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REVIEW

Calcifediol in the management of vitamin D deficiency-related skeletal and extraskeletal diseases: overview and clinical cases

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Abstract

As well as being essential for musculoskeletal health, vitamin D is involved in numerous other physiological processes. Poor vitamin D status is linked to a wide range of diseases, including cardiovascular disease, autoimmune conditions, pulmonary disorders and upper respiratory tract infections. While optimal target concentrations of serum 25-hydroxyvitamin D (25(OH)D) for health maintenance or therapeutic purposes are still the subject of debate, there is reasonable agreement that serum 25(OH)D levels <50 nmol/L (20 ng/mL) constitute vitamin D deficiency and that severe deficiency states (serum 25(OH)D levels <25-30 nmol/L ≈ 10-12 ng/mL) should be avoided. Main strategies to maintain or improve vitamin D status are food supplementation and therapeutic use of medicinal forms of vitamin D. In this review, we examine evidence that implicates vitamin D deficiency in diverse conditions in the clinical settings of endocrinology, rheumatology, pneumology and reproductive health. Cholecalciferol (vitamin D_3) is the most frequently used vitamin D supplement worldwide, though calcifediol (25-hydroxyvitamin D_3) has recently become more widely available. Calcifediol is one step closer than cholecalciferol in the metabolic pathway to biologically active vitamin D. Pharmacokinetic differences between these vitamin D metabolites confer putative advantages for calcifediol in certain clinical situations. The clinical use of calcifediol is explored more closely through case studies, which illustrate its adjunctive role in the treatment of several vitamin D deficiency-related skeletal and extraskeletal diseases.

Keywords: calcifediol, cholecalciferol, pharmacokinetics, vitamin D deficiency, vitamin D endocrine system.

Citation

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Introduction

The prohormone vitamin D is recognized as a key regulator of bone mineralization and calcium and phosphate homeostasis.[1,2] However, extraskeletal actions of the vitamin D endocrine system (VDES) indicate that vitamin D is involved in numerous other physiological processes, including cell proliferation, immune function, central nervous system and cardiovascular system activity, muscle performance and keratinocyte differentiation. Vascular and metabolic properties of vitamin D and involvement of vitamin D in male and female reproductive health have also been reported.[3,4] Moreover, poor vitamin D status is associated with a wide range of diseases, including cardiovascular disease, selected cancers, autoimmune diseases (e.g. type 1 diabetes and rheumatoid arthritis), pulmonary disorders (e.g. asthma and chronic obstructive pulmonary disease (COPD)) and upper respiratory tract infections (e.g. influenza and COVID-19).[3-7]

Individual vitamin D status is best assessed by measuring serum levels of 25-hydroxyvitamin D (25(OH)D). Although values used to define vitamin D deficiency may vary amongst expert groups, in general, serum 25(OH)D concentrations below <50 nmol/L (20 ng/mL) might

be regarded as deficient.[8,9] Agreement is stronger that serum 25(OH)D concentrations below 25-30 mmol/L (10-12 ng/mL) constitute severe vitamin D deficiency and should be avoided in all individuals regardless of age.[9,10] Optimal target serum 25(OH)D concentrations for maintaining adequate musculoskeletal health or for treating vitamin D deficiency-related diseases have yet to be standardized and debate continues.

Worldwide, the most frequently used supplement to treat vitamin D deficiency is cholecalciferol (commonly referred to as vitamin D_3). Calcifediol has recently become more widely available. In contrast to vitamin D_3, calcifediol is independent of hepatic 25-hydroxylation and thus is one step closer in the metabolic pathway to biologically active vitamin D. The additional hydroxyl group on carbon 25 of the calcifediol molecule confers pharmacokinetic properties that may be therapeutically advantageous in certain clinical situations.[11]

In this article, we overview some key clinical areas where vitamin D deficiency is linked with diseases and where vitamin D supplementation has been used as part of an overall strategy to manage these conditions. We also present several illustrative case reports of patients treated with adjunctive calcifediol for vitamin D deficiency-related skeletal and extraskeletal diseases.

Review of conditions associated with vitamin D deficiency

Endocrinological diseases: diabetes, metabolic syndrome, obesity and hyperparathyroidism

Preclinical and epidemiological studies have shown that vitamin D deficiency is associated with decreased insulin release, onset and development of insulin resistance, and type 2 diabetes (T2D).[12–14] Vitamin D acts to reduce inflammation and maintain normal resting levels of Ca^{2+} and reactive oxygen species, both of which are elevated in pancreatic β-cells during the onset of diabetes and result in β-cell death. Genomic effects of vitamin D may also play a role in glycaemic control and T2D. These include epigenetic effects involving vitamin D-induced inactivation of diabetes-related genes by hypermethylation and the presence of genetic polymorphisms of vitamin D-related genes that predispose to impaired glycaemic control and T2D.[12,13]

