

CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Endocrinology Quiz – Case 6

A 66-years-old Caucasian lady presented to the rheumatology clinic with bilateral ankle pain, stiffness and swelling. She was mobilizing with the aid of crutches and noted to have a thin body habitus. There was a medical history of “nutritionally-induced” mild iron deficiency anemia four years previously.

Biochemical tests revealed an adjusted calcium of 1.79 mmol/L (2.10–2.60 mmol/L), phosphate 0.7 mmol/L (0.8–1.45 mmol/L), alkaline phosphatase of 433 IU/L (30–130 IU/L), intact parathyroid hormone 149 pg/mL (10–55 pg/mL), hemoglobin 10.7 g/dL (11.5–16 g/dL) and mean corpuscular volume 79.9 fL (80–96 fL).

Further biochemistry revealed vitamin D deficiency with 25OHD <10 nmol/L. Despite treatment with ergocalciferol tablets (10,000 units for 5 days per week for 8 weeks) there was (clinical, biochemical and radiological) evidence of worsening osteomalacia. An endomyseal IgA test was positive and the patient was therefore referred for an endoscopic evaluation of the upper gastrointestinal (GI) tract. This showed endoscopic and histopathologic (from a duodenal biopsy) appearances characteristic of celiac disease. A baseline dual energy absorptiometry (DXA) scan showed evidence of osteopenia, more marked in the peripheral than the central skeleton. This lady was referred to a dietician for initiation of a strict gluten free diet. Her mobility and overall wellbeing improved substantially within three months of the implementation of a gluten free diet. In a further three months, her weight and vitamin D levels increased and normalised and she was no longer anemic. She maintains a gluten free diet and remains clinically well to this day with normal biochemistry.

Questions

1. What is the bone profile suggestive of? What other biochemical tests should be performed?
2. What are the risk factors for the development of this condition?
3. How is this condition managed?
4. What are the extra-skeletal manifestations of this condition?
5. What is the unifying diagnosis?

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2016, 33(1):132–134

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Comments

Q1. *The bone profile is suggestive of severe vitamin D deficiency. The classical biochemistry associated with severe vitamin D deficiency includes low adjusted serum calcium and phosphate with a high serum alkaline phosphatase (indicative of a mineralization defect) and high serum parathyroid hormone (PTH). Severe vitamin D deficiency usually causes secondary hyperparathyroidism which in turn causes reabsorption of calcium and loss of phosphate in the renal tubules. Despite the high PTH, given the low 25OHD (25-hydroxy vitamin D or calcidiol) levels the 1,25(OH)₂D (1,25-dihydroxy vitamin D or calcitriol) level is low or low/normal, therefore explaining the low calcium level 1,25(OH)₂D induces increased calcium absorption in the intestine and increased release from bone and renal reabsorption). Low calcium and low phosphate are uncommon with mild degrees of vitamin D deficiency. The diagnosis is biochemically confirmed by measuring serum 25–OHD. 1,25–(OH)₂D measurement is generally unhelpful, as vitamin D deficiency is commonly associated with high PTH which will lead to 1α-hydroxylation of the 25–OHD in the kidneys producing 1,25–(OH)₂D. Indeed, 1,25(OH)₂D is commonly within the normal range in mild/moderate vitamin D deficiency but is usually low in severe vitamin D deficiency (due to substrate loss). Therefore, the serum 25OHD level is the best indicator of vitamin D status because it reflects vitamin D from sunlight exposure and dietary intake, as well as conversion from stores in the liver.*

Plain x-rays at sites of bone pain may reveal abnormalities typical of osteomalacia, such as Looser’s zones (pseudo-fractures) and osteopenia. Bone biopsy for histological evidence of osteomalacia is unnecessary, unless the diagnosis is in doubt or when further investigations are indicated to look for an underlying cause of vitamin D deficiency. Renal biochemistry should also be performed as chronic kidney disease may be a cause of renal osteodystrophy, secondary hyperparathyroidism and often vitamin D deficiency. Nephrotic syndrome may reduce levels of 25OHD via a reduction of vitamin D-binding protein.

