

# Calcifediol Rather Than Cholecalciferol for a Patient Submitted to Malabsorptive Bariatric Surgery: A Case Report

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Vitamin D deficiency following malabsorptive bariatric surgery can lead to osteomalacia. We report a patient with severe vitamin D deficiency following malabsorptive bariatric surgery successfully treated with calcifediol but not cholecalciferol. A 40-year-old woman, submitted to biliopancreatic diversion 20 years before and chronically treated with 50,000 IU cholecalciferol weekly, was admitted to our Endocrine Unit because of severe lower back pain, muscle weakness, and generalized muscular hypotrophy, associated with hypocalcemia and elevated PTH levels. Initial evaluation revealed low serum albumin, low albumin-corrected serum calcium (7.36 mg/dL), high serum PTH (240 pg/mL), bone-specific alkaline phosphatase (125 µg/L) and 1,25-dihydroxyvitamin D (112 pg/mL) concentrations, undetectable serum 25-hydroxyvitamin D (<7 ng/mL), and evidence of reduced liver function. Bone mineral density was markedly low. Normocalcemia was initially restored with intravenous albumin and calcium gluconate. Treatment with calcitriol (0.5 µg three times daily) and oral calcium carbonate (1000 mg daily) was simultaneously started and cholecalciferol was replaced with calcifediol [125 µg (5000 IU) daily]. During follow-up the calcifediol dose was progressively tapered to 25 µg (1000 IU) daily and the calcitriol dose was progressively reduced and finally withdrawn. Serum albumin and other biochemical parameters normalized, bone mineral density significantly increased, and the patient's clinical conditions progressively improved, with a substantial recovery of autonomy. Serum vitamin D binding protein at the last observation was in the normal range. Our data suggest that calcifediol might be more efficacious than cholecalciferol for prevention and treatment of vitamin D deficiency in patients treated by malabsorptive bariatric surgery.

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Severe obesity is frequently associated with vitamin D deficiency [1]. The prevalence of vitamin D deficiency in patients who undergo bariatric surgery is dependent on the type of procedure performed. Malabsorptive interventions involve bypassing a large part of the small intestine, so that fat absorption is confined to the more distal sections. Such interventions, despite being associated with a greater weight loss compared with nonmalabsorptive procedures, are even associated with a higher frequency of postoperative vitamin D deficiency, osteomalacia, as well as a high risk of hypocalcemia and fragility fractures [2]. Currently there is no clear consensus on the modality and the doses of vitamin D supplementation in patients previously submitted to bariatric surgery.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; DBP, vitamin D binding protein.

## 1. Case Presentation

A 40-year-old woman presented to the emergency department (February 2016) of a local primary care hospital for a subocclusive episode and admitted to a short-stay observation ward. Current treatment consisted of slow-release tramadol (100 mg daily) and cholecalciferol (50,000 IU weekly). The subocclusive episode resolved spontaneously. Routine blood tests revealed severe hypocalcemia (6.6 mg/dL; normal range, 8.6 to 10.2) and markedly elevated PTH (234 ng/mL; normal range, 8 to 40) levels. The patient was transferred to our unit for further evaluation.

The medical history revealed that she had undergone biliopancreatic diversion for stage III obesity 20 years earlier. Since then, she was submitted to two major surgical procedures for bowel obstruction due to adhesions (at 26 years of age) and for small bowel perforation (at 36 years of age). Thereafter she developed several minor bowel subocclusive episodes that were treated medically.

Five years before the admission to our hospital, the patient discontinued follow-up but continued to take regularly the weekly dose of cholecalciferol (50,000 IU). Careful reevaluation of biochemical data revealed that serum levels of 25-hydroxyvitamin D [25(OH)D] were low (<10 ng/mL) or undetectable during the 5 years prior to the admission, associated with increased levels of PTH and alkaline phosphatase.

Fourteen months before she developed an atraumatic fracture of the right hip, which was treated surgically, and 6 months before a fracture of the first lumbar vertebra was incidentally discovered during evaluation for sudden-onset severe lower back pain with progressive immobilization. Her family history was unremarkable.

