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Case Report

# Effectiveness of intramuscular ergocalciferol treatment in a patient with osteomalacia and insufficiency fractures due to severe vitamin D deficiency after bariatric surgery

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**Abstract**

Vitamin D (vitD) deficiency and bone loss may occur after bariatric surgery and hence, supplementation with high oral doses of vitD may be required. Alternatively, intramuscular depot ergocalciferol, which slowly releases vitD and bypasses the gastrointestinal tract, could be administrated. We present a case of severe vitD deficiency–osteomalacia after gastric bypass operation for morbid obesity, treated with ergocalciferol intramuscularly. A 45-year-old woman was presented with hip pain and muscle weakness, which led ultimately to immobilization in a wheelchair. Fifteen years ago, she underwent roux-en-Y gastric by-pass for morbid obesity. Occasionally, she was treated with multivitamin supplements. On admission, iron deficiency anaemia, vitD deficiency (25OHD: 3.7 ng/ml) and secondary hyperparathyroidism were revealed. Bone turnover markers (BTM) were elevated. Radiological evaluation demonstrated insufficiency fractures on the pubic and left femur and reduced BMD. Osteomalacia due to vitD deficiency and calcium malabsorption were diagnosed. Calcium citrate 500 mg qid and intramuscular ergocalciferol 600,000 IU every 20 days were initiated. One month later, musculoskeletal pain and weakness were resolved and the patient was mobilized. Few months later, vitD, BTM and BMD showed substantial improvement. Intramuscular ergocalciferol administration can improve the clinical and biochemical status and thus, is suggested to prevent and/or treat osteomalacia in such patients.

**Keywords:** Bariatric Surgery, Roux-en-Y Gastric By-pass, Vitamin D Deficiency, Osteomalacia, Ergocalciferol

## Introduction

Obesity is a global and increasing health problem affecting children and adults. According to World Health Organization estimates in 2018, more than 650 million adults are obese worldwide[1]. In long-term, medical treatment and lifestyle modifications are often ineffective to achieve satisfactory weight loss. Thus, various bariatric operations have been introduced to reduce the weight, improve metabolic profile, quality of life and consequently decrease mortality rate[2].

Reflecting the obesity epidemic, the global number of bariatric operations is on the rise, to a point where over 600,000 operations are performed annually worldwide[3]. However, bariatric procedures are not without complications; they induce alterations in gastrointestinal track anatomy, that may cause pronounced malabsorption of essential vitamins (folate, vitamin B12, and vitamin D) and micronutrients (eg, iron, calcium) as well as abnormalities in bone metabolism[4]. Thus, regular oral supplementation with high doses of vitamin D (vitD) in conjunction with calcium is required. According to the American Society for Metabolic and Bariatric Surgery, the Obesity Society and the American Association of Clinical Endocrinologists, patients with vitD deficiency following bariatric surgery should receive high doses of vitD varying from at least 3,000 IU daily up to doses as high as 50,000 IU daily in patients with severe malabsorption[5,6].

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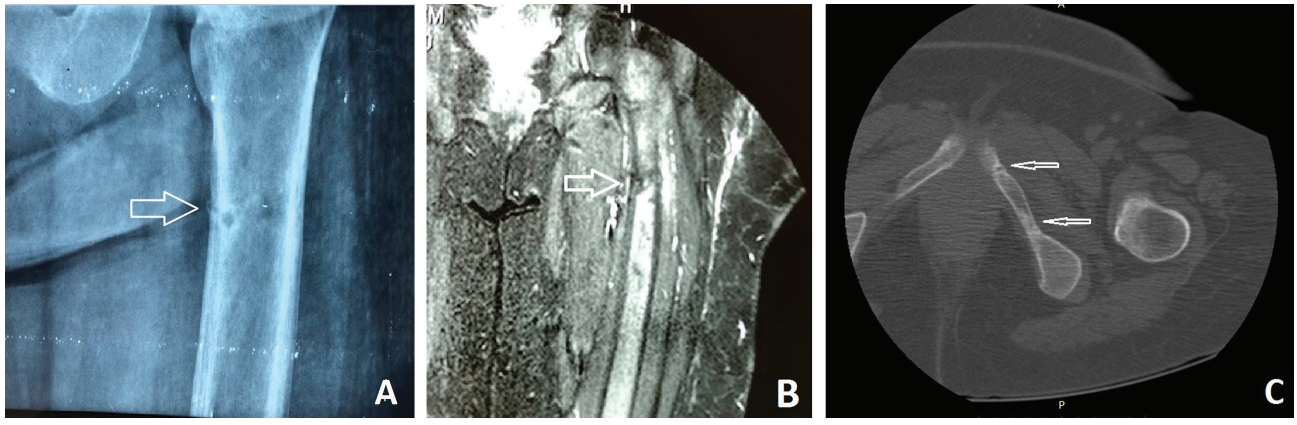


