Vitamin D intoxication and severe hypercalcaemia complicating nutritional supplements misuse

Alamin Alkundi 1,2, Rabiu Momoh 1,3, Abdelmajid Musa 4, Nkemjika Nwafor 4

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 overt-the-counter nutritional supplements. Data on hyper-vitaminosis 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 15000IU (daily requirement: 400 μg), calcium orotate 1000mg, probiotics, glucosamine 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 findings 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) (3.9 mmol/L; reference (ref): 2.2–2.6 mmol/L), acute kidney injury with serum creatinine (166 μmol/L; ref: 64–106 μmol/L), and urea of 13.4 mmol/L (ref: 2.5–7.8 mmol/L). He presented a serum magnesium level of 1.04 mmol/L (ref: 0.7–1.0 mmol/L) and serum vitamin D of >400 nmol/L (ref: >50 nmol/L). Further serum 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 serum vitamin D levels, normal serum thyroid function, a normal early morning cortisol level, normal serum 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 hydrocephalus.
► 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.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Alkundi A, Momoh R, Musa A, et al. BMJ Case Rep 2022;15:e250553. doi:10.1136/bcr-2022-250553

© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.
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 1  Serial serum electrolyte studies

| Parameter                     | 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)     | 3.9                                       | 3.3                      | 3.1   | 3.1   | 2.9   | 2.7   | 3.2   | 3.2   | 2.7   |
| Calcium, mmol/L (2.2–2.6)    |                                           | 3.4                      | 3.5   | 3.3   | 2.9   | 3.0   | 3.1   | 3.2   | 3.1   |
| ALB, g/L (35.0–50.0)         |                                           | 3.3                      | 3.2   | 3.2   | 3.1   | 2.9   | 3.3   | 2.8   | 2.9   |
| SCORCA, mmol/L (2.2–2.6)     |                                           |                          |       |       |       |       |       |       |       |
| 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 (44.0–104.0) | 164  | 119  | 122  | 119  | 116  | 111  | 107  | 100  | 98   |
| EGFR, mL/min/1.73 m²         |                                           | 57                        | 55    | 57    | 59    | 62    | 65    | 70    | 72    |
| Potassium chloride, mmol/L (95.0–108.0) | 107  | 102  | 105  | 105   | 105   | 105   | 105   | 105   | 106   |
| TBIL, µmol/L (0.0–29.0)      | 8                                         | 14                        | 10    | 7     |       |       |       |       |       |
| ALKP, U/L (30.0–130.0)       | 102                                       | 99                        | 105   | 91    | 91    | 106   |       |       |       |
| ALT, U/L (0.0–70.0)          | 27                                        | 24                        | 24    | 22    |       |       |       |       |       |
| 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.

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

| Parameter                  | 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                                      |                          |       |       |       |
| 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. Neuropsychiatric 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, hypercalciiuria, 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 nmol/L. 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.2

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 kerb 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.

**Acknowledgements** The authors thank their patient for granting consent towards this publication and thereby promoting medical knowledge. We would also like to thank Editage (www.editage.com) for English language editing.

**Contributors** AA identified this case as being suitable for possible reporting. He was also involved in the planning, patient’s consenting process, acquisition of data, analysis and interpretation of data. RM was involved in the planning sessions for this case report. He was also involved in data analysis and manuscript development. He is the submitting author for this case report and will be managing correspondence on behalf of other co-authors. AM was involved in the planning sessions for this case report. He was involved in obtaining the patient’s consent for this report. He also participated in the acquisition of data for this report. NN was involved in the planning for this case report, as well as in manuscript development.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Consent obtained directly from patient(s)

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

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.

**ORCID iDs**

- Alkundi A http://orcid.org/0000-0003-0488-220X
- Rabiu Momoh http://orcid.org/0000-0001-8412-0912

**REFERENCES**

1. Sharma UK, Dutta D, Sharma N, et al. The increasing problem of subclinical and overt hypervitaminosis D in India: an institutional experience and review. *Nutrition* 2017;34:76–81.
2. Ellis S, Tsopanis G, Lad T. Risks of the “Sunshine pill” – a case of hypervitaminosis D. *Cin Med* 2018;18:311–3.
3. Marcinowksa-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, et al. Vitamin D toxicity - a clinical perspective. *Front Endocrinol* 2018;9:550.
4. Çağlar A, Tuğçe Çağlar H, Çağlar HT. Vitamin D intoxication due to misuse: 5-year experience. *Arch Pediatr* 2021;28:222–225.
5. Lam A, Bradley G. Use of self-prescribed nonprescription medications and dietary supplements among assisted living facility residents. *J Am Pharm Assoc* 2006;46:574–81.
6. Joshi R. Hypercalcemia due to hypervitaminosis D: report of seven patients. *J Trop Pediatr* 2009;55:396–8.