A meta-analysis of individuals with prediabetes (*n*=3792) found that vitamin D supplementation was associated with marked improvement in fasting blood glucose, haemoglobin A_{1c} (HbA_{1c}) and fasting insulin levels compared with controls.[15] Conversely, a large randomized controlled trial (RCT) not included in the meta-analysis reported no significant difference in the risk of T2D between vitamin D_3 supplementation (4000 IU per day) and placebo in individuals with prediabetes (*n*=2423), despite an increase in serum 25(OH)D concentrations from 70 nmol/L (27.7 ng/mL) at baseline to 135 nmol/L (54.3 ng/mL) over a median of 2.5 years of follow-up.[16] A possible explanation for the absence of effect is that vitamin D supplementation is effective only in deficiency states.[8]

A systematic review (14 studies) reported a link between serum 25(OH)D concentration and metabolic syndrome, with four out of five observational studies supporting a significant association with the individual components of obesity, dyslipidaemia, blood pressure, and insulin and glucose metabolism. This association was supported by evidence from seven RCTs indicating that vitamin D supplementation had a significant effect on abdominal obesity, blood pressure, and insulin and glucose metabolism.[17] A meta-analysis of cardiometabolic risk factors in elderly individuals (12 trials and 1328 participants) found that vitamin D supplementation significantly reduced total cholesterol and triglyceride levels compared with placebo. The beneficial effect of vitamin D supplementation was significantly greater with longer-term (>6 months) *versus* shorter-term (≤6 months) treatment.[18]

An inverse correlation between vitamin D status and obesity has been described.[14] Vitamin D_3 is lipophilic and thus sequesters in adipose tissue. Greater adipose stores in individuals with obesity may serve as a reservoir for vitamin D_3, predisposing them to 25(OH)D deficiency.[19] Lifestyle factors, such as less sun exposure and lower dietary intake of vitamin D-enriched foods, may also play a role in 25(OH)D deficiency in individuals with obesity.[20] As discussed later in the review, the more hydrophilic nature of calcifediol makes it less prone to sequestration and thus more suitable for use in the presence of obesity.

A major complication of poor vitamin D status is secondary hyperparathyroidism and the associated dysregulation of calcium and phosphorus homeostasis, which is essential for bone mineralization. Although impaired skeletal health is the main effect of secondary hyperparathyroidism, extraskeletal organs that express vitamin D and/or parathyroid receptors may also be affected, which can lead to chronic kidney disease and cardiovascular complications.[21,22] In patients with progressive secondary hyperparathyroidism, such as those with moderate or severe chronic kidney disease, calcifediol appears to be more beneficial than cholecalciferol

in controlling parathyroid hormone levels and resolving phosphorus/calcium metabolism dysregulation.[23]

Vitamin D deficiency is highly prevalent in patients with primary hyperparathyroidism (PHPT) and is associated with a more severe disease phenotype.[24] The mechanism for this association may involve a higher turnover of vitamin D metabolites.[25] Moreover, patients with PHPT with vitamin D deficiency are at greater risk of developing hungry bone syndrome after parathyroidectomy.[24] Although there is not enough evidence to recommend using calcifediol as a treatment for patients with PHPT and vitamin D deficiency, a retrospective study showed that patients with PHPT and concurrent vitamin D deficiency could be treated effectively with vitamin D_3 50,000 IU once weekly or 1000–2000 IU once daily, without increasing serum calcium to dangerous levels.[26]

Rheumatological diseases: postmenopausal osteoporosis, sarcopenia and inflammatory diseases

Due to deterioration of musculoskeletal health, older men and women are at a higher risk of developing osteoporosis and sarcopenia, which increases the likelihood of falls and fractures.[27] Low vitamin D status has been identified as one of the factors associated with osteoporosis and fractures,[2] and is highly prevalent in women in post-menopause and older men. Guidelines vary considerably with respect to the dose of vitamin D recommended for older adults – ranging from 200 IU (5 µg) to 2000 IU (50 µg) per day.

