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Bisphosphonates in the renal patient

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Over the past decade, bisphosphonate use in patients with various forms of kidney disease has become widespread. The extensive take up of these agents by nephrologists reflects the twin perceptions that bisphosphonates are generally safe in patients with kidney disease, and that skeletal protection, readily demonstrable in bisphosphonate-treated populations without kidney disease, is also achievable in patients with chronic kidney disease (CKD) and other forms of nephropathy. Unfortunately, both of these perceptions are based on limited evidence and somewhat tenuous extrapolations [1,2].

The case for bisphosphonates in patients with renal disease

In the non-renal population, convincing evidence exists to show that bisphosphonates can effectively prevent, or at least attenuate, bone loss in glucocorticoid-treated patients [3–8]. There is evidence of significant fracture reduction in this patient group. Benefit is also

seen in glucocorticoid-treated patients with normal or near normal renal function and inflammatory disease [5]. It was reasonable, therefore, to hope that similar gains would be realized in bisphosphonate-treated patients with renal disease. Most studied have been patients undergoing renal transplantation, one of a cluster of scenarios associated with exceptionally rapid bone loss [9–11]. Fracture rates, already high in the dialysed CKD population, rise further following transplantation [12]. A number of small randomized studies have now been published and the consistent picture that has emerged is one of the effective protection of bone mineral density (BMD) in bisphosphonate-treated transplant recipients, generally without evidence of reduction of fracture rate [13–15]. The failure to demonstrate the clinical outcome that really matters, namely reduction of fracture rate, may reflect inadequate statistical power of the completed studies or a genuine absence of a significant impact of bisphosphonates in this patient group [16]. The latter explanation would imply that the CKD and transplanted population differ importantly from the general population, in whom evidence of clinical benefit is well established. Such a notion is certainly plausible—bone mineral density is only one of the determinants of bone strength, the others collectively falling under the umbrella of ‘bone quality’. Bone quality is a somewhat enigmatic concept that probably comprises a range of components including bone composition, micro architecture,

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turnover and geometry. Because the CKD population manifests an exceptionally wide range of abnormal turnover and microarchitecture, it is certainly feasible that this essentially unmeasured component of strength serves to obscure the effect of bone density [17].

Very large studies of bisphosphonate-treated post-menopausal populations have shown similar efficacy in subgroups with renal impairment [18]. Less clear, however, is whether the same conclusions can be drawn from studies of bisphosphonate use in glucocorticoid-treated patients. Here subgroup analysis is more difficult, although it is likely that those recruited to the several large published studies included substantial numbers with impaired renal function [4–6,8].

Safety

Two broad areas of concern arise in relation to bisphosphonate use in patients with renal disease. First, there is fairly convincing evidence of direct nephrotoxicity of some bisphosphonates, particularly at high dose when used in oncological settings. Ibandronate may be less problematic in this respect [19,20]. In practice, however, and subject to generally well-established precautions, nephrotoxicity from these drugs when used at recommended doses appears to be uncommon and rarely of clinical significance.

The second area of concern relates to the skeleton itself. Bisphosphonates bind to hydroxy apatite and powerfully impair resorptive activity, and thus reduce bone turnover rate. It is this action that is responsible for the consistent improvement of bone density seen in the non-CKD population following initiation of bisphosphonate therapy. It is this very action, however, that could, in some circumstances, compromise bone quality. Increased micro fracturing has been reported in bisphosphonate-treated dogs [21]. In the CKD population, and in particular in those with advanced disease on dialysis, bone turnover rates vary over a wide range, with a substantial proportion of the population manifesting extremely low bone turnover [22]. These patients with adynamic bone disease have impaired ability to buffer calcium loads, a tendency to hypercalcaemia, as well as increased fracture rates and prevalence of soft tissue calcification. It is quite possible that these disturbances are further impaired following administration of bisphosphonates to this subgroup and it is counter-intuitive to think that reduction of an already abnormally low bone turnover rate would improve bone strength [15]. Some data serve to reassure, however. In subgroup analyses of bisphosphonate-treated post-menopausal patients, individuals with GFR at CKD stage 2–4 did not show evidence of increased toxicity or adverse effect [18]. Safety may, therefore, be more of a theoretical than a practical concern.

