Cardiac disease is a common cause of morbidity in dialysis patients. Traditional and unique risk factors have both been incriminated in the pathogenesis of abnormal cardiac function in these patients. In the present report, we focus on the role of hypocalcemia post parathyroidectomy as a cause of abnormal myocardial function leading to pulmonary edema in a young peritoneal dialysis patient with angiographically-proven normal coronary arteries. The pulmonary edema reversed with correction of the hypocalcemia. Hypocalcemia should be added to the differential diagnosis of contributors to cardiac dysfunction in patients on dialysis. Post parathyroidectomy, patients may be at particular risk for this complication because of severe, protracted hypocalcemia.

Keywords
End-stage renal disease, hypocalcemia, renal bone disease, parathyroidectomy, systolic dysfunction, pulmonary edema

Introduction
In patients with chronic kidney disease (CKD), hypocalcemia commonly occurs after parathyroidectomy for hyperparathyroidism. In patients with advanced osteitis fibrosa, postoperative hypocalcemia may be severe and prolonged. This phenomenon, also called “hungry bone syndrome,” may result from changes in calcium homeostasis that favor calcium uptake by bone when the release of parathyroid hormone (PTH) suddenly decreases (1–3).

The incidence of hungry bone syndrome in the dialysis population has not been systemically evaluated. In a retrospective review of 148 dialysis patients who had undergone parathyroidectomy as definitive treatment of severe hyperparathyroidism, the incidence of hungry bone syndrome was 20%, and in those patients, hospitalization was extended by 8 days (2). In a more recent retrospective analysis assessing calcium requirements after parathyroidectomy in an end-stage renal disease population (3), severe hypocalcemia (defined as serum calcium below 7.5 mg/dL) was observed in 45% of patients 6 weeks after surgery, despite treatment with high daily doses of elemental calcium (1.7 – 3.6 g) and active vitamin D (1 – 2 μg).

Profound hypocalcemia may be associated with life-threatening complications including seizures, neuromuscular irritability, gastrointestinal ileus, and a variety of cardiovascular abnormalities (4). Cardiovascular consequences reported to date include arrhythmia, conduction delays, and reversible systolic dysfunction (5–10).

In this report, we describe a patient with pulmonary edema and systolic dysfunction occurring in the setting of severe hypocalcemia after surgical parathyroidectomy.

Case report
A 27-year-old woman on continuous ambulatory peritoneal dialysis (CAPD) presented to the emergency room with a 7-day history of exertional dyspnea that rapidly progressed to orthopnea and paroxysmal nocturnal dyspnea. She also reported cough, nausea, vomiting, and bilateral positional chest pain that worsened during inspiration. Review of systems was negative for fever, symptoms of upper respiratory tract infection, retrosternal chest discomfort, or abdominal pain. There was no history of infectious contacts. She admitted to noncompliance with medications. Past medical history was negative for angina, myocardial infarction, valvular heart disease, pericarditis, and liver disease. She denied illicit drug
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use or alcohol abuse. Her only risk factors for coronary artery disease were hypertension and CKD. The cause of her renal disease remains unknown.

About 2 years before the reported presentation, this patient had been initiated onto CAPD for non-cardiac complications of uremia. The course on CAPD was unremarkable for mechanical complications or peritonitis. Eight months before the reported presentation, the patient underwent a partial parathyroidectomy for refractory hyperparathyroidism, with 3.5 glands excised. Her postoperative hypocalcemia was treated with increasing daily doses of oral calcium and calcitriol (2 μg) supplements, and her usual CAPD prescription of alternating 2.5% and 1.5% glucose solutions in 2-L twin-bag exchanges (8 L in total daily) was maintained. On this regime, intact PTH, calcium, phosphate, and alkaline phosphatase slowly normalized.

On physical examination, she was alert, oriented in three spheres, but in moderate respiratory distress with an oxygen saturation of 87% on room air that increased with oxygen support. Heart rate was 104 bpm, and her pulse was regular. Blood pressure was 190/110 mmHg. Temperature 36.7°C. Chest examination revealed diffuse bilateral crackles. Cardiac exam revealed marked jugular venous distension, bilateral peripheral pitting edema, and abnormal abdominal jugular reflux. Heart sounds, S1 and S2 were normal. There was presence of S3. No murmurs were reported.

Laboratory investigations revealed total serum calcium 1.7 mmol/L, serum phosphate 1.83 mmol/L, albumin 36 g/L, creatine kinase 239 IU/L, and troponin T 0.09 μg/L. All other electrolytes were within normal limits. Electrocardiogram (ECG) demonstrated nonreversible segments, with voltage criteria for left ventricular hypertrophy (LVH), and prolonged QT interval. Neither ischemic changes nor arrhythmias were noted on serial ECG recordings. An urgent echocardiogram (echo) demonstrated normal LV chamber size with regional variability, including inferior wall akinesis and mild mitral regurgitation. The left atrium was mildly dilated. A small circumferential pericardial effusion and a transient right atrium inversion were found, suggestive of increased intrapericardial pressure. Estimated ejection fraction was 40% – 59%. Chest radiography confirmed severe pulmonary edema.

Initial management focused on treatment of emergent hypertension. The patient was placed on telemetry and treated with intravenous infusions of labetalol and nitroglycerin and aggressive diuresis. She was admitted to the coronary care unit and underwent coronary angiography, which revealed completely patent coronary arteries. Treatment of hypocalcemia consisted of oral calcium carbonate, intravenous calcium chloride 4 g (680 mg elemental), and calcitriol 2 μg daily in divided doses. No changes were made to the dialysate prescription. Serum calcium levels, ECG, and echo were closely monitored. The patient’s symptoms improved, with normalization of calcium levels. Serial ECG recordings demonstrated that, with improvement of congestive heart failure symptoms and serum calcium, LVH and prolonged QT interval resolved completely (Figure 1).