**Figure 1.** A) X-rays, B) CT scan demonstrating insufficiency fractures (Looser zones) at the ischium and ilium ramus (thin arrows) and left femur (arrow) before im ergocalciferol administration. C) left femur T2-weighed out of phase MRI scan: incomplete linear interruption of bone continuity and high intensity signal due to bone marrow oedema (arrow).

**Table 1.** Biochemical and hormonal parameters before, 1, 2, 3 and 6 months after im ergocalciferol administration. Ca, P, CaU24h, PU24h: Serum and urinary calcium and phosphate levels, Alb: albumin, PTH: parathyroid hormone, vitD: vitamin D, ALP: alkaline phosphatase, P1NP: procollagen I aminopropeptide, β-CTX: C-terminal cross-linked telopeptide of type I collagen.

| Months | Ca (mg/dl) | P (mg/dl) | Alb (g/dl) | CaU24h (mg/24h) | PUr24h (mg/24h) | VitD (ng/ml) | PTH (pg/ml) | ALP (IU/L) | P1NP (ng/ml) | β-CTX (ng/ml) |
|---|---|---|---|---|---|---|---|---|---|---|
| before | 8.3 | 1.7 | 3 | 30 | 200 | 3.7 | 334 | 173 | 196.6 | 2.02 |
| 1 | 8.8 | 2.7 | 3.1 | | | 8.1 | 175 | 199 | 330.7 | 3.31 |
| 2 | 8.7 | 3.5 | 3.3 | 60 | 750 | 9.4 | 109 | 206 | 668.2 | 4.25 |
| 3 | 9.3 | 3.5 | 3.6 | | | 13.7 | 83 | 219 | 691.2 | 2.26 |
| 6 | 9.1 | 3.3 | 3.7 | 85 | 480 | 14.2 | 35.7 | 164 | 366 | 1.16 |

However, the optimal route of administration and the doses of vitD supplementation in such patients have not been established. Intramuscular (im) depot formulations of vitD (cholecalciferol or ergocalciferol) which slowly release vitD and by-pass the gastrointestinal tract are an option.

In this report, we present a case of severe vitD deficiency and osteomalacia after a Roux-en-Y gastric bypass (RYGB) operation for morbid obesity treated effectively with intramuscularly ergocalciferol 600,000IU every 20 days.

## Case presentation

A 45-year-old woman (BMI 43 Kg/m$^2$) was admitted to the Endocrinology Department of a tertiary care Hospital due to pain at the upper third of left hip and pelvis and muscle weakness over the previous 3 months. Her medical history revealed that fifteen years ago she had undergone RYGB for treatment of morbid obesity. Since then she was treated with multivitamin supplements occasionally. During the last 3 months, she was consuming regularly oral multivitamin supplements including iron, calcium carbonate (500-1000 mg/daily) and vitD (25,000 IU/weekly). Following a neurological examination due to persistent symptoms, anti-epileptics and analgesics were also initiated. Despite this treatment, she complained for severe progressive hip pain and muscle weakness, leading to immobilization in a wheelchair during the last month.