Nutritional status was inadequate. Physical examination revealed pigeon chest, arterial hypotension, and generalized muscular hypotrophy due to immobilization. Chvostek and Trousseau signs were negative. Other vital signs were normal. Her weight was 65 kg and height 1.63 m (body mass index, 24.5 kg/m<sup>2</sup>). Intestinal function was characterized by mild steatorrhea, which persisted when the vitamin D therapeutic regimen was modified (see later). Upon questioning, both the patient and her relatives assured full adherence to cholecalciferol therapy.

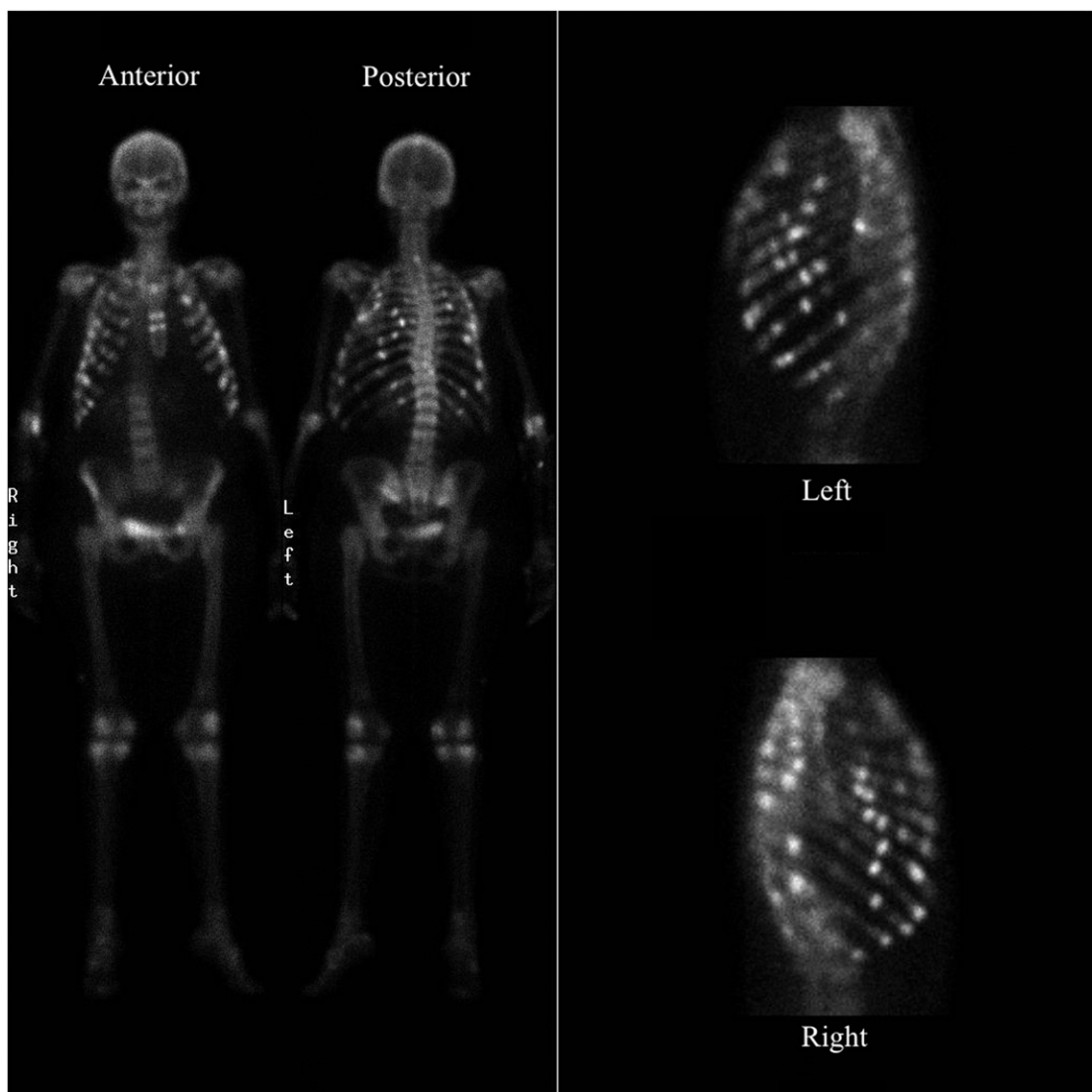
Laboratory examination revealed macrocytic-normochromic anemia: hemoglobin 8.8 g/dL (normal range, 11.5 to 15.5), cell volume 103.1 fL (normal range, 80 to 96), cell hemoglobin content 31.8 pg (normal range, 27 to 32).

