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Vitamin D intoxication and severe hypercalcaemia complicating nutritional supplements misuse

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SUMMARY

This case report discusses an uncommon presentation of vitamin D intoxication and severe hypercalcaemia attributed to misuse of multiple nutritional supplements (>20 active agents). A review of this case, supported by accumulated literature, lends room to further public health safety discussions. The multisystemic clinical manifestations of vitamin D toxicity can be debilitating, hence the need to prevent its occurrence.

BACKGROUND

Patients often pursue unconventional or alternative therapy, the health outcomes of which remain controversial. An example is the use of over-the-counter nutritional supplements. Data on hypervitaminosis D or vitamin D toxicity are limited. This case report aims to contribute to the body of knowledge regarding this topic, which is of public health importance. Considering this topic, issues such as the potential interaction of over-the-counter and prescribed medications, market regulations of nutritional supplements, the misuse of these supplements in sports, and the potential harm among unsuspecting population groups (eg, children and the elderly) remain matters of public health significance that need to be addressed.

CASE PRESENTATION

A middle-aged male was referred to the hospital by a general practitioner after complaining of recurrent vomiting, nausea, abdominal pain, leg cramps, tinnitus, dry mouth, increased thirst, diarrhoea, and weight loss (28 lbs (12.7 kg)). The patient had experienced the complaints for nearly 3 months, with onset noticed approximately 1 month after commencing a vitamin regimen therapy on the advice of a private nutritionist. The patient had been taking the following daily: vitamin D 15 000IU (daily requirement: 10mcg (or 400IU per day)), vitamin K2 100mcg (daily requirement: 100–300 µg), vitamin C, vitamin B9 (folate) 1000mcg (daily requirement: 400 µg), vitamin B2 (riboflavin), vitamin B6, omega-3 2000mg twice daily (daily requirement: 200–500mg), selenium, bioactiver, zinc picolinate 15mg (daily requirement: 11mg), vitamin B3 50mg (daily requirement: 16mg), super-12 complex 1000 µg Lugol's iodine drops 15% one drop, borax powder (sodium tetraborate decahydrate), l-lysine powder 500cmg (daily requirement of l-lysine: 1000–1500 µg) with NAC (N-acetyl cysteine) 600mg (daily requirement: 600–1800mg), wobenzym N 400, astaxanthin softgel 18mg, magnesium malate 1000mg,

magnesium citrate 1480mg, pure taurine 1–2g per day, glycine powder 1g, high strength choline (+inositol) 100mg, calcium orotate 1000mg, probiotic, glucosamide and chondroitin complex, and sodium chloride.

The patient discontinued the intake of supplements on developing the above-listed symptoms, but his symptoms persisted. He had the following past medical history: bovine spinal tuberculosis, left vestibular schwannoma with hearing loss (operated by retro-sigmoid approach), hydrocephalus treated with a ventricular peritoneal shunt, bacterial meningitis, and chronic rhinosinusitis. On examination, he appeared cachectic with mild diffuse abdominal tenderness and no other significant finding on systemic examination. Vital signs were unremarkable.

INVESTIGATIONS

An initial set of blood tests performed by the patient's general practitioner revealed elevated serum calcium (albumin adjusted) (3.9mmol/L; reference (ref): 2.2–2.6mmol/L), acute kidney injury with serum creatinine (166µmol/L; ref: 64–106µmol/L), and urea of 13.4mmol/L; ref: 2.5–7.8mmol/L). He presented a serum magnesium level of 1.04mmol/L (ref: 0.7–1.0mmol/L) and serum vitamin D of >400nmol/L (ref: >50 (vitamin D sufficiency)). Further serial daily electrolytes results can be seen in [table 1](#).

No positive findings were detected on performing faecal bacteriology and parasitology tests. [Table 2](#) presents results pertaining to serial vitamin D levels, normal serum thyroid function, a normal early morning cortisol level, normal serial parathyroid hormone level, and a negative coeliac screen result for the patient's recurrent loose bowel.

Radiological imaging studies were performed to rule out malignancy as follows:

- ▶ MRI of head: No obvious relapsed/recurrent acoustic neuroma and no hydrocephalous.
- ▶ Positron emission tomography scan: An overt fluorodeoxyglucose (FDG)-avid malignancy was not identified. No overt sepsis focus was present. No systemic inflammatory process was identified.
- ▶ CT chest/abdomen/pelvis: Calcified nodules were seen bilaterally in the upper lobes and were more pronounced in the right apex. No new lung consolidation, collapse, or endobronchial lesions were detected. The central airways were patent. No lymphadenopathy or pleural or pericardial effusions were observed. There was no cardiomegaly or mediastinal mass.