Several clinical studies have highlighted the benefit of calcifediol over cholecalciferol for improving vitamin D status in women in post-menopause with vitamin D deficiency.[28-32] In a large RCT, calcifediol 266 µg once monthly was superior to cholecalciferol 25,000 IU once monthly for improving vitamin D status in women in post-menopause (n=303) with baseline serum 25(OH)D concentrations <50 nmol/L (20 ng/mL). At 4 months, significantly more women treated with calcifediol than with cholecalciferol (35.0% *versus* 8.2%; p<0.0001) had attained serum 25(OH)D concentrations >75 nmol/L (30 ng/mL). The mean change from baseline in serum 25(OH)D levels was most marked after 1 month of treatment (24.3 *versus* 12.8 nmol/L ≈ 9.7 *versus* 5.1 ng/mL), reflecting the greater potency of calcifediol and more rapid response compared with cholecalciferol.[28] Other RCTs similarly demonstrated a more rapid achievement of target serum 25(OH)D concentrations (>75 nmol/L ≈ 30 ng/mL) with calcifediol compared with cholecalciferol in women in post-menopause with low baseline vitamin status (20-60 nmol/L ≈ 8-24 ng/mL).[30,31] A RCT compared weekly alendronate 70 mg in combination with calcifediol or cholecalciferol at a monthly total dose of 625 µg in 362 women in post-menopause with osteoporosis or osteopenia. Outcomes with alendronate plus calcifediol were superior to those with alendronate plus cholecalciferol, as assessed by significant (both p<0.05) increases in the lumbar T-score (0.26 ± 0.35 *versus* 0.13 ± 0.30) and serum 25(OH)D concentration (51.5 ± 51.7 *versus* 15.3 ± 19 nmol/L ≈ 20.6 ± 20.7 *versus* 6.1 ± 7.6 ng/mL) at 1-year follow-up.[32]

Epidemiological evidence indicates that vitamin D deficiency is significantly associated with an increased incidence of autoimmune rheumatic diseases, including systemic lupus erythematosus, undifferentiated connective tissue disease and rheumatoid arthritis, compared with the healthy population.[33] In addition, numerous studies have shown that lower vitamin D status correlates with greater disease activity in rheumatoid arthritis and other inflammatory rheumatic diseases.[34,35]

The role of the VDES in inflammatory diseases is supported by the known actions of vitamin D and its receptor. Expression in most immune cells of the vitamin D receptor (VDR) and 1α-hydroxylase, the vitamin D-activating enzyme, suggests modulatory effects on immune function at various levels.[36,37] Active vitamin D acts to modulate multiple components of the innate and adaptive immune systems and may stabilize endothelial membranes.[37] Together with VDR signalling, vitamin D suppresses autoimmunity and has an inflammatory effect by favouring chemotaxis, antimicrobial peptide production and macrophage differentiation; inhibiting the production of pro-inflammatory cytokines, maturation of dendritic cells and differentiation of T helper 1 and 17 cells; and promoting the immunoregulatory functions of regulatory T cells.[36,38]

Meta-analyses of vitamin D supplementation in patients with rheumatoid arthritis have reported controversial results. One group of investigators (6 RCTs, 438 patients) found that vitamin D supplementation as the main intervention was associated with significant improvements in the Disease Activity Score 28 (DAS-28), erythrocyte sedimentation rate and tender joint count compared with standard treatment control conditions.[39] Another group (8 RCTs, 544 patients) found no significant effects for vitamin D supplementation *versus* placebo on the risk of flares in patients in remission or on DAS-28 evolution in patients with active disease. However, only three of the eight RCTs included patients with proven vitamin D deficiency.[40] Until the association between vitamin D status and rheumatoid arthritis becomes clear, a prudent clinical approach may be to monitor 25(OH)D concentrations at baseline and during follow-up and supplement with vitamin D in the case of 25(OH)D deficiency.[41]

More recently, the vitamin D and omega-3 trial (VITAL), a large nationwide RCT from the USA involving more than 25,000 participants, found that vitamin D supplementation for 5 years, with or without omega-3, reduced incident autoimmune disease (rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, inflammatory bowel disease and other) by 22%.[42]

Respiratory diseases

Multiple epidemiological studies have shown that low serum 25(OH)D levels are associated with impaired pulmonary function and an increased incidence of inflammatory respiratory diseases, including asthma, COPD, acute lung injury, cystic fibrosis, pneumonia and tuberculosis.[4,43,44] Low serum 25(OH)D concentrations may also be associated with a greater risk of COVID-19 infection and a higher likelihood of severe disease.[45-47]

Some meta-analyses have reported that vitamin D protects against the development of acute respiratory tract infections.[48,49] A large analysis involving 48,488 participants enrolled in 43 RCTs found that vitamin D supplementation reduced the risk of acute respiratory tract infection compared with placebo (OR 0.92; 95% CI 0.65-0.94), though study heterogeneity was significant. Protective effects were observed in trials in which vitamin D was administered in a daily dosing regimen (OR 0.78; 95% CI 0.65-0.94), at daily dose equivalents of 400-1000 IU (OR 0.70; 95% CI 0.55-0.89), for a duration of up to 12 months (OR 0.82; 95% CI 0.72-0.93), including in children aged 1-16 years at enrolment (OR 0.71; 95% CI 0.57-0.90).[49] Conversely, in a population of mostly vitamin D replete older Australian adults (*n*=15,373), routine vitamin D supplementation (monthly bolus doses of 60,000 IU) had no clinically relevant effects on acute respiratory tract infections compared with placebo.[50]

