Transplant Recipients on the Edge of the Hypocalcemia Abyss

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Hypovitaminosis D is a risk factor for transplant-related osteoporosis. Its contribution to severe hypocalcemia in transplant recipients is less well recognized. We present 2 cases to illustrate how risk factors specific to transplant recipients significantly increase the risk of development of severe hypocalcemia, on a background of unrecognized vitamin D deficiency. Regular surveillance of calcium homeostasis should be incorporated into routine clinical care of transplant recipients. J Heart Lung Transplant 2009;28:93–5. Copyright © 2009 by the International Society for Heart and Lung Transplantation.

The unique milieu of transplantation, created by the combination of specific immunosuppressive medications on a background of chronic illness, exposes transplant recipients to significant risk of hypocalcemia, which can frequently escape medical attention. Although hypovitaminosis D is a well-recognized contributor to transplant-related disorders of bone mineralization,[1–4] its relationship to the development of severe and life-threatening hypocalcemia is under-recognized. We present 2 cases to illustrate how risk factors specific to transplant recipients may lead to unrecognized decreases in serum calcium concentration to clinically important low levels, highlighting the importance of regular surveillance of calcium homeostasis in transplant recipients.

CASE 1

A 59-year-old man was admitted for bilateral sequential single-lung transplantation for idiopathic pulmonary fibrosis (IPF). He received antibiotics and high-dose steroid therapy (prednisolone 80 mg/day) prior to his admission for exacerbation of his IPF. Routine postoperative biochemistry demonstrated acute hypocalcemia with an ionized calcium (iCa) concentration of 0.96 mmol/liter (3.84 mg/dl) (Table 1 and Figure 1), subsequently found to be secondary to severe untreated vitamin D deficiency. Risk factors for hypocalcemia included dietary deficiency in hospital and sunlight avoidance, in an effort to prevent skin cancer. Initial attempted correction of hypocalcemia with calcitriol and calcium supplement was unsuccessful. The patient remained asymptomatic and serum calcium concentration only eventually normalized after vitamin D was restored to sufficiency in combination with calcium supplementation (Figure 1).

CASE 2

A 45-year-old man who underwent bilateral sequential single-lung transplantation for cystic fibrosis 13 years earlier presented with a 2-day history of peri-oral and peripheral numbness at the out-patient clinic, following recent upper respiratory tract infection necessitating an increased dose of prednisolone (from the usual dose of 6 mg/day to 70 mg/day, which was tapered over 3 weeks). Other medications included tacrolimus 0.3 mg twice daily, azathioprine 25 mg/day, pancreatic enzyme supplement (Creon 10,000 to 20,000 U per meal), esomeprazole 20 mg/day, pantoprazole 40 mg/day and calcium carbonate 600 mg/day. Trousseau's and Chvostek's signs were negative. Biochemistry confirmed severe hypocalcemia with an iCa concentration of 0.72 mmol/liter (2.88 mg/dl), with secondary hyperparathyroidism on a background of hypomagnesemia and severe vitamin D deficiency (Table 1). Cholecalciferol, calcitriol, magnesium supplement and calcium citrate were commenced. Normocalcemia was achieved after 1 week, and calcitriol was ceased once serum calcium concentration began to rise (Figure 1).

DISCUSSION

Causes of hypocalcemia in transplant recipients are multifactorial, including increased loss of calcium and decreased gastrointestinal absorption. Glucocorticoids are commonly used in high doses immediately post-transplant (Case 1) or during infective exacerbation of underlying pulmonary conditions (Case 2). Such high doses may precipitate hypocalcemia, possibly due to renal calcium wasting[5] and reduction of intestinal calcium absorption.[6]

Hypovitaminosis D is well recognized in transplant recipients,[1–3] and vitamin D sufficiency is emphasized in the prevention and treatment of transplant-related

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Table 1. Baseline Biochemistry of Patients[a]

