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Editorial

Nephrotic syndrome: Don't forget the bones!

Many features of the nephrotic syndrome and its treatment can impact adversely on bone turnover, mineralization and volume. They can be considered in terms of the disease process causing a patient to become nephrotic, the pathophysiology of the nephrotic state itself and the consequences of treatment. Just as in many areas of nephrology, there is no 'best' clinical response and management remains an evidence-free zone.

THE DISEASE PROCESS

The nephrotic syndrome often occurs as part of a systemic illness resulting in an 'inflammatory state'. Inflammation is often associated with impaired coupling of bone formation and resorption that favours loss of bone mass. The increased osteoclastic bone resorption accompanying inflammation is thought to be mediated by TNFα and other cytokines rather than by the RANKL, RANK, OPG pathway.

PATHOPHYSIOLOGY OF THE NEPHROTIC STATE

Deficiency or insufficiency of 25-hydroxyvitamin D (25(OH)D) is common in the general community and is associated with lower levels of bone mineral density (BMD) and a heightened risk of falls and fractures.[1] Vitamin D deficiency is also common in patients with chronic kidney disease (CKD)[2,3] and is likely to be more prevalent when patients are nephrotic. Both 25(OH)D and calcitriol are transported by vitamin D binding globulin and albumin, which are depleted by heavy proteinuria – albumin losses possibly contributing more to reduced levels of 25(OH)D.[4] Because 25(OH)D is metabolized to calcitriol in the kidney, lower 25(OH)D levels and progressive renal damage contribute to lower calcitriol levels and in turn, reduced vitamin D mediated dietary calcium uptake. Together, these changes contribute to secondary hyperparathyroidism and increased bone turnover.

Diabetes is one of the causes of a persistent nephrotic syndrome, and this condition demonstrates the interaction of a number of factors predisposing to abnormal bone. Patients with CKD stage 5 and type 1 diabetes have lower levels of 25(OH)D and BMD when compared with the remainder of patients with CKD stage 5.[5] Systemic inflammation often accompanies diabetic complications and may adversely affect BMD. Normal portal insulin levels are required for production of insulin-like growth factor-1 (IGF-1), which is bound in bone matrix and is released during bone matrix resorption. It has been proposed that IGF release promotes the recruitment of osteoblasts to the bone surface and initiates refilling of resorption pits.[6]

CONSEQUENCES OF TREATMENT

Glucocorticoids are a component of most specific treatment regimens when the nephrotic syndrome is caused by glomerulonephritis. When prednisone doses exceed 5 mg/day, a reduction of BMD is common, particularly in the first several months of treatment. Glucocorticoid use is associated with reduced osteoblastic bone formation, increased apoptosis of both osteocytes and osteoblasts and an increased ratio of RANKL to OPG that favours osteoclastic bone resorption. Glucocorticoids also affect bone indirectly; reducing intestinal calcium absorption, increasing urinary calcium losses (which are also increased by loop diuretics) and reducing levels of sex steroids, all of which contribute to bone loss. Warfarin, heparin and bed rest, all of which are suggested as treatment options in the nephrotic syndrome, are also associated with progressive decreases in BMD.[7]

PROTECTING THE BONES

The aim of bone prophylaxis is to reduce the risk of fracture, pain and deformity and particularly in the elderly to reduce fracture-related mortality. There are no published guidelines for bone prophylaxis when treating the nephrotic syndrome (PubMed search August 2007), but general principles can be applied. For patients likely to be treated with intermittent or prolonged courses of glucocorticoids or with high dose regimens, assessment should incorporate the underlying risk for osteoporosis and fracture as well as features associated with CKD such as the presence of hyperparathyroidism and hyperphosphatemia. Patients at particular risk for osteoporosis include postmenopausal women, hypogonadal males, men and women over age 65 years and those with a history of fracture, low BMD, low body weight or poor exercise capacity. In these patients, either before glucocorticoid or anticoagulant therapy is commenced or shortly after treatment starts, it is reasonable to assess the BMD by dual energy X-ray absorptiometry and a lateral X-ray of the spine for prevalent vertebral fractures. In all patients, levels of 25(OH)D and parathyroid hormone (PTH) should be checked and in some patients, hypogonadal levels of oestradiol, testosterone and gonadotropins may support the use of hormone replacement therapy.

Unless contraindicated by hypercalcaemia, it is reasonable to treat all patients commenced on glucocorticoids with calcium (e.g. calcium carbonate 600–1200 mg daily)

and cholecalciferol or ergocalciferol (1000–2000 IU daily). However, if initial 25(OH)D levels are deficient (generally defined in the normal population as <30 nmol/L) or insufficient (generally defined as <60 nmol/L), higher doses of cholecalciferol or ergocalciferol will be required. This may be the only treatment necessary for patients at low risk of fracture (a normal BMD, no prevalent fractures and few risk fractors) and likely to be treated with glucocorticoids for periods up to 3 months. Some support for these suggestions comes from a randomised prospective study of children with nephrotic syndrome, in which treatment with vitamin D 400 IU/day plus calcium 1 g/day reduced but did not completely prevent decreases in BMD.[8] Calcitriol at doses of 0.5–0.75 μg/day has proven efficacy in other settings to protect against glucocorticoid-induced loss of BMD[9,10] and may be particularly valuable if renal function is impaired or secondary hyperparathyroidism is present. Oral and intravenous bisphosphonate therapy is effective in reducing declines in BMD (and can sometimes even improve BMD) during glucocorticoid treatment. Biphosphonate treatment may be more effective than vitamin D and calcium alone,[11] particularly when glucocorticoid doses are high. However, for patients with significantly reduced levels of glomerular filtration rate (GFR), bisphosphonate use may require dose modification and for patients with low bone turnover, concern has been expressed that bisphosphonates may further reduce remodeling and contribute to a progressive degradation of microarchitecture. Gastro-oesophageal reflux disease is generally a contraindication to oral bisphosphonates and, in view of recent concern regarding the low but significant risk of osteonecrosis of the jaw, it is preferable that these drugs be avoided for possibly 6–12 months prior to major dental work. Intravenous pamidronate generally reduces bone resorption for around 3 months when patients have a normal GFR and this drug may be convenient for 'covering' a short course of glucocorticoid treatment. Pamidronate does not appear to adversely influence bone growth in children, avoids the need for additional oral medication and has been used to reduce the risk of bone loss in children with nephropathy.[12] Intravenous zoledronic acid can provide bone protection for longer periods of up to 12 months or more. There are few data available for the effect of other agents such as selective oestrogen receptor modulators (SERMs), PTH and strontium on the course of glucocorticoid induced osteoporosis, although these agents have proven efficacy for improving bone density and reducing fracture risk in the treatment of osteoporosis. Bone turnover markers checked prior to and during treatment may assist in assessing treatment responses, but are unproven in the setting of glucocorticoid therapy and may be less reliable when renal function declines. Levels of bone specific alkaline phosphatase and the bone isoenzyme of tartrate resistant acid phosphatase (TRACP 5b) are not influenced by renal function but are unproven in this setting.

Management of the nephrotic syndrome is often complex and just as renal physicians generally rely on a patient's general practitioner and endocrinologist to monitor and alter insulin therapy, it may sometimes be prudent to 'outsource' management of bone disease to a bone clinic or a physician with expertise in this area. But the most important bone prophylaxis is to remember they are there!

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