Other significant laboratory values included: low serum total calcium (6.4 mg/dL), phosphate (1.1 mg/dL; normal range, 2.7 to 4.5), albumin (2.8 g/dL; normal range, 3.6 to 5.2), and albumin-corrected serum total calcium (7.36 mg/dL) concentrations; normal magnesium (2.12 mg/dL; normal range, 1.6 to 2.6), undetectable levels of 25(OH)D; and high levels of bone-specific alkaline phosphatase (BSAP; 125 µg/L; normal range, 2 to 28), 1,25-dihydroxyvitamin D (112 pg/mL; normal range, 20 to 67), and PTH (240 pg/mL). Liver function tests were consistent with a reduced synthesis function, as revealed by low serum levels of albumin, cholinesterase (2435 IU/L; normal range, 4200 to 11,200), and transferrin (1.8 g/L; normal range, 2 to 3.6). Other measurements related to the nutritional status, namely retinol-binding protein (undetectable), prealbumin (13 mg/dL; normal range, 20 to 40), were consistent with the severely deficient nutritional status despite an average daily caloric intake of 1800 kcal, but a low daily calcium intake (about 200 mg/d).

Chest x-rays showed a mild bilateral pleural effusion. Numerous areas of pathological uptake at the ribs, stern, hips, and cranium, suggestive for metabolic osteopathy, were detected at <sup>99m</sup>Tc-oxidronate whole-body scan (Fig. 1). Dual x-ray absorptiometry revealed a severe reduction in bone mineral density (BMD), both at the total hip (0.417 g/cm<sup>2</sup>, z score -4.3) and lumbar spine (0.491 g/cm<sup>2</sup>, z score -5.3). X-rays of long bones and hips revealed diffuse and marked osteopenia.

All of these features were consistent with the consequence of chronic hypocalcemia and osteomalacia due to severe vitamin D deficiency.

The patient was initially treated with intravenous albumin and calcium gluconate and started with calcitriol (0.5 µg three times daily) and oral calcium carbonate (1000 mg daily);



**Figure 1.**  $^{99m}\text{Tc}$ -oxidronate whole-body scan: numerous areas of pathological uptake at the ribs, stern, hips, and cranium are present, consistent with a bone metabolic disorder.

cholecalciferol supplementation was replaced with calcifediol [125  $\mu\text{g}$  (5000 IU) daily]; at the same time, caloric intake was raised up to 2500 kcal/d, with a high protein content. After 1 week serum albumin and calcium levels normalized. Serum PTH progressively decreased with a parallel increase of serum phosphorus, and both reached normal levels after 1 month. Serum 25(OH)D became detectable (7.8 ng/mL) after 4 days and reached a serum concentration of 30.6 ng/mL after 30 days. Serum levels of BSAP progressively declined up to 70  $\mu\text{g/mL}$  at discharge from our unit. The patient's clinical conditions progressively improved, with a substantial reduction of back pain and asthenia; furthermore, a rehabilitative program was started, which led to a substantial recovery of autonomy.

During follow-up the calcifediol dose was progressively reduced up to the current dosage of 25  $\mu\text{g}$  (1000 IU) daily, and calcitriol was definitively withdrawn after 2 months. Serum levels of calcium, phosphorus, 25(OH)D, 1,25-dihydroxyvitamin D, and PTH remained in the normal range.

At the latest observation (January 2017) serum albumin was 3.6 g/dL, albumin-corrected total calcium was 8.8 mg/dL, phosphate was 3.1 mg/dL, PTH was 46 pg/mL, 25(OH)D was 28 ng/mL, and BSAP was 27  $\mu\text{g/mL}$  (Fig. 2); however, some nutrition indexes remained below the normal reference range.

Dual x-ray absorptiometry revealed a marked improvement of BMD both at the total hip ( $0.581 \text{ g/cm}^2$ ,  $z$  score  $-2.8$ ) and at the lumbar spine ( $0.695 \text{ g/cm}^2$ ,  $z$  score  $-3.5$ ), with an increase of about 40% at both sites.

