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Case Report

Fallout Following Unproven Prophylactic Use of Exogenous Vitamin D for COVID-19

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Abstract: The ongoing COVID-19 (Coronavirus Disease of 2019) pandemic has devastated the human race socially, psychologically, mentally, medically, and economically. It has greatly impacted both developed and developing societies. No region of the earth has been spared of the adverse consequences of the disease. To date, the treatment of the disease has remained ill-defined. Additionally, there are no standard preventive regimens for the disease except for non-pharmacologic interventions and vaccinations. However, several unproven preventive medications are awash in social media including the use of chloroquine, Zinc, Ivermectin, Vitamin D, and so many others as prophylactic agents for COVID-19. This has led to the unregulated/unsupervised self-induced consumption of these unproven medications that may be deleterious to health if taken in excess. Herein is a case of a 24-year-old undergraduate who self-medicated with a high dosage of exogenous Vitamin D for unproven COVID-19 prophylaxis for 2 months. He developed Vitamin D Toxicity (VDT) and manifested with varying clinical (dehydration, hypertension, acute abdomen) and metabolic (hypercalcemia, hypokalemia, alkalosis, hyperphosphatemia, hypoparathyroidism, hypercalciuria, and crystalluria) consequences all related to VDT. However, hypercalcemia was the initiating metabolic disorder for all the clinical and the other metabolic derangements. He was admitted, managed accordingly, and discharged home in good clinical condition. Regulations and public health enlightenment of these unproven medications, including Vitamin D, for COVID-19 prophylaxis, should be prioritized to stem the deleterious effect of these agents. These measures will limit the current pandemic to a viral pandemic rather than a pandemic of drug misuse and overdose.

Keywords: Hypervitaminosis D, Vitamin D Toxicity, Hypercalcemia

1. Introduction

For more than two years, the entire world has been embroiled with the COVID-19 (Coronavirus Disease of 2019) pandemic which has brought enormous burden both socially, psychologically, mentally, and economically [1]. The pandemic has continued unabated in several continents despite all measures focused against it to date [2]. Currently, there are no effective treatment measures as regards the causative agent of the disease [3]. However, many experts have issued guidelines on its management strategies [4, 5].

Additionally, there are no widely accepted effective preventive regimens for the disease yet besides the non-pharmacologic practices and the current global vaccination approach [6]. However, several reports are awash in social media regarding many orthodox and non-orthodox regimens that could effectively prevent the disease [7, 8]. Drugs like Chloroquine, Zinc, Ivermectin, Vitamin D supplementation, and several others have been advocated without scientific proof/evidence [7, 8]. Most of these drugs

are not regulated and can easily be procured over-the-counter with attendant deleterious health consequences if consumed in excess [8, 9].

Herein is a case of a 24-year undergraduate, who self-medicated with high doses of exogenous Vitamin D for COVID-19 prophylaxis for about 2 months and subsequently developed Vitamin D Toxicity (VDT).

2. Case Report

A 24-year-old University undergraduate was rushed into the accident and emergency unit of a privately owned specialist hospital (Green Care Consultants Hospital, Port Harcourt, Nigeria) on account of severe abdominal pain and vomiting all of two hours duration before his presentatation. He affirmed to have been experiencing frequent micturition, excessive thirst, lower limb muscle weakness, constipation, anorexia, nausea, and vomiting for a few days before the onset of the presenting symptoms. He had no history of any granulomatous disease or lymphoma. On further questioning about recent drug history, he claimed to be have been on Vitamin D supplements (VDS) which he procured over-the-counter for two months until the onset of symptoms. When asked why the VDS for that long, he claimed to have lost his father to COVID-19 and a health worker suggested that taking the VDS will prevent COVID-19. He has been taking two Vitamin D soft gels (Pharm Care, United States of America) containing 10,000 IU vitamin D-3 [25(OH)D] twice daily for that long.