	Case 1	Case 2	Reference
Sodium	140	139	137–147 mmol/liter
Potassium	4.1	3.9	3.5–5.5 mmol/liter
Chloride	102	105	95–110 mmol/liter
Bicarbonate	25	28	24–31 mmol/liter
Urea nitrogen	18.2 (6.5)	19 (6.8)	8.4–23.8 mg/dl (3–8.5 mmol/liter)
Creatinine	1.13 (100)	1.58 (140)	0.68–1.38 mg/dl (60–120 μmol/liter)
Corrected calcium	7.32 (1.83)	4.2 (1.05)	8.4–10.4 mg/dl (2.1–2.6 mmol/liter)
Ionized calcium	3.84 (0.96)	2.88 (0.72)	4.6–5.2 mg/dl (1.15–1.3 mmol/liter)
Phosphate	4.74 (1.53)	3.13 (1.01)	2.17–4.33 mg/dl (0.7–1.4 mmol/liter)
Magnesium	2.58 (1.06)	1.41 (0.58)	1.7–2.56 mg/dl (0.7–1.05 mmol/liter)
Parathyroid hormone	13.8	63	1–7 ng/ml
25-hydroxyvitamin D	<6 (<15)	<6 (<15)	>24 ng/ml (>60 mmol/liter)
1,25-hydroxyvitamin D	39.6 (103)	25.4 (66)	13.8–46.2 pg/ml (36–120 pmol/liter)

[a]Système Internationale (SI) units indicated in parentheses.

osteoporosis. However, the contribution of vitamin D deficiency to the development of severe hypocalcemia in transplant recipients is underappreciated, and therefore underdiagnosed and undertreated, leading to progressive hypocalcemia at life-threatening levels before a diagnosis is made. Both patients in our series were severely vitamin D deficient. The combination of sun avoidance to prevent skin malignancies, and reduced physical activity with reduction in time spent outdoors due to underlying chronic diseases, contribute to severe vitamin D deficiency. Patients with cystic fibrosis (Case 2) are particularly at risk due to poor absorption of dietary vitamin D secondary to underlying pancreatic insufficiency, and standard vitamin D replacement doses are frequently inadequate.[7]

Hypocalcemia secondary to vitamin D deficiency in the general population is uncommon due to the multiple compensatory mechanisms available to restore calcium balance. Such mechanisms are, however, frequently impaired in transplant recipients, increasing their risk of severe hypocalcemia from vitamin D deficiency.

Vitamin D deficiency reduces gastrointestinal calcium absorption. Such negative calcium balance usually leads to compensatory secondary hyperparathyroidism, as evident in both cases, which helps to restore normocalcemia by increasing bone resorption directly, and indirectly via increasing formation of 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$) to increase intestinal calcium absorption. However, the $1,25\text{-}(OH)_2D$ concentrations

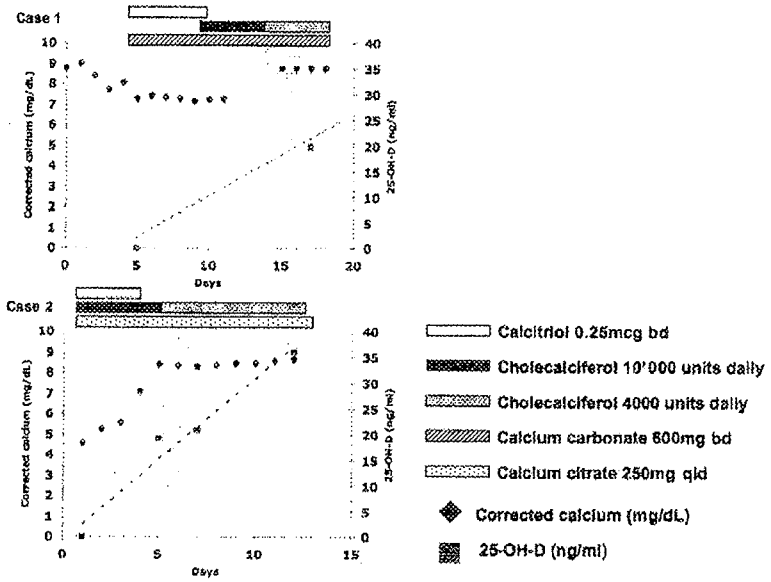

Figure 1. Normalization of serum corrected calcium concentration with vitamin D metabolites and calcium supplements. Shaded area indicates correlation of achievement of normocalcemia with vitamin D sufficiency (>16 ng/ml).

were "normal" in both patients. These apparently normal levels were inappropriate for the degree of hypocalcemia, as they should be markedly elevated to compensate for hypocalcemia. This signified severe substrate (25-OH vitamin D) deficiency in our patients (undetectable in both cases), leading to failure to achieve an appropriately high $1,25\text{-}(OH)_2D$ concentration, even under maximal stimulation by very high circulating parathyroid hormone (PTH) levels.

Several medications commonly used among transplant recipients may cause hypomagnesemia (Case 2), including proton-pump inhibitor[8] and tacrolimus,[9] leading to PTH resistance, which counteracts the effectiveness of such compensatory mechanisms. PTH secretion is also reduced when hypomagnesemia becomes more severe. In addition, magnesium depletion can occur on a tissue level. Hypocalcemia has been reported to respond to magnesium supplement in patients with normomagnesemic magnesium depletion.[10] Magnesium level should therefore be checked in all hypocalcemic patients, and magnesium supplementation may be considered in resistant cases even if serum magnesium concentration is normal.