Serum concentration of vitamin D binding protein (DBP), measured using a turbidimetric method [Dako, Denmark; adapted to Roche ModularP (Roche Diagnostics)] in a serum sample collected at this time, was 403 mg/L, a value slightly above the mean of the normal reference population [3].

## 2. Discussion

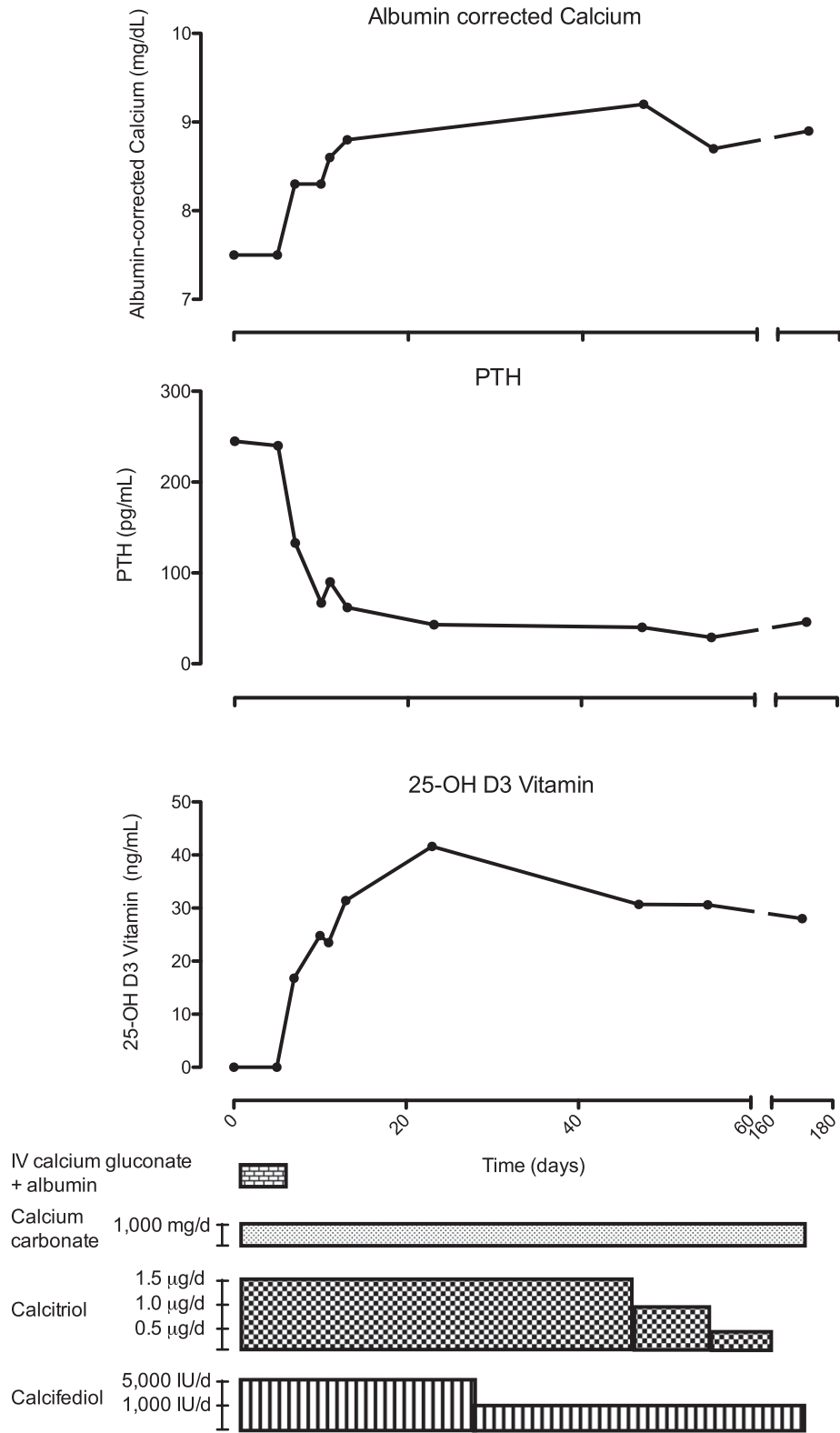
Vitamin D deficiency is very common in obese patients and its origin is multifactorial. Sequestration and dilution of vitamin D in the adipose tissue, reduced sun exposure, and the influence of the inflammatory status related to obesity on vitamin D metabolism are advocated as the main determinants of the low vitamin D status among these patients [4, 5]. The current guidelines of the US Endocrine Society recommend for obese subjects a vitamin D intake twofold to threefold higher than for healthy, normal-weight adults [6].