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Table 1 Serial serum electrolyte studies

| | Test done with referring GP (pre-hospital) | Day 1 (of hospital stay) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
|---|--|--------------------------|-------|-------|--------|--------|-------|-------|-------|
| Amylase, U/L (0.0–125.0) | | | | | | 113 | | | |
| Calcium, mmol/L (2.2–2.6) | 3.9 ! | 3.2 ! | 3.1 ! | 3.1 ! | 2.9 ! | 2.7 ! | 3.2 ! | 2.7 ! | 2.7 ! |
| ALB, g/L (35.0–50.0) | | 34 ! | 32 ! | 33 ! | 29 ! | 30 ! | 33 ! | 32 ! | 31 ! |
| SCORCA, mmol/L (2.2–2.6) | | 3.3 ! | 3.2 ! | 3.2 ! | 3.1 ! | 2.9 ! | 3.3 ! | 2.8 ! | 2.9 ! |
| CRP, mg/L (0.0–10.0) | | 6.0 | 9.0 | 6.0 | 17.0 ! | 11.0 ! | | 6.0 | 4.0 |
| Sodium, mmol/L (133.0–146.0) | | 149 ! | 143 | 144 | 144 | 143 | 143 | 141 | 141 |
| Potassium, mmol/L (3.5–5.3) | | 4.1 | 4.1 | 4.2 | 4.2 | 5.0 | 4.3 | 4.0 | 4.0 |
| Creatinine, µmol/L (64.0–104.0) | 166 ! | 119 ! | 122 ! | 119 ! | 116 ! | 111 ! | 107 ! | 100 | 98 |
| EGFR, mL/min/1.73 m ² | | 57 | 55 | 57 | 59 | 62 | 65 | 70 | 72 |
| Potassium chloride, mmol/L (95.0–108.0) | | 107 | 102 | 105 | 108 | 105 | 105 | 105 | 106 |
| TBIL, µmol/L (0.0–29.0) | | 8 | 14 | 10 | | 7 | | | 15 |
| ALKP, U/L (30.0–130.0) | | 102 | 99 | 105 | | 91 | 106 | | 93 |
| ALT, U/L (0.0–70.0) | | 27 | 24 | 24 | | 22 | | | 25 |
| Magnesium, mmol/L (0.70–1.00) | 1.04 ! | 0.90 | 0.86 | 0.89 | 0.84 | 0.84 | | 0.85 | |
| Urea, mmol/L (2.5–7.8) | 13.4 | | | | | | | | |

The ! indicates an abnormal value but does not indicate whether this significant and is no measure of severity.

ALB, albumin; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; CORCA, Corrected calcium ; CRP, C reactive protein; EGFR, estimated glomerular filtration rate; GP, general practitioner; TBIL, total bilirubin.

Incidental pulmonary emboli were not observed. A notable paucity of intra-abdominal fat was observed. Focal hepatic lesions were not observed. A few calcified granuloma-type nodules were noted in the spleen. The kidneys and adrenal glands appeared normal. The prostate was enlarged. No significant bowel abnormalities were noted.

TREATMENT

The patient was admitted to hospital for 8 days and rehydrated using intravenous fluid therapy. He underwent daily blood tests to monitor the progress of care. Oral bisphosphonate therapy was also initiated. During the hospital stay, he underwent dietetic and pharmacy service reviews. He was discharged after adequate counselling sessions and was recommended follow-up with regular blood tests. Oral bisphosphonates and antiemetics were continued post-hospital discharge.

OUTCOME AND FOLLOW-UP

After continued oral bisphosphonate treatment, the patient was followed up 2 months after hospital discharge at an endocrinology outpatient clinic. His corrected serum calcium level had dropped to 2.6 mmol/L, while the serum vitamin D level remained >400 nmol/L. A plan to monitor both parameters on an outpatient basis was established to track the declining levels to reference limits.

DISCUSSION

Compared with studies among the general population, nutritional supplement misuse or abuse has been extensively documented and reviewed among athletes. The present case describes the misuse of supplements with more than 20 active agents in a middle-aged man, who was not a professional athlete, with resultant vitamin D intoxication and hypercalcaemia.

Table 2 Thyroid function test, serial vitamin D levels and parathormone levels, early morning cortisol levels, and coeliac screen results

| | Test done with referring GP (pre-hospital) | Day 1 (of hospital stay) | Day 2 | Day 3 | Day 7 |
|----------------------------|--|--------------------------|-------|--------|--------|
| TSH, mIU/L (0.40–5.00) | | | | 2.10 | |
| Free T4, pmol/L (9.0–19.0) | | | | 11 | |
| Vitamin D, nmol/L | | >400 ! | | >400 ! | >400 ! |
| PTH, pmol/L (1.6–7.2) | | 3.5 | 3.1 | | |
| Cortisol, nmol/L (140–690) | | | 506 | | |
| IgA TTG antibodies, U/mL | | | | | 0.5 |
| IgG TTG antibodies, U/mL | | | | | <0.1 |

Reference ranges for both IgA and IgG TTG antibodies: <7 U/mL, negative; 7–10 U/mL, equivocal; >10 U/mL, positive.