Treatment of hypocalcemia should focus on the underlying pathophysiology. Although calcium supplementation is important, and hypomagnesemia should be corrected to enhance PTH action, the importance of vitamin D repletion with high-dose cholecalciferol is frequently neglected. In severe vitamin D deficiency, high-dose cholecalciferol (e.g., 10,000 U/day) is required to both adequately replace and rapidly restore vitamin D stores, as evidenced by serum 25-hydroxyvitamin D (25-OHD) concentrations. Standard replacement with 1,000 U/day is inadequate. Figure 1 clearly demonstrates achievement of normocalcemia correlating with vitamin D repletion. From our 2 cases, it appears that a serum 25-OHD concentration of between 40 and 50 nmol/liter (16 to 20 ng/ml) is required before serum calcium concentration rises adequately.

Calcitriol has been shown to be effective in preventing bone loss after transplantation by increasing intestinal calcium absorption and reducing secondary hyperparathyroidism.[1,2] However, it may not be as effective in the treatment of hypocalcemia secondary to severe vitamin D deficiency, as illustrated by our 2 cases. Although calcitriol is the most active form of vitamin D metabolite, treatment with calcitriol should be reserved for patients with renal insufficiency and insufficient 1-α hydroxylation. Calcitriol may be used in the initial phase to increase serum calcium concentration more rapidly, but could be safely tapered once hypocalcemia has improved, as illustrated in our series. Vitamin D repletion with cholecalciferol allows physiologic conversion to $1,25\text{-}(OH)_2D$, and effective and safe restoration of calcium homeostasis. Iatrogenic dosing with calcitriol is imprecise, where low doses can be ineffective and high doses may increase the risk of hypercalcemia and hypercalciuria.

By reducing gastric acidity, proton-pump inhibitors reduce absorption of calcium carbonate, rendering calcium supplement in the form of calcium carbonate less effective. Calcium citrate is the preferred supplement as its absorption is pH independent and its bioavailability at least 20% higher than that of calcium carbonate.[11]

In conclusion, transplant recipients are at risk of severe hypocalcemia because of unrecognized vitamin D deficiency as well as the side-effects of several medications commonly used in the transplant setting. Monitoring of vitamin D status should be routine practice during follow-up reviews at transplant clinics to ensure sufficiency (aiming at a goal of at least 40 nmol/liter [$\geq$16 ng/ml] to prevent hypocalcemia). Vitamin D sufficiency should be emphasized in transplant recipients not only for bone protection, but also for the prevention of life-threatening hypocalcemia.

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REFERENCES

1. Stein E, Ebeling P, Shane E. Post-transplantation osteoporosis. Endocrinol Metab Clin N Am 2007;36:937-63.
2. Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab 2005;90:2456-65.
3. Cohen A, Addonizio LJ, Lamour JM, et al. Osteoporosis in adult survivors of adolescent cardiac transplantation may be related to hyperparathyroidism, mild renal insufficiency, and increased bone turnover. J Heart Lung Transplant 2005;24:696-702.
4. Kapetanakis EI, Antonopoulos AS, Antoniou TA, et al. Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J Heart Lung Transplant 2005; 24:526-32.
5. Suzuki Y, Ichikawa Y, Saito E, Homma M. Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy. Metabolism 1983;32:151-6.
6. Kimberg DV, Baerg RD, Gershon E, Graudusius RT. Effect of cortisone treatment on the active transport of calcium by the small intestine. J Clin Invest 1971;50:1309-21.
7. Boyle MP, Noschese ML, Watts SL, et al. Failure of high-dose ergocalciferol to correct vitamin D deficiency in adults with cystic fibrosis. Am J Respir Crit Care Med 2005;172:212-7.
8. Law FT, Epstein MT, McGrath S. Proton pump inhibitors cause hypomagnesaemic hypoparathyroidism. Endocrine J 2006;53 (abstract 154).
9. Margreitter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet 2002;359:741-6.
10. Flink EB. Magnesium deficiency. Etiology and clinical spectrum. Acta Med Scand 1981;647(suppl):125-37.
11. Sakhaee K, Bhuket T, Adams-Huet B, Rao DS. Meta-analysis of calcium bioavailability: a comparison of calcium citrate with calcium carbonate. Am J Ther 1999;6:313-21.