Benefits of vitamin D supplementation have been reported in asthma and COPD, though studies differed in terms of population (children and/or adults) and type and regimen of vitamin D supplementation. A meta-analysis of individual participant data that included children and adults (*n*=955) from seven RCTs found that vitamin D_3 supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids (adjusted incidence rate ratio 0.74).[51] In the Asthma Control in Asthmatic Patients with Vitamin D Deficiency (ACViD) RCT involving adult patients with asthma and serum 25(OH)D_3 concentrations below 75 nmol/L (30 ng/mL), supplementation with weekly oral calcifediol 266 µg improved asthma control compared with placebo during 6 months of follow-up.[52] However, not all studies of vitamin D in asthma have been positive. In the Vitamin D to Prevent Severe Asthma Exacerbations (VDKA) study of children with asthma and low vitamin D levels (<75 nmol/L ≈ 30 ng/mL), supplementation with vitamin D_3 4000 IU/day failed to significantly improve the time to a severe asthma exacerbation compared with placebo over a 48-week study period.[53]

In the Vitamin D Supplementation in Chronic Obstructive Pulmonary Disease (ViDiCO) RCT in patients with COPD, vitamin D_3 supplementation protected against moderate or severe exacerbations compared with placebo in patients with baseline serum 25(OH)D concentrations <50 nmol/L (20 ng/mL) but not in those with concentrations ≥50 nmol/L (20 ng/mL). Adjusted hazard ratios were 0.57 (95% CI 0.35-0.92) and 1.45 (95% CI 0.81-2.62), respectively.[54] Similarly, a *post hoc* analysis of a RCT in older adults with asthma and/or COPD showed that vitamin D_3 supplementation reduced exacerbation risk in those with low baseline 25(OH)D levels (<25 nmol/L ≈ 10 ng/mL).[55]

A systematic review and meta-analysis concluded that vitamin D supplementation may reduce rates of COVID-19 infection, intensive care unit admission and mortality.[56] However, in a large population-based study conducted in Catalonia, superior outcomes in patients with COVID-19 previously supplemented with vitamin D were observed only when serum 25(OH)D concentrations ≥75 nmol/L (30 ng/mL) were achieved, with either cholecalciferol or calcifediol supplementation.[57]

In patients hospitalized for COVID-19 and not previously supplemented with vitamin D, calcifediol (532 µg on day 1 then 266 µg on days 3, 7, 15 and 30) significantly reduced intensive care unit admission and mortality compared with no treatment.[58]

Reproductive health

Accumulating data from animal and clinical studies support a role for vitamin D in both male and female fertility. VDR-knockout mice were found to have significant gonadal insufficiency, decreased sperm count and motility, and histological abnormalities of the testes, ovary and uterus.[59] Observational studies have reported an association between vitamin D deficiency and reduced fertility, adverse pregnancy outcomes and a low vitamin D content in breast milk.[60] A meta-analysis of 11 published cohort studies involving 2700 women undergoing assisted reproductive treatment (IVF, intracytoplasmic sperm injection or frozen embryo transfer) reported that vitamin D status was favourably associated with reproductive outcomes, including positive pregnancy test results, clinical pregnancies and live births.[61] Similarly, a meta-analysis of 15 cohort studies of vitamin D status in 3711 women undergoing IVF reported that vitamin D sufficiency was associated with better outcomes, including higher rates of biochemical pregnancy and ongoing pregnancy compared with vitamin D deficiency.[62] Al-

though both meta-analyses demonstrated an association between vitamin D sufficiency and increased fertility in assisted reproductive treatment, definitions of vitamin D sufficiency, insufficiency and deficiency differed between studies.[61,62] A prospective cohort study that compared women (*n*=1191) with vitamin D sufficiency (25(OH)D ≥75 nmol/L ≈ 30 ng/mL) and those with insufficiency (<75 nmol/L ≈ 30 ng/mL) at preconception concluded that vitamin D sufficiency was associated with higher rates of clinical pregnancy and live birth, and a reduced risk of pregnancy loss, compared with vitamin D insufficiency.[63] A recent meta-analysis that included ten studies (*n*=7663) found that vitamin D deficiency (<50 nmol/L ≈ 20 ng/mL) and insufficiency (50–75 nmol/L ≈ 20-30 ng/mL) were both associated with an increased risk of miscarriage compared with women who were vitamin D replete (>75 nmol/L ≈ 30 ng/mL).[64] In a meta-analysis of 14 studies, women experiencing recurrent miscarriages had significantly lower serum vitamin D concentrations compared with those who completed a normal pregnancy.[65] Despite these findings, it remains unclear whether vitamin D supplementation improves fertility or decreases the risk of adverse pregnancy outcomes such as pre-eclampsia, low birth weight and neonatal mortality.[60]

Pharmacokinetics of calcifediol and therapeutic advantages

Cholecalciferol and calcifediol are both safe and effective for preventing or correcting vitamin D deficiency, though pharmacokinetic differences between the supplements may favour use of calcifediol in certain clinical situations.

