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Competing interests
The authors declare no competing interests.

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TRANSPLANTATION

Supplemental vitamin D: will do no harm and might do good

John Cunningham

Vitamin D insufficiency is endemic amongst renal transplant recipients, as it is in other individuals with chronic diseases, both within and beyond nephrology. Few data exist to guide vitamin D replacement strategies, but indirect evidence points to likely skeletal, and possibly extraskeletal, benefits from supplementation.

The scourge of vitamin D deficiency and rickets was of such concern in the pre-vitamin D era that it resulted in the publication of at least one journal, aptly named *The Cripples' Journal*, which focused largely on diseases related to vitamin D deficiency. The stated aim of that journal was "to deal as comprehensively as possible with all subjects affecting orthopaedics," to "appeal to all institutions, medical men, nursing staffs and helpers" and finally to "use its influence in the task of moulding public opinion".[1]

Appreciation of the beneficial effects of adequate sun exposure and the availability of the therapeutic vitamin D supplements, cholecalciferol and ergocalciferol, have greatly reduced—although not eliminated—these diseases, whose prevalence remains high in vulnerable pockets of individuals in general 'healthy' populations and higher still in patients with chronic diseases of almost any kind.[2]

Analysis of the renal transplant population provides an instructive case in point. Patients entering the world of transplantation, particularly those who have had an extended period on maintenance dialysis, exhibit a wide range of disturbances of bone and mineral metabolism, the main clinical expression of which is a very high fracture rate. The role of deficiency of native vitamin D in the genesis of this skeletal morbidity and the associated mineral metabolism disturbances has received surprisingly little attention, with the main focus being instead on the adequacy, or otherwise, of calcitriol generation by the renal allograft and on the utility of antiresorptive agents in preventing accelerated bone loss.[3,4] The vitamin D status of renal transplant recipients is further compromised by sun avoidance, immunosuppressive agents and also possibly by phosphatonin-driven catabolism of 25-hydroxyvitamin D.[5]

Courbebaisse *et al.*[6] have published a study of 49 renal transplant recipients treated with a regimen of cholecalciferol 100,000 IU once every 2 weeks from month 4 to month 6 (the equivalent of about 7,000 IU per day) after transplantation and 100,000 IU once every 8 weeks from month 6 to month 12 (the equivalent of about 1,800 IU per day). Serum concentrations of calcium, phosphate, 25-hydroxyvitamin D and parathyroid hormone (PTH) in these patients were compared with those in 47 untreated patients who had similar baseline characteristics. The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines for the initiation of vitamin D therapy in chronic kidney disease and following renal transplantation were used to identify suitable patients and to gauge the adequacy of their response, but the cutoff value recommended (30 ng/ml) has limited validity and would be seen by many as inappropriately low. Median 25-hydroxyvitamin D concentration increased from 14 ng/ml to 43 ng/ml between months 4 and 6 in treated patients and remained at or below 30 ng/ml in only 6% of treated patients at 6 months, although this figure had increased to 51% by 12 months. In the control group, only three of 47 patients (6%) had a serum 25-hydroxyvitamin D level above 30 ng/ml at 12 months. Treated patients exhibited minor transient increases in serum calcium and phosphate levels with small, sustained reductions in serum PTH.

The results and the design of this study need to be considered in the context of several other issues that are at best only partially resolved. For example, more detailed analysis of the effect of cholecalciferol administration on vitamin D metabolism would be very interesting. Were the reductions in PTH attributable to increased circulating calcitriol concentration or were they a result of the increased 25-hydroxyvitamin concentration either acting directly as the vitamin D receptor ligand or indirectly via local generation of calcitriol in the parathyroid gland? What constitutes unequivocal vitamin D sufficiency in the renal transplant recipient, or indeed in anybody else? Various definitions have been applied including the threshold for elevation of PTH, the threshold for abolition of the seasonal variation of 25-hydroxyvitamin D concentration and the top of the dose–response curve relating 25-hydroxyvitamin D concentration