The patient remained in hospital for 15 days and was discharged on maintenance therapy of oral calcitriol 2 μg twice daily and calcium carbonate 750 mg three times daily. Corrected serum calcium was 2.4 mmol/L. She was discharged with close outpatient follow-up in the PD clinic, where the importance of compliance to medications was reinforced at each visit. Repeat echo at day 60 demonstrated improvement in wall motion abnormalities. The inferior wall was no longer akinetic. Only the basal inferior segment was reported as hypokinetic. Additionally, findings associated with diastolic dysfunction, including impaired LV relaxation and concentric LVH persisted. Ejection fraction improved and was reported as normal.

Discussion
Cardiomyopathy associated with surgically-induced hypoparathyroidism in patients receiving renal replacement therapy is reported only rarely (8,10). The present report describes a patient with significant risk factors for but no prior history of cardiac disease, who presented with reversible cardiomyopathy 8 months after parathyroidectomy for the treatment of severe refractory hyperparathyroidism. Coronary angiography confirmed the absence of occult atherosclerotic heart disease. The ECG and echo performed before and after treatment demonstrated reversal of impaired electrical conduction and systolic function with correction of hypocalcemia.

In patients with CKD or on renal replacement therapy, active vitamin D deficiency and osteitis fibrosa may impact greatly on the course and management of hypocalcemia observed after parathyroidectomy (1–3). Impaired renal conversion of 25-hydroxyvitamin D to biochemically active 1,25-hydroxyvitamin D may
result in resistance to calcium therapy through decreased intestinal absorption (11). In patients with renal bone disease, parathyroidectomy may result in hungry bone syndrome or a marked net increase of bone minerals, especially calcium, after PTH withdrawal (1–3). Despite these phenomena, such patients only very rarely present with myocardial conduction abnormalities or systolic cardiac dysfunction in the absence of underlying heart disease or hypervolemia, possibly for one of several reasons:

- First, hypocalcemia may present with neuromuscular complications manifest as involuntary muscle twitches or tetany, which if brought to the attention of medical personnel, allows hypocalcemia to possibly be corrected before the development of heart failure (8).
- An alternative hypothesis, supported by 2 case reports to date, suggests that an abrupt decline in calcium level is a prerequisite for myocardial dysfunction (8).

**FIGURE 1** Electrocardiogram (A) on admission: nonreversible segments (NVR), left ventricular hypertrophy (LVH), prolonged QT; (B) on discharge: normal (Ca 2.3 mmol).
In regard to our patient, it is likely that hypocalcemia was related to an abrupt decline in calcium secondary to cessation of calcium and calcitriol in the setting of hungry bone syndrome and vitamin D deficiency. The indispensable role of ionized calcium in myocardial contractility is well established (12). Arise in cytoplasmic free calcium is essential for actin–myosin interactions facilitated by troponin C. Anything that modifies myocellular calcium interactions or sensitivity may alter relaxation and contribute to diastolic dysfunction (13). Moreover, the degree of influx of extracellular calcium influences myocyte inotropic, and hence systolic, function (12). Thus, the biochemical basis of cardiac dysfunction in cases of hypoparathyroidism may be related to hypocalcemia, a notion supported in the literature (8) and from our experience by findings of improved myocardial performance with normalization of free calcium.

The current case describes a patient who presented with pulmonary edema in the setting of emergent hypertension and evidence from cardiac investigations demonstrating impaired LV systolic function. The cause of the pulmonary edema was likely a combination of systolic dysfunction from hypocalcemia and diastolic dysfunction secondary to severe hypertension. Severe hypertension has been shown to consistently affect myocardial relaxation in the absence of changes to LV ejection fraction (13). The mechanisms remain unknown, but may be related to protein kinase A phosphorylation of troponin I, rather than to changes in calcium concentration or sensitivity (13). Although dietary calcium supplementation has been associated with significant reductions in both systolic and diastolic pressure (11), there is no established association between hypocalcemia and severe hypertension. Also, pharmacologic agents that affect either myocellular calcium concentration or calcium sensitivity, when applied to intact normal hearts, have no effect on diastolic pressure–volume relations (13). For our patient, treatment of hypocalcemia to normal serum levels resulted in normalization of ejection fraction and LV inferior wall akinesis by echo, evidence of improved myocardial inotropy. Findings of diastolic dysfunction remain unchanged on repeat echo.

Conclusions
We report a case of acute pulmonary edema in the setting of hypocalcemia complicated by severe hypertension. Hypocalcemia was likely related to cessation of calcium and calcitriol in the setting of hungry bone syndrome secondary to impaired PTH response post parathyroidectomy in a dialysis patient with renal bone disease. Pulmonary edema was likely related to a combination of diastolic dysfunction in the setting of severe hypertension and systolic dysfunction secondary to hypocalcemia. We believe that systolic dysfunction was secondary to hypocalcemia for the following reasons:

- There was no underlying coronary artery disease.
- There was no clinical improvement with antihypertensive and diuretic medications alone.
- Regional wall motion abnormalities by echo dramatically improved with correction of calcium.

This case illustrates that renal bone disease may persist for months to years. Patient compliance with calcium and vitamin D supplementation is essential for management of hungry bone syndrome. Abrupt cessation of calcium and vitamin D supplementation may result in symptomatic hypocalcemia. Hypocalcemia is a rare but reversible cause of potentially life-threatening cardiac dysfunction.

References

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