The two papers published in the present issue of Nephrology, Dialysis, Transplantation are timely. Fujii *et al.* [19] studied glucocorticoid-treated patients with CKD. This study assessed the effect of risedronate in patients who had received glucocorticoids for at least 6 months. A total of 114 patients were studied, 88 of whom had received active vitamin D and were randomly assigned to continue with active vitamin D alone, or to receive risedronate at a dose of 2.5 mg daily in addition. The remaining 26 patients, none of whom had received active vitamin D, were assigned to risedronate alone. The results showed significant increases of BMD in risedronate-treated patients (2.8% and 2.5% with and without vitamin D, respectively). In contrast, bone density decreased by 1% in patients who took active vitamin D alone. These changes were seen at the lumbar spine only, there being no significant differences at the femoral neck. Markers of bone turnover decreased predictably in risedronate-treated patients. Renal function in these patients was described as normal or mildly impaired. In fact, mean creatinine clearance was between 95 and 105 ml/min in the three groups at baseline, without significant change during the 1-year observation period. These patients were, therefore, suffering from only minimally impaired renal function. Fracture rates were not reported. The study by Kikuchi *et al.* [20], also published in this issue, investigated patients with glomerulopathy and a wide spectrum of renal function and level of proteinuria. Patients were randomized to receive risedronate 2.5 mg daily, risedronate plus alfacalcidol 0.5 µg daily, or alfacalcidol alone. These treatments were initiated at the same time as high-dose glucocorticoid therapy. Patients treated with alfacalcidol alone exhibited substantial loss of bone density after 1 year of treatment, this being significantly different from the changes in risedronate-treated patients, for whom bone density did not change significantly. As expected, markers of bone turnover decreased in risedronate-treated patients. No fractures occurred during the study.

The studies by Fujii *et al.* [23] and Kikuchi *et al.* [24] do not shed important new light on this issue, merely supporting existing data concerning generally good tolerability and capacity to protect bone mineral density in patients with glomerulopathy and/or mild CKD. Because of the limited conclusions that can be drawn from these studies, there remains a disturbing lack of evidence to justify the widespread use of bisphosphonates with patients with CKD. Although bone density is clearly protected in glucocorticoid-treated and post-transplant patients given prophylactic bisphosphonates, few data exist to support an indication based on fracture reduction in these groups. A more positive view can be based in the analysis of Miller *et al.* [18] where bisphosphonate-treated osteoporotic women experienced improved

BMD and fracture rate regardless of their level of renal function.

How should we take this issue forward? Clearly the present evidence base is compromised by the relatively small size of the studies published to date. Additionally, many of the studies have failed to take adequate account of the heterogeneity of bone disease that exists in the clinical material. Thus, further studies might prove more informative if patients were treated or assessed in a manner appropriate to their underlying bone disease. Ideally this implies performing bone biopsies at the inception of such studies, although limited benefit might be obtained more simply by a pre-assessment, using indirect measures of bone turnover such as parathyroid hormone and bone-derived biochemical markers. In addition, we should focus on the development of therapies that have the potential to increase bone formation rate, this being the only logical approach to skeletal protection in patients with adynamic bone disease. This sub-group in particular is extremely unlikely to benefit from bisphosphonate therapy and there exist quite compelling arguments for withholding treatments in patients in whom low bone turnover is suspected.

Conflict of interest statement. None declared.

(See related articles by Kikuchi *et al.* Effect of risedronate on high-dose corticosteroid-induced bone loss in patients with glomerular disease. *Nephrol Dial Transplant* 2007; 22: 1593–1600; and Fujii *et al.* Risedronate, an effective treatment for glucocorticoid-induced bone loss in CKD patients with or without concomitant active vitamin D (PRIUS-CKD). *Nephrol Dial Transplant* 2007; 22: 1601–1607.)

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