Bariatric surgery for morbid obesity, particularly malabsorptive procedures such as biliopancreatic diversion, is a well-known cause of severe vitamin D deficiency. Indeed, despite the substantial weight loss following surgery and the use of vitamin D supplements in large doses, data show that hypovitaminosis D persists and sometimes even worsens thereby [7]. The American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery recommend the use of at least 3000 IU daily of cholecalciferol in all patients following bariatric surgery, and the use of larger doses (up to 50,000 IU daily) in patients with severe malabsorption states [8].

The patient described herein reflects the complexity of hypovitaminosis D management after malabsorptive bariatric surgery. Indeed, despite the use of generous weekly doses of cholecalciferol, she presented with undetectable serum levels of 25(OH)D and a clinical picture characterized by hypocalcemia, muscle weakness, back pain, and osteomalacia, complicated by atraumatic fractures.

Several mechanisms may contribute to the low serum 25(OH)D levels in our patient, including malnutrition and its consequences, and malabsorption. Malnutrition may cause impaired liver function, which may be associated with decreased levels of DBP and albumin and, in severe cases, inability to hydroxylase vitamin D [9]. As a matter of fact, at initial observation serum albumin, as well as other serum parameters, revealed an impaired liver function, which improved during the follow-up. Unfortunately, we did not routinely measure serum DBP. We were able to perform this assay only in a serum sample collected when the general conditions of the patient were substantially improved, and at this time the concentration was normal. We cannot exclude that lower values could be present in an early phase, but no stored serum samples were available for measuring DBP. This possibility could be inferred on the basis of sequential measurement of albumin, which showed an increase of ~30% at the latest measurement compared with baseline.

It is well known that chronic malabsorption of liposoluble substances, such as cholecalciferol, may occur following biliopancreatic diversion. Pharmacokinetic studies in healthy subjects have shown that oral calcifediol supplementation is twofold to threefold more potent in rising serum 25(OH)D concentration than cholecalciferol [10, 11]. Moreover, it is well known that malabsorption of cholecalciferol and, to a lower extent, of calcifediol occurs after gastrectomy, in celiac diseases and other small bowel diseases [10, 12]. Based on these considerations, we tested the hypothesis that calcifediol, a more polar, water-soluble vitamin D metabolite that does not require hepatic 25-hydroxylation, might be more effective than cholecalciferol in restoring a normal vitamin D status. As a matter of fact, this treatment resulted in a rapid, progressive, and stable normalization of serum levels of 25(OH)D and biochemical parameters of calcium phosphate metabolism, marked improvement of BMD, and resolution of the clinical symptoms. The large increase of BMD over the 8-month period is likely related to the improvement of vitamin D status and mineralization of unmineralized matrix.



**Figure 2.** Serum levels of total albumin–corrected calcium, PTH, and 25(OH)D at baseline and during follow-up, according to the treatment given to the patient. All parameters at the last observation were in the normal range.

It might be speculated that differences in therapeutic regimens, weekly for cholecalciferol and daily for calcifediol, could account for the greater therapeutic efficacy of the latter. In this regard, it is of note that no difference in the steady-state serum 25(OH)D levels were observed when daily and weekly regimens of both vitamin D compounds were compared [11, 13].

No evidence-based guidelines for vitamin D supplementation after malabsorptive bariatric surgery are available and no clinical trial on the use of calcifediol in this setting has been performed, as yet.

In summary, the use of calcifediol rather than cholecalciferol, and the improvement of the nutritional status, have contributed to the attainment of normal serum levels of 25(OH)D in our patient. Based on our observation, we suggest that calcifediol should be considered as an alternative to cholecalciferol in patients after malabsorptive bariatric surgery, a condition in which lipid malabsorption and impaired liver function are present.

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Disclosure Summary: The authors have nothing to disclose.

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