Similarly liver function tests should be requested as severe liver disease causes vitamin D deficiency.

Q2. Risk factors for developing vitamin D deficiency and insufficiency include the following:

- Limited sun exposure; high risk groups include those with pigmented skin, the elderly, institutionalized, Asian women covering their bodies in clothing and people that tend to excessively use high factor sunscreens. For the elderly, the reduced vitamin D relates to less 7-dehydrocholesterol storage in the skin, reduced production rates of vitamin D and limited sun exposure. Dark skinned people have high melanin which absorbs UV radiation. Finally, sun-avoidance behaviors of fair skinned people are likely implicated
- Poor nutrition (e.g. in institutionalized, elderly and people who do not consume fish and dairy products)
- Type 2 diabetes mellitus (DM)
- Obese children and adults (body mass index [BMI] >30 kg/m²) and those with the metabolic syndrome
- Malabsorption (e.g. inflammatory bowel disease, celiac disease, cystic fibrosis, pancreatitis, short bowel syndrome and radiation enteritis). Bariatric surgery, especially biliopancreatic bypass, is a common cause of vitamin D deficiency nowadays. Gastrectomy and related procedures can also cause vitamin D deficiency.
- Drugs that induce the P450 enzymes (antiepileptic medication, rifampicin etc.), isoniazid (impairs 25-hydroxylation), and highly active antiretroviral treatment (HAART). Cytochrome P450 enzyme inducers are implicated because they accelerate degradation of vitamin D compounds
- Severe liver disease
- Renal causes – renal insufficiency, ageing, nephrotic syndrome
- Chronic illnesses requiring prolonged hospitalization
- Primary hyperparathyroidism.

Vitamin D deficiency is common and affects about 57% of adult hospitalized patients, 25–50% of nursing home or housebound residents, 44% of elderly ambulatory females and 23% of patients with hip fractures.

Q3. Before any discussion on the management of vitamin D deficiency, it is crucial to consider what the definition of a normal vitamin D level is. The “cut-off” value for a “normal” vitamin D level is somewhat arbitrary. Optimal vitamin D status, reflecting optimal bone health and calcium handling, is thought to relate to 25OHD values of ≥ 75 nmol/L (30 $\mu\text{g/L}$). According to an Australian and New Zealand position statement, optimal musculoskeletal health is achieved when the serum 25OHD level is ≥ 50 nmol/L at the end of winter (10–20 nmol/L higher at summer, to account for seasonal decrease). Similarly, the

Institute of Medicine (IoM) has recommended “for vitamin D, RDAs (recommended daily allowance) of 600 IU per day for ages 1–70 years and 800 IU per day for ages ≥ 71 years, corresponding to a serum 25OHD of at least 50 nmol/L, meet the requirements of at least 97.5% of the population”. The same group did not find convincing evidence that by achieving levels >75 nmol/L there was any additional benefit.

The two commonly available forms of vitamin D supplements are ergocalciferol (yeast derived vitamin D₂) and cholecalciferol (fish or lanolin derived vitamin D₃). Both are available for oral use, but ergocalciferol is available for intramuscular use as well. The oral route is generally preferred, unless there are concerns regarding concordance or malabsorption. Dosing frequency was thought to be less important than cumulative amount. However, emerging evidence from three large double-blind, placebo controlled, randomized-controlled trials in elderly, ambulant subjects suggests that infrequent high dose vitamin D administration being either ineffective or detrimental to falls and/or fractures.

The treatment regimen suggested for patients with vitamin D deficiency (25OHD ≤ 25 nmol/L) involves replacement doses of vitamin D; examples include vitamin D 10,000 IU daily or 60,000 IU weekly over 8–12 weeks (enough to restore vitamin D stores). This acute phase should be followed by a maintenance phase; examples of maintenance regimes would include vitamin D of 1,000–2,000 IU daily or 10,000 IU weekly or 40,000 IU monthly. For moderate-to-severe deficiency (25–50 nmol/L) 3,000–5,000 IU of vitamin D per day is recommended for 6–8 weeks. For the general adult population, vitamin D intakes of at least 600 IU and 800 IU per day are recommended for those aged ≤ 70 and >70 years, respectively. It is also recommended that intakes above 4,000 IU per day are to be avoided; this is a conservative estimate based on chronic disease outcomes, all-cause mortality and some emerging evidence documenting a detrimental effect on health when 25OHD levels exceed 125 nmol/L.