Cholecalciferol is activated to biologically active vitamin D following a two-stage hydroxylation process that involves 25-hydroxylase in the liver followed by 1α-hydroxylase in the kidney. In contrast, calcifediol is activated solely by 1α-hydroxylase and is thus independent of hepatic function.[11,66]

Comparative studies indicate an approximate three-fold to six-fold greater potency for calcifediol *versus* cholecalciferol and, hence, the rationale for using lower dosages.[67] Pharmacokinetic studies and numerous comparative clinical studies, including multiple RCTs that evaluated vitamin D status mainly in postmenopausal women and older adults, have shown that mean serum 25(OH)D concentrations increase more rapidly with calcifediol than cholecalciferol at comparable doses.[67-69]

Calcifediol has a linear dose–response curve irrespective of baseline serum 25(OH)D concentration whereas cholecalciferol-induced increases in 25(OH)D concentrations are lower at higher baseline 25(OH)D concentrations.[67] As calcifediol is more hydrophilic than cholecalciferol, it is less likely to be sequestered in adipose tissue.[11,19,70] Due to the lipophilicity and relatively slow turnover of cholecalciferol in the body, its elimination half-life (approximately 2 months) is considerably longer than that of calcifediol (approximately 2-3 weeks).[66,67] This, together with factors affecting the absorption (depends on the presence of bile acids and micelle formation) and metabolic conversion (age-related and disease-related decreases in hepatic 25-hydroxylase activity) of cholecalciferol lead to a less predictable dose response compared with calcifediol.[67]

The pharmacokinetic properties of calcifediol support recommendations for its use in patients with 25(OH)D synthesis impairment (i.e. those treated with antiepileptic drugs), less vitamin D bioavailability (i.e. obesity) or severe malabsorption (i.e. bariatric surgery).[71]

Real-world clinical cases of patients with vitamin D deficiency treated with calcifediol

We present several clinical cases that highlight real-world experience of patients with vitamin D deficiency receiving calcifediol for VDES-related skeletal and extraskeletal diseases. The cases involve the specialty areas of endocrinology (obesity and T2D; secondary hyperparathyroidism), rheumatology (corticosteroid-induced osteoporosis), pneumology (asthma) and gynaecology (fertility and post-menopause).

Patient with obesity and T2D

A 62-year-old woman was referred for grade III obesity, weight gain and decompensated T2D. Her medical history included peripheral venous insufficiency, grade III obesity, T2D, background diabetic retinopathy, dyslipidaemia, arterial hypertension, glaucoma, osteoarthritis and obstructive sleep apnoea syndrome. Current treatments were metformin (1000 mg daily), atorvastatin (20 mg daily), irbesartan (300 mg daily), atenolol (50 mg daily), acetylsalicylic acid (100 mg daily), analgesics (paracetamol and metamizole) as required, and nocturnal continuous positive airway pressure (8 cm H_2O pressure).

The patient presented occasional diabetic symptoms (nocturia and polyuria) without hypoglycaemia, plus significant weight gain (20 kg in 6 months) related to

increased food intake and limited mobility. She had recently improved her diet but did not exercise due to muscle weakness and knee osteoarthritis. She received lifestyle education and began treatment with semaglutide 0.25 mg/week for 4 weeks, increasing to 0.5 mg weekly thereafter.

The patient was in general good health. Recorded measurements were blood pressure (after 5-minute rest) 138/77 mmHg, heart rate 79 bpm, body mass index (BMI) 49.74 kg/m^2 and waist circumference 136.5 cm. Biochemical analyses (prior to intensification of antidiabetic therapy) indicated abnormal glucose (174 mg/dL) and HbA_{1c} (8.23%) levels.

At first review 4 months after antidiabetic therapy intensification, capillary glycaemia results were improved, and the patient reported less diabetic symptomatology. She had ostensibly decreased her appetite and lost weight but continued to take no exercise due to the persistence of muscle weakness.

At a second follow-up visit (4 months later), her BMI was 46.7 kg/m^2 and waist circumference was 129.5 cm. Biochemical tests showed abnormal HbA_{1c} (7.46%), glucose (139 mg/dL), phosphorus (2.4 mg/dL), parathyroid hormone (71 pg/mL) and 25(OH)D (18.3 nmol/L ≈ 7.3 ng/mL) concentrations. Calcium (8.6 mg/dL), magnesium (1.9 mg/dL) and estimated glomerular filtration rate (91 mL/min) were within normal ranges. Vitamin D deficiency was diagnosed. Due to the patient's work activity as a seamstress and absence of outdoor exercise, her sun exposure was insufficient to achieve normal vitamin D levels. In addition, dietary vitamin D intake was below recommended daily requirements, possibly due to dietary restrictions enhanced by antidiabetic therapy that induced weight loss in preference to appetite reduction. Biochemical data from both visits excluded underlying causes for hypovitaminosis D.