On admission, laboratory examination revealed iron deficiency anaemia [Ht 23%, Hb 8g/dl, MCV 71.8, MCH 20, Ferritin 3 μg/L (NR 12-200)] vitamin B12 deficiency [144 ng/l, (NR 165-1162)], vitD deficiency [25OHD 3.7 ng/ml (NR 20-50)] and secondary hyperparathyroidism [PTH 334 pg/ml (NR 15-66)]. This reference range of 25OHD is advocated by the Hellenic Endocrine Society[7]. Serum 25OHD levels were determined by enzyme immunoassay [Architect 25-OH vitamin D; Abbott, Ireland] The sensitivity of this assay is 1.6 ng/ml (4 nmol/L) and intra- and inter-assay coefficients of variation is <5%. Serum calcium, albumin, phosphate levels and 24-hours urinary calcium levels (CaUr24h) were low. Bone turnover markers (BTM), namely procollagen

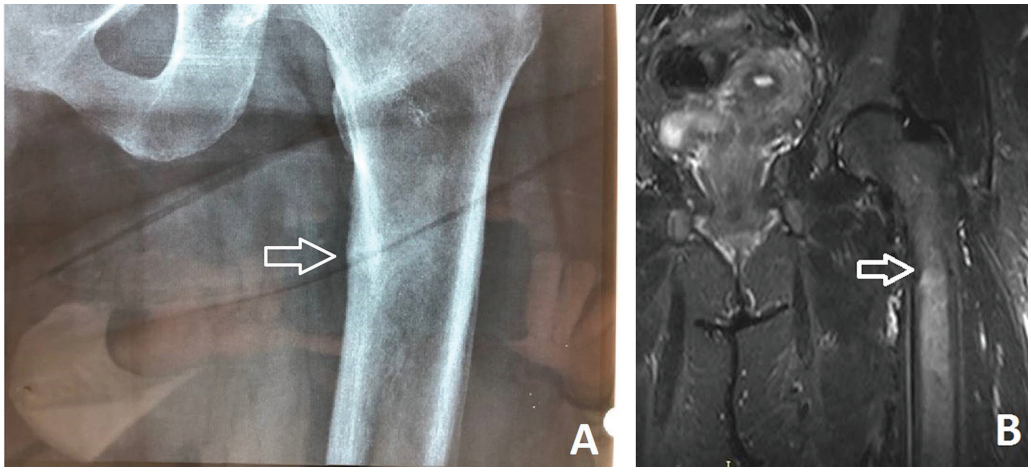


**Figure 2.** A) X-rays demonstrating restoration of bone continuity B) left femur T2-weighed out of phase MRI scan demonstrating bone healing and normalization of the magnetic signal, 6 months after im ergocalciferol initiation.

I aminopropeptide [(P1NP)], C-terminal cross-linked telopeptide of type I collagen (βCTX) were elevated (Table 1). Radiological evaluation: X-rays, computed tomography (CT) and magnetic resonance imaging (MRI) scans demonstrated insufficiency fractures of the ischium, ilium ramus and left femur (Figure 1). Dual x-ray absorptiometry revealed reduced lumbar spine (Tscore -2.8, BMD 0.740 mg/cm$^2$) and hip (Tscore -2.9, BMD 0.586 mg/cm$^2$) bone mineral density (BMD). All these findings were consistent with the diagnosis of osteomalacia due to severe vitD deficiency and calcium malabsorption.

The patient was initially treated with intravenous iron, and calcium gluconate and intravenous infusion of alpha-calcidol 2 μg/daily. At the same time, calcium citrate 500 mg qid was started orally. Five days later, intravenous alpha-calcidol was replaced with im ergocalciferol 600,000 IU every 20 days and calcium citrate 2000 mg was continued daily to correct vitD deficiency whereas, anti-epileptics and analgesics were discontinued. In the meantime, a physiotherapy program for muscular enhancing was started.

One month later, calcium and phosphate reached normal levels, PTH decreased and 25OHD became 8.1 ng/ml. Moreover and most importantly, patient's clinical status was impressively improved, musculoskeletal pain and weakness resolved and the patient was mobilized almost completely. Left femur X-ray imaging revealed a marked progression of insufficiency fracture healing (Figure 2A). Within two months, hyperparathyroidism and vitD status were improved further and BTM were increased. Six months later, serum calcium and phosphate levels remained in the normal range while vitD and the BTM were improved further (Table 1). Radiological evaluation with MRI (Figure 2B) and BMD (lumbar spine Tscore -1.3, BMD 1.030 mg/cm$^2$, hip Tscore -0.7, BMD 0.895 mg/cm$^2$) showed a substantial further improvement. To correct anemia, hydroxocobalamin and iron were also administered. Thereafter, 25OHD progressively increased, BTM progressively declined and ergocalciferol intervals were increased up to the current interval of 30 days. Written informed consent was obtained from the patient for publication of this case and accompanying images.

