elimination of B2M and protein bound retention solutes. Given the inferior dialytic clearance of B2M and p-cresol by peritoneal dialysis as compared to hemodialysis, patients on peritoneal dialysis are more dependent on residual renal function at least as far as the removal of these retention solutes is concerned. Very recently, high serum levels of both solutes were shown to be independently associated with increased mortality. Undoubtedly these observations will encourage nephrologists to broaden their view on adequacy beyond Kt/Vurea. All together, these data moreover provide additional support for the integrative care concept.


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Calcineurin-inhibitors and bone pain after organ transplantation

To the Editor: Collini et al.1 report two kidney graft recipients with post-transplant lower limbs transient joint pain. Bone scintigraphy and magnetic resonance (MR) imaging of the symptomatic joints showed increased tracer uptake and bone marrow edema, respectively. As already suggested by others, they incriminate calcineurin-inhibitors as the cause of this syndrome.

I do not believe that this hypothesis is warranted. Indeed, identical symptoms have been described in kidney graft recipients before the calcineurin-inhibitors era.2 The clinical presentation best fits with the microtraumatic hypothesis we initially proposed.3 Indeed, in multiple reports, MR imaging consistently showed bone marrow edema and/or hemorrhage. The demonstration in some patients of bands of hypersignal within areas of bone marrow edema further supports the notion of impaction. In addition, Yamamoto et al.4 recently showed in non-transplanted patients that similar MR imaging lesions of symptomatic areas correspond histologically to insufficiency fracture. Bone marrow infiltration with low intensity signal on T1-weighted MR image corresponds histologically to viable bone and marrow tissue with associated callus, edema, and vascular granulation. More interestingly, the presence in some T1-weighted MR images of a focal band beneath the articular cartilage corresponded to a fracture line and its associated repair tissue.

I suggest that a microfracture is the cause of this syndrome and that inadapted physical activity level imposed on a fragilized post-transplant bone could favor its occurrence. The onset of the symptoms is thus unlikely to be prevented by a reduction of calcineurin-inhibitors dose, in contrast to the authors’ suggestion.


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Response to ‘Calcineurin-inhibitors and bone pain after organ transplantation’

Dr Goffin makes an interesting objection to the theory of calcineurin-inhibitor-induced pain syndrome. We are familiar with his hypothesis, which we were unfortunately unable to deal with due to limits on the length of the paper.

It is true that there is no direct demonstration of the existence of calcineurin-inhibitor-induced pain syndrome. The hypothesis of microtraumas occurring in bone already weakened by steroid therapy at high doses in the immediate post-transplant period has its validity,2,3 and it is possible that these repeated microtraumas in such a delicate period could cause this syndrome. Moreover, this agrees with the descriptions made before the calcineurin-inhibitors era,4 with the cases described under therapy with other types of drugs5 and with the recent comments by Yamamoto et al.6

But the hypothesis of Grotz et al.7 is equally valid: in the transplant patients affected by this syndrome there is, in fact, no demonstration of the ‘insufficiency fractures’ which would be at the base of the alterations which are found with the magnetic resonance imaging. In addition,
the syndrome sometimes affects the joints and bones of the upper limbs, which are more rarely subject to microtrauma, or at least more rarely subject to microtraumas, which affect all of the joints contemporaneously. What is more, the facts that therapy with non-steroidal anti-inflammatory drugs has not been effective and that the calcium channel blockers which likely reduce intraosseus hypertension are successful in treating bone and joint pain, both support Grotz’s theory.

The two hypotheses therefore seem to be equally plausible, and it is possible that it is a multifactorial syndrome in which the drug-related intraosseus hypertension may be associated with repeated microtraumas. Only a bone biopsy during the acute phase (ethically debatable) could resolve the question.

What is clear is that it is not a reflex sympathetic dystrophy syndrome as some authors still claim, but rather that it is a syndrome in itself, which resolves spontaneously and in which the use of non-steroidal anti-inflammatory drugs is contraindicated.


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Are renin–angiotensin system inhibitors optimally prescribed?

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To the Editor: The renal community has recently enjoyed a spirited reexamination of the role of angiotensin converting enzyme inhibitors (ACEIs) in the treatment of chronic kidney disease. The core renal concept of the effectiveness of ACEIs has been challenged in Kidney International by Suissa et al.,1 several subsequent letters (Kidney Int, volume 70, October 2006), a previous meta-analysis, and results from the ALLHAT study. These criticisms have elicited several vigorous counter-responses.2,3

This debate appears to presume that ACEIs have been optimally used, both in clinical studies and in the community. If ACEIs can be prescribed in more effective manner, there are implications for both viewpoints.

The defense of ACEIs is based on several carefully performed large studies. Though convincing to many, it should be noted that the statistically significant renal protection demonstrated by either ACEIs or angiotensin 2 type 1 receptor blockers, as compared with controls, was clinically modest. Twenty to forty per cent of treated patients typically doubled their serum creatinine levels within relatively short follow-up periods. Even supporters of renin–angiotensin system (RAS) blockers must concede that the mere prescription of an RAS blocker is an ineffective therapy for too many patients.

However, it is possible that these modest results (or the absence of any favorable result in other analyses) may derive in part from the manner in which RAS blockers have been prescribed. Brenner and others have recommended a different approach to RAS blocker prescription, which was subsequently termed ‘flexible and goal-oriented’ and reviewed in detail.4 This approach recognizes that lowering blood pressure and urinary protein loss provides continually increasing renal protection until the levels of ~120 mm Hg systolic (perhaps lower) and 300–500 mg proteinuria per day, respectively. Therefore, the goal-oriented approach recommends that both of these goals must be achieved in order to presume optimal renal prognosis.

In no study of RAS blockers to date, have patients consistently reached both goals. Clearly, more intensive RAS blockade than previously prescribed is needed to reach these stringent goals: multiple, complementary RAS blockers, higher doses, and considerable effort. Moreover, interindividual variations in the ACEI insertion/deletion genotype, and in other factors, make it unlikely that a single protocol or approach will be broadly effective. Recognizing this, the goal-oriented approach de-emphasizes broadly applied protocols. Instead, it proposes a more flexible approach to RAS blockade and hypertension that addresses interindividual variations.

The evaluation of whether ACEIs (or RAS blockers in general) are effective treatment for chronic kidney disease should consider whether improved results might be obtained with different strategies.