The semaglutide dose was further increased from 0.5 mg to 1 mg weekly and calcium/cholecalciferol (600 mg/2000 IU) was prescribed twice daily. However, biochemical analyses indicated a persistence of vitamin D deficiency, with a serum 25(OH)D concentration of 45.3 nmol/L (18.1 ng/mL). Cholecalciferol was replaced with calcifediol, at a dose of 266 µg/week for 1 month, then 266 µg every 2 weeks, whilst maintaining daily calcium supplementation.

At the third review, the patient reported that her muscle strength had improved, and she had begun to partake in progressive physical exercise. Her weight was reduced to 116.7 kg. Her serum 25(OH)D concentration was normalized to 90.7 nmol/L (36.3 ng/mL) and glycaemic control was within recommended limits (HbA_{1c} 6.48%).

Calcifediol is more hydrophilic than cholecalciferol, making it less prone to adipose tissue sequestration. Hence, calcifediol may be more suitable to treat hypovitaminosis D in patients with higher degrees of obesity associated with increased vitamin D requirements.

Patient with secondary hyperparathyroidism

A 67-year-old male ex-smoker was referred for hyperparathyroidism. His medical history included obesity, dyslipidaemia, arterial hypertension, benign prostatic hypertrophy and oral candidiasis. Previous surgical interventions were appendectomy and basal cell carcinoma. Current treatments were olmesartan/amlodipine (40/10 mg daily), tamsulosin (0.4 mg daily), tadalafil (5 mg daily) and simvastatin (40 mg daily).

At presentation, the patient reported occasional headaches, asthenia, variable mood, occasional diarrhoea, numbness and occasional spasms in the hands. No weakness, myalgia, paraesthesias or other symptoms suggestive of hormonal dysfunction or alteration of calcium haemostasis were observed. Due to diarrheal episodes, the patient had restricted his intake of dairy products. After intervention for basal cell carcinoma, he decreased his sun exposure through photoprotective measures, such as sunscreen, hat, clothes and sunglasses. Outdoor activities were performed during hours of lower solar irradiation, even on cloudy days.

The patient's BMI was 31 kg/m^2, and his waist circumference was 114 cm. He was in general good health with blood pressure of 127/79 mmHg and heart rate of 92 bpm. He had rhythmic cardiac auscultation without murmurs or extra tones, and peripheral pulses. Electrocardiogram was normal. Pulmonary examination revealed preserved vesicular murmur. Neurological examination indicated abnormally reactive pupils, with preserved saccadic eye movements.

Biochemical analyses revealed abnormalities in albumin-adjusted calcium (7.6 mg/dL), parathyroid hormone (142.3 pg/mL) and 25(OH)D (9.3 nmol/L ≈ 3.7 ng/mL) concentrations. Other results were within the normal range, including albumin (4 g/dL), phosphorus (2.6 mg/dL), alkaline phosphatase (97 IU/L) and estimated glomerular filtration rate (84 mL/min).

As clinical and biochemical data excluded other causes of hypovitaminosis D, hyperparathyroidism secondary to severe vitamin D deficiency was diagnosed.

Calcifediol (266 µg/week for 1 month, then 266 µg every 2 weeks) was prescribed along with calcium supplementation (calcium carbonate tablets 1500 mg/day).

At follow-up, the patient's self-reported adherence was adequate, spasms were absent, and muscle strength and mood were improved. Serum concentrations of 25(OH)D (78 nmol/L ≈ 31.2 ng/mL), calcium (9.1 mg/dL) and parathyroid hormone (63.1 pg/mL) were normalized. Other biochemical results (e.g. phosphorus 3.9 mg/dL) were within the normal range.

In patients with severe vitamin D deficiency and secondary hyperparathyroidism, calcifediol appears to be more beneficial than cholecalciferol. Calcifediol has higher intestinal absorption, greater potency and quicker action than cholecalciferol. In addition, the half-life of calcifediol allows for a varying administration interval (i.e. every 1, 2, 3 or 4 weeks), which can facilitate dose titration and enhance patient adherence.

Patient with corticosteroid-induced osteoporosis

A 78-year-old man presented with recent-onset (in the previous month) low back pain upon waking. He had been under treatment for psoriatic arthritis for 7 years, initially with oral methotrexate then switching to leflunomide 20 mg/day and low-dose prednisone (2.5-5 mg/day). Leflunomide was stopped after 2 years due to disseminated tuberculosis. Since the age of 76 years, the patient had received only prednisone 5 mg/day, which maintained his inflammatory arthropathy in low disease activity or remission.

Physical examination was unremarkable except for tenderness of the lower dorsal and upper lumbar vertebrae. There was no evidence of painful or swelling joints. A thoracic and lumbar X-ray revealed a severe (grade 3) T11 vertebral fracture, not present in previous imaging studies. Laboratory parameters were normal for calcium, phosphorus, total alkaline phosphatase and parathormone, whereas 25(OH)D levels of 20 nmol/L (8 ng/mL) were indicative of severe vitamin D deficiency.