## Discussion

In this report, we discuss the case of severe vitD deficiency–osteomalacia accompanied by insufficiency fractures presented 15 year after RYGB for morbid obesity. Given the severity of the clinical status and the malabsorption syndrome, a treatment with ergocalciferol intramuscularly every 20 days, in combination with calcium citrate, was applied. Following this intervention, an impressive improvement in clinical and biochemical status was observed. The transient early increase in BTM followed by a decrease is likely related to the healing of osteomalacia due to the improvement of vitD and calcium status. The increase of BTM is also explained by the rise in serum PTH, which if left uncorrected, promotes bone loss.

RYGB is a common and efficient treatment for morbid obesity. It is performed to induce gastric restriction and intestinal malabsorbtion[8]. A small gastric pouch, which is drained into the distal jejunum, is formed. In this respect, the greater portion of the stomach, the duodenum and a portion of proximal jejunum are bypassed causing severe malabsorption of calcium and fat-soluble vitamins such as vitD, among others.

VitD deficiency leads to a reduced intestinal calcium and phosphate absorption, leading to secondary hyperparathyroidism. Without adequate treatment, a substantial proportion of mineralized bone matrix will be replaced by poorly mineralized bone leading to osteomalacia

and insufficiency fractures, the characteristic radiologic finding in osteomalacia. The above factors caused the limited ambulation of the patient. In addition, the anti-epileptics that the patient received for a short period may also partially contribute to vitD deficiency as they can increase vitD catabolism to inactive metabolites.

Recent reports highlight the association of RYGB with negative skeletal consequences including high bone turnover, significant decline in BMD, deterioration of microarchitecture and increased fracture risk 2-5 years after surgery[9,10,11]. Lindeman et al showed that BMD declined by 7.8% at the spine and 15.3% at the total hip 5 years after RYGB, although the rate of bone loss was higher in the first 2 years after surgery with parallel deterioration of trabecular and cortical microarchitecture[9].

Osteomalacia is not an uncommon finding after RYBG or biliopancreatic diversion[12-16]. Its management as a complication of bariatric operation, although simple, is very challenging. A wide range of vitD doses and regimens, including ergo- or chole-calciferol, in oral or parenteral ways, daily or intermittent schedules are used. However, the data are divergent regarding the most efficient form of vitD. 25OHD2 half-life is slightly shorter than that of 25OHD3, 25OHD2 has a lower affinity than 25OHD3 to vitD-binding protein (DBP)[17]. Thus, it is likely that treatment with vitD2 may neither increase serum 25OHD nor decrease PTH as efficiently as vitD3[18]. In this respect, a meta-analysis of randomized control trials evaluating serum 25OHD levels after chole- or ergo-calciferol supplementation, showed a slightly better effect with cholecalciferol[19].

Current evidence suggests that mean 25OHD levels remain low (<20 ng/dl) after bariatric surgery despite different vitD supplementation regimens. A systematic review showed that vitD deficiency was corrected using supplemental doses from 1100 to 7100 IU/day, in addition to the usual maintenance daily dose of 400-2000 IU[20].

Regarding treatment practices, aggressive calcium (1,8 g daily) and vitD supplementation (ergocalciferol 50,000 IU daily) to correct vitD deficiency and osteomalacia after RYGB had been reported for the first time in 2004[12]. Pharmacological doses of ergocalciferol (100,000 IU daily) with calcium carbonate (1.0–2.5 g daily) after RYGB, were administrated in 5 patients with osteomalacia associated with marrow fibrosis, diagnosed by bone biopsy[14]. In both reports, patients' clinical symptoms, biochemical and radiological findings were improved after treatment. In a patient that suffered from osteomalacic myopathy, muscle pain, strength and clinical status improved notably after im supplementation of ergocalciferol (400,000 IU) every month for 2 consecutive months which was administered in combination with calcium and cholecalciferol[21]. Furthermore, in a recent study, daily treatment with oral calcifediol (5000 IU), a vitD metabolite that does not require hepatic 25-hydroxylation, together with oral calcium carbonate, seemed to correct vitD status more than cholecalciferol in a patient with severe vitD deficiency-osteomalacia following biliopancreatic diversion[22]. Overall, oral calcifediol seems to be 2-5-fold more potent and with a higher rate of intestinal absorption than oral cholecalciferol[23].