Q4. Vitamin D is involved in other cellular functions apart from skeletal health; the vitamin D receptor (VDR) is indeed found in all nucleated cells. About 3% of the human genome is under the control of 1,25(OH)₂D. Also, at least ten tissues outside the kidneys have 1 α -hydroxylase activity and can activate vitamin D (via autocrine and paracrine means). It is therefore possible that vitamin D has a wider spectrum of influence in cellular functions and systems and is of similar importance to other hormones that stimulate intracellular receptors.

Vitamin D affects muscle function; VDR is found in muscular tissue and proximal myopathy is not uncommon in vitamin D deficient states. In hereditary vitamin D deficiency, there is profound muscular weakness. Vitamin D supplementation is likely to improve muscular function; several meta-analyses have reported reduced frequency of falls in the elderly, but as previously mentioned there are some studies showing an absent or negative impact.

Low 25OHD is associated with increased prevalence of hypertension, type 2 DM, obesity and the metabolic syndrome, all of which are major risk factors for the development of cardiovascular disease. Some, but not all, interventional studies show a potential modest beneficial effect of vitamin D supplementation in the prevention of cardiovascular risk parameters such as type 2 DM and cardiovascular disease *per se*.

There is mounting evidence of an association (but not causation) between vitamin D deficiency and an increased risk of disorders of the immune system (from infections, such as tuberculosis [TB], to autoimmune conditions, such as type 1 DM, inflammatory bowel disease and multiple sclerosis), neoplastic disease and cognitive and neuropsychiatric illness.

Finally, vitamin D levels may influence mortality; most studies have reported increased mortality among people with vitamin D deficiency, whereas some have reported a J- or U-shaped relationship. A meta-analysis of RCTs reported that vitamin D supplementation resulted in a reduction of (all-cause) mortality.

Q5. Celiac disease. The triad of iron deficiency anemia, vitamin D deficiency and weight loss ("thin body habitus") should have triggered screening for celiac disease at an earlier stage. It is worth noting that celiac disease can present with malabsorptive features (such as anemia, vitamin and mineral deficiency and hypoalbuminemia) in the absence of gastrointestinal symptoms (such as diarrhea, dyspepsia, abdominal pain and bloating), especially in older children and adolescents. Therefore the absence of gastrointestinal symptoms should not preclude celiac screening. Similarly, celiac disease should be considered in the differential diagnosis of patients presenting with anemia.

On the other hand, celiac disease should be strongly considered in cases of osteomalacia refractory to treatment. Case reports have described cases of severe osteomalacia that caused symptoms for years (often in association with iron deficiency anemia also refractory to treatment) before the diagnosis of celiac disease was made; resolution of osteomalacia was reported on introduction of a gluten free diet.

At a microscopic level, celiac disease is an autoimmune condition where antibodies are directed against the gliadin part of gluten. This results in an inflammatory reaction characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. An as yet unidentified factor seems to trigger the disease in genetically predisposed individuals. It is associated with other autoimmune conditions and there is evidence for a strong genetic component (HLA genes).

At presentation with celiac disease, bone mineral density (BMD) is often already reduced. In a prospective study of newly diag-

nosed patients with celiac disease, BMD was reduced in 45% of subjects at both the left hip and lumbar spine. Duodenal villous atrophy (likely acting via malabsorption) was the main predictor of low BMD. When patients with celiac disease who were established and compliant with a gluten free diet were examined, a reduced BMD was observed at all sites investigated, but was more marked in the peripheral skeleton where it was significantly associated with high PTH (secondary hyperparathyroidism is more detrimental to the peripheral than the central skeleton). Nevertheless, treatment with a gluten free diet has been reported to improve the lumbar spine BMD.

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