A dual-energy X-ray absorptiometry (DXA) scan performed some weeks later showed very low bone mineral density (BMD): T-score −4.26 at the lumbar spine, −1.47 at the femoral neck and −3.27 at the total hip. The Trabecular Bone Score was 1.162, indicating a markedly degraded bone microarchitecture. The patient was diagnosed with glucocorticoid-induced osteoporosis complicated by a vertebral fracture and was at high risk of new vertebral and non-vertebral fractures.

Analgesia and home rest for a few days were recommended. As the patient's dietary calcium consumption was low, he was encouraged to consume more dairy products to achieve a daily calcium intake of 1-1.2 g. Due to the extremely low 25(OH)D levels, we chose to treat with a more potent vitamin D metabolite. Calcifediol 266 µg was prescribed to be taken once weekly for 5 weeks, then once monthly until further monitoring of serum 25(OH)D concentrations. The patient also began a 24-month course of teriparatide 20 µg/day.

After 3 months, the patient's back pain had improved significantly. However, despite good treatment adherence, his serum 25(OH)D levels remained low at 40 nmol/L (16.3 ng/mL) with normal calcium. Teriparatide is known to stimulate kidney 1α-hydroxylases, resulting in conversion of 25(OH)D to 1,25-dihydroxyvitamin D,[72] which can cause a decrease in 25(OH)D levels. Higher doses of calcifediol are required in some patients. The calcifediol dose was increased two-fold to 266 µg every other week. With this adjusted regimen, the patient achieved 25(OH)D concentrations of 75 nmol/L (30 ng/mL) within 6 months.

After 24 months of treatment, the patient had not suffered any new fractures. DXA scan T-scores were −3.93 (+5.7%) at the lumbar spine, −1.47 (no significant change) at the femoral neck and −3.27 (+1.5%) at the total hip. His 25(OH)D concentration was 94 nmol/L (37.6 ng/mL) with normal calcium and phosphorus.

Teriparatide was discontinued and oral bisphosphates were initiated. Six months later, the patient's 25(OH)D concentration was 98 nmol/L (39.1 ng/mL). The calcifediol regimen was adjusted to 266 µg every 3 weeks.

Maintaining serum 25(OH)D concentrations above 75 nmol/L (30 ng/ml) is recommended in patients with osteoporosis,[71] not only to avoid the development of secondary hyperparathyroidism but also to elicit a better BMD response with antiresorptives or bone-forming agents.

Patient with asthma

A 52-year-old woman reported a worsening of asthma symptoms in the previous 2 months in the form of increased daytime coughing, night-time wheezing causing sleep disruption and dyspnoea on minimal activity such as walking. She had comorbid chronic rhinosinusitis. She had given up smoking at age 36 (8 pack-years cumulative smoking). Her usual treatment was on-demand nasal fluticasone propionate and salbutamol. Due to symptom worsening, her primary care physician had initiated treatment with fluticasone furoate–vilanterol (92/22 µg) once daily, which partially improved her asthma control.

At the first clinic visit the patient was aware and oriented. Cardiac and pulmonary auscultation showed normal function. Oxygen saturation measured by pulse oximetry

was 98%, and heart rate was 84 bpm. Biochemical and haematological analyses revealed abnormalities in eosinophils (450 cells/µL; 4.6%) and serum 25(OH)D concentration (35 nmol/L ≈ 14 ng/mL), indicating vitamin D deficiency.

There was no evidence of pulmonary infiltrates on chest X-ray. The patient had a forced vital capacity (FVC) of 3900 mL (83%), a forced expiratory volume in the first second (FEV_1) of 2320 mL (61%) and a FEV_1/FVC ratio of 59%. A bronchodilator test showed improvement in FEV_1 to 2720 mL (+17%). The fractional exhaled nitric oxide test was 23 ppb. The Asthma Control Test was 17 points and the Test of Adherence to Inhalers was 53 points. The final diagnosis was moderate, persistent allergic asthma with partial control and erratic therapeutic non-adherence, and vitamin D deficiency.

Basic treatment with inhaled combination fluticasone furoate–vilanterol (92/22 µg) was maintained, and montelukast (10 mg once daily) was added. Nasal fluticasone propionate (two puffs per nostril every 24 hours) and on-demand salbutamol were also prescribed. The need for therapeutic adherence was emphasized. As vitamin D deficiency is considered to aggravate asthma, calcifediol (266 µg once monthly) was started. Calcifediol was selected based on its ability to rapidly correct serum 25(OH)D concentrations because it does not require hepatic hydroxylation.