The ! indicates an abnormal value but does not indicate whether this significant and is no measure of severity.

GP, general practitioner; Ig, immunoglobulin; PTH, parathyroid hormone; T4, thyroxine; TSH, thyroid-stimulating hormone ; TTG, tissue transglutaminase.

Globally, there is a growing trend of hypervitaminosis D, a clinical condition characterised by elevated serum vitamin D3 levels. This term is often used interchangeably with vitamin D intoxication; however, some reports have described hypervitaminosis D as serum vitamin D3 level >250 nmol/L and vitamin D intoxication as levels >375 nmol/L. It has been reported that hypervitaminosis D is more likely to occur in females, children, and surgical populations.¹

Vitamin D is a fat-soluble vitamin in the body, along with vitamins A, E, and K. As a result, it undergoes widespread adipose tissue distribution. Recommended vitamin D requirements can be obtained from the diet (eg, wild mushrooms, oily fish), from sunlight through the skin (via ultraviolet-B-mediated conversion of 7-dehydrocholesterol), and are available as dietary supplements (in the form of pills). Given its slow turnover (half-life of approximately 2 months), during which vitamin D toxicity develops, symptoms can last for several weeks.²

The manifestations of vitamin D intoxication (in terms of symptoms and signs) are often multisystemic and are largely derived from its resultant effects of hypercalcaemia. Neuro-psychiatric features include drowsiness, confusion, apathy, psychosis, depression, stupor, and coma. Possible gastrointestinal features of vitamin D toxicity include anorexia, abdominal pain, vomiting, constipation, peptic ulcers, and pancreatitis. Hypertension and arrhythmias, such as shortened QT interval, ST-segment changes, and bradyarrhythmias, encompass cardiovascular signs of vitamin D intoxication. Renal system features of vitamin D intoxication include polyuria, polydipsia, dehydration, hypercalcaemia, nephrocalcinosis, and renal failure. Other features such as keratopathy, arthralgia, and hearing impairment or loss have also been reported with vitamin D toxicity.³

In a retrospective study assessing 38 children (aged 0.3 to 4 years) who had a diagnosis of vitamin D intoxication, Çağlar *et al* revealed that vomiting, loss of appetite, and constipation were the most common presentations among examined children (65.8%, 47.4%, and 31.6%, respectively). The authors also stated that the admission serum calcium level was 3.75 ± 0.5 mmol/L and the admission vitamin D level was 396 ± 110 ng/mL. Nephrocalcinosis was detected in 15% of the 38 cases reviewed.⁴

Lam *et al* discussed the prevalence of non-prescription medications and dietary supplements among 45 residents at two assisted-living facilities in the USA. The authors revealed that participants used a mean of 3.4 products. Product classes used by residents, based on frequency, were nutritional supplements (32% of products), followed by gastrointestinal products (17%), analgesics (16.3%), herbal products (14.4%), topical agents (12%), and cold/cough products (8.5%). The potential misuse of products was detected among 51% of these participants. Duplication (70%), potential drug/disease/food interactions (20.8%), and other inappropriate use (9.1%) were misuse patterns documented. Approximately three-quarters of these participants believed that consuming these products helped maintain their health. Nearly 50% of participants wanted more product information. Almost half of the residents received product information from friends and family. Only 40% of these participants turned to their physicians and nurses for information, whereas 11% asked pharmacists for advice.⁵

Known treatment modalities for vitamin D intoxication-related hypercalcaemia include discontinuation of vitamin D, hydration, establishing a low calcium-containing diet, steroids, and possible bisphosphonate therapy (agents that inhibit osteoclastic

activities, thereby reducing serum calcium). Radiologic exclusion of complications, including nephrocalcinosis, should be undertaken. Further regulatory measures and education of the populace can help curb the misuse of nutritional supplements to avoid untoward complications.⁶

Learning points

- ▶ Patients are encouraged to seek the opinion of their general practitioners regarding any alternative therapy or over-the-counter medications they may be taking or desire to initiate.
- ▶ Nutritional causes of hypercalcaemia should always be excluded early in patients before investigating alternate pathological causes.
- ▶ This case report further highlights the potential toxicity of supplements that are largely considered safe until taken in unsafe amounts or in unsafe combinations.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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