately identify "high risk" subjects who may benefit from preventive treatments before fractures occur.

Subjects at high risk for osteoporosis include all postmenopausal women who have one or more additional risk factors for osteoporosis besides menopause such as age above age 65 years, personal history of fracture as an adult, history of fracture in a first-degree adult relative, poor health/frailty, cigarette smoking, low body weight, low calcium intake, alcoholism, and inadequate physical activity.[1,2] Other risk factors that are common to both men and women include chronic medical problems such as diabetes mellitus, rheumatoid arthritis, hypogonadism, and chronic corticosteroids use. **Patients** with chronic renal failure (CRF) may be at a particularly increased risk for osteoporosis and its related fractures given the high prevalence of some of the known risk factors for osteoporosis such as sex hormone deficiency, immobilization, sedentary life style, and treatment with corticosteroids.[3,4] Additional risk factors specific for renal failure include uremia, acidosis, and vitamin D deficiency.

Prevalence of Osteoporosis

Although osteoporosis is an infrequent histomorphometric finding in bone biopsies from subjects with CRF,[5] patients with end stage renal failure (ESRD) are at increased risk for fracture regardless of the type of metabolic bone disease.[6,7] Preliminary data show higher risk for hip fractures in elderly women with ESRD compared to controls (RR 6.4 in 50-69-year-old patients with ERSD, and 2.6 in patients aged 70 to 84 years).[8] In one study[9] of 88 chronic haemodialysis patients, 43 (48.9%) had low bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DEXA). Of those, 17(19.3%) had osteoporosis range BMD. In another study of 250 dialysis patients,[10] the prevalence of osteopenia (Z-score<-2) at the lumbar spine, femoral neck, and ultra distal radius was 8%, 13%, and 20% respectively.

Diagnosis of Osteoporosis

The diagnosis of osteoporosis in subjects with CRF is not easy to make due to several factors. First, the effects of renal osteodystrophy (ROD), extracellular calcifications and superimposed hypophosphatemic osteomalacia may confound measurement of BMD by DEXA in patients with renal failure.[11,12] Second, low BMD and fractures could result not only from osteoporosis but also from other causes of renal osteodystrophy such as osteomalacia, adynamic bone disease, and secondary hyperparathyroidism. In recent years, the spectrum of bone disease has changed and adynamic bone disease has become the most prevalent bone lesion in predialysis and dialysis populations.[13,14] Both adynamic bone disease and osteomalacia are associated with low bone turnover and could theoretically get worse with osteoclastic inhibitors. Hence the diagnosis of osteoporosis must rely on excluding these causes. Helpful tests include bone turnover markers and double tetracycline-labeled bone biopsy.[15-17] The clinical utility of the latter procedure is limited however due to its invasive nature and other factors such as patients' acceptability and difficulties in finding experienced teams and appropriate laboratory facilities. Bone markers such as bone specific alkaline phosphatase (bAP), parathyroid hormone (PTH), osteocalcin (OC), and

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pyridinoline (PYD), are excellent markers of bone turnover in ERSD patients[18,19] and can distinguish the type of bone disease (high turnover vs. normal or low turnover). In general, high bone turnover is encountered when PTH levels are above 200 pg/ml (upper limit of normal 65pg/ml), OC > 50 ng/ml, bAP > 20 ng/ml, or PYD values higher than the upper limit (mean + 2 SD) of the normal range. A combination of the above values will exclude low bone turnover states in almost all cases.[19-22]

Prevention and Treatment of Osteoporosis

Postmenopausal bone loss has been successfully prevented with various agents such as oestrogens,[23-25] selective oestrogen receptor modulators,[26] bisphosphonates,[27] and calcitonin.[28] Unfortunately however, none of these therapies has been examined in a prospective manner in patients with CRF.

Bisphosphonates

Among all available agents, bisphosphonates are the most effective in increasing BMD and decreasing fracture risk.[29] Bisphosphonates have been proved effective in the prevention of post transplant bone loss and fractures[30,31] and corticosteroid induced bone loss,[32-34] in addition to reducing the incidence of fractures in postmenopausal women and men with osteoporosis.[35,36] They have also been used effectively for many years in Paget's disease of bone.[37] Bisphosphonates, however, are currently not recommended for use in patients with renal impairment (creatinine clearance <35 ml/min). Preliminary data would suggest however that oral bisphosphonates seem to be safe and effective down to glomerular filtration rates of 15 ml/min.[38] One particular bisphosphonate, pamidronate, has been safely used for the last few years for the treatment of hypercalcaemia of malignancy, including patients with renal failure and patients on haemodialysis.[39-43] It has also been safely and effectively used in the prevention of post-transplant bone loss in subjects undergoing kidney or other organ transplants.[30,31] In one randomized trial[44] of 26 male patients with ERSD, intravenous pamidronate infusion (0.5 mg/kg in 500 ml 0.9% saline) immediately before and 3 months after kidney transplant was associated with a significant mean increase in BMD of 6.4% at the spine and 9% at the femoral neck in the treatment group (n=13) compared to the control group (n=12) at one year. Apart from transient asymptomatic hypocalcaemia occurring in 2 patients a few days post infusion, no significant adverse effects of pamidronate were noted. In particular, this study did not demonstrate any significant detrimental effect on renal function. Fever and myalgias are significantly more common after infusion of pamidronate compared to placebo.[37,45] However, the incidence of fever and myalgias diminish significantly with subsequent infusions of pamidronate.[46-48] In one of the above studies, 45% febrile reactions occurred after 1st infusion, 21% after 2nd infusion and 4% for the subsequent infusions. None of the subjects discontinued the study because of these side effects. In studies comparing pamidronate with other bisphosphonates such as etidronate, the former was found to be more effective,[49,50] and is relatively free of the mineralization inhibiting toxicity reported with etidronate.[51] An additional advantage of the intravenous pamidronate regimen is that it ensures high compliance and avoids the practical difficulties of oral bisphosphonates in the complex renal patients receiving multiple therapies.

Vitamin D Analogues

Administration of active vitamin D metabolites is an established treatment in end-stage renal failure. For several years, the fear of accelerating the decline in renal function hampered the use of active vitamin D analogues in early renal failure, but recent studies, including a large histomorphometry study, have shown beneficial effects on bone and no hazards to renal function from treatment with low to moderate doses of active vitamin D analogues (e.g. 0.5-0.75 mcg/day of one alpha hydroxylated vitamin D) in patients with mild to moderate CRF.[52,53] The use of higher doses of active vitamin D analogues, to suppress PTH, is often limited by hypercalcaemia and hyperphosphataemia. Clinical trials of cinacalcet HCl, the first calcimimetic to be approved for treatment of secondary hyperparathyroidism in dialysis patients, have demonstrated suppression of circulating PTH levels without increments in the calcium-phosphorus product.[54] Whether this agent will improve BMD and reduce fractures remains to be established.

Summary and Recommendations

In summary, the diagnosis of osteoporosis in subjects with CRF is not straightforward since low BMD and fractures could result from secondary hyperparathyroidism, adynamic bone disease, and osteomalacia as well as osteoporosis. Helpful tests include bone turnover markers and double tetracycline-labeled bone biopsy. In patients with confirmed osteoporosis, preliminary data suggest that bisphosphonates seem to be safe and effective down to glomerular filtration rates of 15 ml/min. Low to moderate doses of vitamin D analogues are also helpful in such patients.

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