At 6-month review, the patient reported symptomatic improvement in asthma, which was accompanied by improvement in the Asthma Control Test (increased to 23 points), indicating good control and normalization of lung function (FEV_1 >80%). Supplementation with calcifediol had normalized serum 25(OH)D concentrations and was well tolerated without adverse effects. The patient was able to lead a normal life without need to increase the dose of inhaled corticosteroid.

Couple undergoing fertility treatment

A couple attended a fertility clinic with a history of three consecutive miscarriages in the first trimester within the previous 1.5 years. Both individuals were healthy, 37 years of age, with no toxic habits or diseases of interest in their personal history and unremarkable physical examinations.

The infertility study revealed slight hypospermia but otherwise normal seminal parameters. Karyotypes, ultrasonographic antral follicle count and hormonal determinations were normal in both individuals. Of interest was the serum 25(OH)D concentration of 17.5 nmol/L (7 ng/mL) in the man and 30 nmol/L (12 ng/mL) in the woman. In view of the known implications of vitamin D deficiency on male and female fertility, calcifediol 266 µg weekly was prescribed for both. Four months later, serum 25(OH)D concentrations were normalized to 120 nmol/L (48 ng/mL) in the man and 112 nmol/L (45 ng/mL) in the woman. In both individuals, the calcifediol regimen was reduced to a monthly maintenance dose of 266 µg.

In vitro fertilization treatment was indicated for the couple. This consisted of standard controlled ovarian stimulation with recombinant follicle-stimulating hormone at variable doses and human menopausal gonadotropin; pituitary suppression with antigonadotropin-releasing hormone and induction of follicular maturation with a combination of recombinant human chorionic gonadotropin and gonadotropin-releasing hormone agonist in a dual regimen, repeated for three consecutive cycles until a total oocyte retrieval of 12 metaphase II oocytes, was completed.

With evolutionary data of ten progressing embryos, preimplantation genetic diagnosis was carried out for embryo selection, ultimately obtaining two embryos with normal chromosomal study that were cryopreserved.

More recently, following embryo transfer of a previously cryopreserved blastocyst performed in a spontaneous cycle, the patient delivered a 3845 g male vaginally, without complications, after labour induction of her fourth pregnancy.

This case report aligns with the body of evidence linking 25(OH)D deficiency with fertility issues.[73]

Postmenopausal woman with osteoporosis

A 68-year-old woman presented with acute low back pain after carrying her grandchild. She had entered menopause at 46 years and had a family history of hip fracture. At the age of 64, she suffered a right wrist fracture after a fall on her outstretched hand. Daily supplements of calcium/cholecalciferol (600 mg/400 IU) were started. No DXA scan was performed at that time. Her diet was low in calcium intake (around 400 mg/day), and she did not exercise regularly. Her medical history included arterial hypertension, dyslipidaemia and obesity. She had no history of smoking or alcohol consumption and had not received any bone loss-associated drugs.

On physical examination, the patient had tenderness of the lower lumbar vertebrae. A lumbar spine X-ray revealed a mild (grade 1) L3 vertebral fracture, which was not present in previous studies. Biochemical analysis showed low 25-hydroxyvitamin D levels (42.43 nmol/L ≈ 17 ng/mL).

Laboratory results for calcium, phosphorus, total alkaline phosphatase and parathormone were within the normal range. The estimated glomerular filtration rate was 80 mL/min/1.73 m^2. A DXA scan revealed low BMD, with T-scores of −2.8 at the lumbar spine, −2.1 at the femoral neck and −1.8 at the total hip.

The patient was diagnosed with postmenopausal osteoporosis. Treatment was started with alendronate 70 mg weekly. Despite supplementation with calcium and cholecalciferol, she remained vitamin D deficient, prompting a change to a more potent form of vitamin D. Calcifediol was started at a dose of 266 µg/month in order to achieve 25-hydroxyvitamin D levels above 75 nmol/L (30 ng/mL) as recommended for osteoporotic patients.[71] Calcium supplementation was maintained with calcium carbonate tablets 600 mg/day.

After 1 year of follow-up, the patient had not experienced any new fractures and her 25(OH)D levels were maintained within a normal range.

Conclusions

As vitamin D has an integral role in numerous physiological processes, it is important to prevent deficiency states. The clinical cases illustrate that hypovitaminosis D is a widespread phenomenon that can contribute to a diverse range of conditions across multiple therapeutic areas. As the literature suggests, preventing or correcting poor vitamin D status may be an effective adjunctive management approach. To avoid the long-term consequences of prolonged vitamin D deficiency, calcifediol, due to its favourable pharmacokinetic properties, provides an attractive therapeutic option particularly in patients who require rapid correction of serum 25(OH)D concentrations. The case studies show the potential for clinical benefit with therapeutic use of calcifediol to correct vitamin D deficiency. However, the findings must be weighed against the inability of case studies to prove a cause–effect relationship for an intervention and the potential therapeutic contributions of other treatments.

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