There are currently scarce data concerning the long-term bioavailability of im vitD (ergo- or chole-calciferol). Romagnoli et al (2008) studied the effect of a single, oral or im dose of as high as 300,000 IU of either ergocalciferol or cholecalciferol on serum 25OHD levels in the elderly. Mean 25OHD levels were significantly higher with respect to the baseline in both forms and routes at 60 days[24]. However, increments in 25OHD levels were higher after oral cholecalciferol administration compared to the other forms and routes. Cipriani et al, extended the duration of the abovementioned observation, demonstrating that the oil depot im forms of vitD induced a slow increase of 25OHD levels for up to 120 days[25]. Another important advantage of im forms is the lack of 25OHD fluctuations and the high rate of patient's compliance. The pharmacokinetic profile of im administration supports the consideration that this approach could be the best choice in the treatment of vitD deficiency, due to a bariatric surgery, like in our case.

Although ergocalciferol seems slightly less potent than cholecalciferol[19] it can be considered as an alternative treatment of severe symptomatic vitD deficiency and osteomalacia. Unfortunately, high dose parental preparations of both cholecalciferol and ergocalciferol are not easily available in Greece. The only preparation that is available, through special request in the Greek Agency of Medicine is ergocalciferol. This, together with the uncertainties for the optimal doses were the main reasons why we used ergocalciferol in our patient. Although there are no specific guidelines concerning the frequency of ergocalciferol administration in such patients, a common approach in clinical practice is its administration in 20 days intervals.

Apart from vitD, intestinal fractional calcium absorption decreases significantly after RYGB. In particular, Schafer et al reported a decrease from 33% preoperatively to 7% 6 months postoperatively even after restoration of normal vitD status and calcium[26]. Regarding calcium salts supplementation, an important factor influencing their absorption and bioavailability is gastric acid secretion[27]. In contrast to calcium carbonate, calcium citrate has been shown to be more soluble in water and releases Ca2+ without reaction with gastric acid and thus, its absorption is not impaired in achloridria[28]. The superiority of calcium citrate has been shown in several studies. For example, calcium citrate compared with calcium carbonate in healthy postmenopausal women, provided a 94% higher increase in the area under the curve of serum calcium and an increase of 41% in urinary calcium[29].

Calcium citrate supplementation is also suggested by the Bariatric Surgery guidelines[5,6]. According to a small comparative study of eighteen patients after RYGB operation, calcium citrate could be considered as the preferred form compared to calcium carbonate, due to its absorption in the absence of low pH[30]. This higher availability of calcium citrate in the absence of low PH can in part counterbalance the reduced calcium intestinal absorption and the impaired

vitD metabolism after RYGB operation. Thus, the decision to use calcium citrate instead of calcium carbonate in our case was due to the fact that the absorption and the bioavailability of calcium carbonate is impaired in states of achlorydria or following RYGB operation.

In conclusion, prompt correction of vitD and mineral deficiencies are necessary in patients that underwent bariatric procedures. Intramuscular ergocalciferol administration rather than oral cholecalciferol can improve their clinical and biochemical status and is therefore suggested as an alternative approach in the prevention and/or treatment of osteomalacia. Long-term studies are needed to determine the appropriate doses of vitD administration in such patients.

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*Authors' contribution*

*LP examined the patient, wrote the article, and approved the final version to be published. CG examined and followed the patient, collected data and approved the final version to be published. ST contributed intellectually, critically reviewed and revised the article and approved the final version to be published. AM diagnosed the patient, carried out the laboratory work and approved the final version to be published. EG carried out the laboratory work and approved the final version to be published. KL reviewed the radiological work-up and approved the final version to be published. TK assigned duties, revised the manuscript and approved the final version to be published.*

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