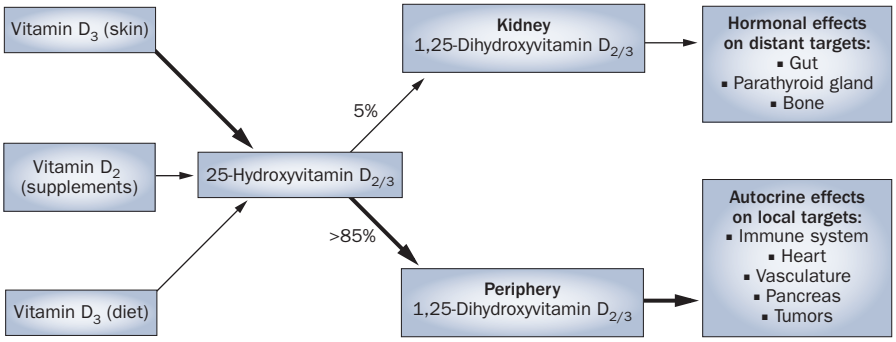

Figure 1 | The metabolism of vitamin D. The majority of available vitamin D is utilized for the local generation of the active dihydroxylated ligand for local use (autocrine effects) in nonclassic target tissues such as the immune system, heart, vasculature and pancreas. Hormonal calcitriol generated in the kidney acts on classic targets that are related to bone and mineral metabolism. Abbreviations: vitamin D_2, ergocalciferol; vitamin D_3, cholecalciferol. Redrawn wth permission from R. P. Heaney

with intestinal calcium absorption.[7] Of note is that the available toxicity data indicate that a very large therapeutic window exists with toxic effects virtually unknown at doses up to 30,000 IU per day or 25-hydroxyvitamin D concentrations up to 200 ng/ml (500 nmol/l).[8]

Alongside these largely 'bone and mineral' considerations is the realization that the actions of vitamin D spread beyond its classic targets (bone, kidney, gut and parathyroid glands) and that other cell types, including cardiac and vascular tissue, pancreas, prostate, and cells of the immune system also express the nuclear vitamin D receptor, making them potential targets for hormonal calcitriol produced in the kidneys (Figure 1). Many of these tissues have also been shown to express 25-hydroxyvitamin D 1-hydroxylase, which serves to make them potential targets for 25-hydroxyvitamin D as well. Quantitatively, only a small proportion of the hepatic metabolite, 25-hydroxyvitamin D, is converted into hormonal calcitriol in the kidneys. The bulk of the metabolite acts as a substrate for 25-hydroxyvitamin D 1-hydroxylase in other tissues, where local calcitriol generation has autocrine effects that probably require much higher concentrations than are achieved from physiological, or even pharmacological, replacement of deficient calcitriol in patients with kidney disease (Figure 1).

A direct cause-and-effect relationship between generous vitamin D supplementation and improved health has not been easy to establish, although indirect evidence exists to support a link. Various sources support the notion that optimizing vitamin D status might lead to improvements in immune and arterial function, resistance to infection and inhibition of the development of tumors.[2,9] These sources include considerations of evolutionary plausibility (our hunter–gatherer forebears were the recipients of very large doses of ultraviolet B radiation) and modern epidemiology (low 25-hydroxyvitamin D levels are associated with various cancers, diabetes mellitus, multiple sclerosis and tuberculosis), as well as data from laboratory studies. Such thinking implies that in renal transplantation and other chronic diseases we should be using larger doses of cholecalciferol and aim to achieve much higher 25-hydroxyvitamin D concentrations than hitherto achieved. To reach such levels by increasing ultraviolet B exposure would conflict with requirements for skin health; oral supplementation with cholecalciferol is the only realistic option, particularly in dermatologically vulnerable transplant recipients. A study by Walsh *et al.* showed that conventional low-dose maintenance vitamin D supplementation at 800 IU per day had little or no effect on 25-hydroxyvitamin D levels in transplant recipients.[10] Courbebaisse *et al.*[6] found that 25-hydroxyvitamin D concentration actually decreased during the phase of maintenance vitamin D_3 supplementation given at the equivalent of 1,800 units per day and that at least 7,000 units per day was needed to achieve vitamin D sufficiency in this population.

> ...the actions of vitamin D spread beyond its classic targets...

Answers to these questions about vitamin D sufficiency might take some time in coming and will probably emerge initially from large studies in the nonrenal population, which is likely to comprise the initial substrate for much-needed large trials of therapy with cholecalciferol focusing on patient level outcomes. In the meantime, clinicians will have to decide whether the 'will do no harm and might do good' argument justifies the routine use of generous native vitamin D supplementation in the renal transplant population.

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The author declares associations with the following companies: Cytochroma and Abbott. See the article online for full details of the relationships.

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