On general physical examination, he was found to be acutely ill-looking, afebrile (36.4°C), dehydrated, not pale, not cyanosed, not icteric with a respiratory rate of 28 cycles/minute, heart rate of 87 beats/minute, blood pressure was 140/90 mmHg, and he had a body mass index of 23.2 kg/m^2 (weight: 67kg; height: 1.7m). On further systemic physical examination, marked abdominal epigastric tenderness was noticed and it was observed that he had depressed neuromuscular excitability with reduced muscle power of both the upper and lower limbs. The other systemic physical examination findings were unremarkable. At this point, a provisional diagnosis of acute abdomen to rule out gastroenteritis and Vitamin D Toxicity (VDT) was made. He was immediately admitted into the male medical ward, stabilized medically and urgent laboratory investigations including an abdominal ultrasound scan (USS) were ordered.

The results of the initial set of investigations and their results are displayed in Table 1. Following the review of those initial results, a confirmed diagnosis of VDT was made associated with clinical (dehydration, hypertension, peptic ulceration) and several metabolic derangements including hypervitaminosis D, hypercalcemia, hypokalemia, metabolic alkalosis, hyperphosphatemia, hypoparathyroidism, hypercalciuria, and crystalluria (Table 1). However, hypercalcemia was believed by the managing team to be the cardinal initiating event of the VDT in this index case and requires emergency treatment. Hence, the immediate goal of emergency treatment was to slowly lower the plasma calcium to a level that is not immediately dangerous to the patient. To achieve this, the VDS was immediately discontinued and all calcium-containing diets withdrawn. Most of his management protocols were based on vigorous intravenous (IV) isotonic sodium chloride fluids for rehydration and to enhance renal function, IV furosemide to increase urinary calcium clearance and to avoid fluid overload, IV hydrocortisone to inhibit intestinal calcium absorption, enhance urinary calcium excretion, and inhibition activation of active vitamin D, and intranasal calcitonin to inhibit osteoclastic bone resorption.

Ant-hypertensive for the raised blood pressure and proton-pump inhibitors/antacids for the clinically suspected peptic ulceration were also offered with a dramatic response.

Table 1. *Results and interpretations of the initial investigations.*

Initial investigations	Results	RI	Interpretations
Plasma sodium, mmol/L	139	135 – 142	Normal
Plasma potassium, mmol/L	3.3	3.5 – 5.0	Low: Hypokalemia
Plasma bicarbonate, mmol/L	34	23 – 30	High: Indicates MA
Plasma chloride, mmol/L	103	98 – 107	Normal
Plasma urea, mmol/L	8.4	2.1 – 7.1	Elevated; indicates dehydration
Plasma creatinine, umol/L	115	80 – 115	Elevated but normal for age and sex
Plasma uric acid, mmol/L	0.4	0.21–0.45	Normal for age and sex
Total plasma calcium, mmol/L	3.30	2.15 – 2.55	High: Hypercalcemia
Free plasma calcium, mmol/L	2.1	1.15 – 1.33	High: Hypercalcemia
Plasma magnesium, mmol/L	0.7	0.6 – 1.0	Normal
Plasma phosphate, mmol/L	1.9	0.85 – 1.45	High: Hyperphosphatemia
Plasma albumin, g/L	35.0	35 – 55	Mild Hypoalbuminemia
AAPC, mmo/L	3.40	2.15 – 2.55	High: Hypercalcemia
Serum 25(OH)D, nmol/L	415	25 – 165	High: Hypervitaminosis D
Serum 25(OH)$_2$D, pmol/L	210	26 – 144	High: Hypervitaminosis D
Serum Intact PTH, ng/L	2.0	10 – 65	Low: Hypoparathyroidism
UCaER/24 hours, mmol/L	10.7	<7.50	High: Hypercalciuria
Urinalysis/Urine MCS	UCD	NA	Normal
Abdominal USS	Normal	NA	Normal

RI: Reference interval; MA: metabolic alkalosis; AKI: acute kidney injury; AAC: albumin-adjusted plasma calcium; PTH: parathyroid hormone; UCaER: Urine calcium excretion rate; MCS: urine microscopy, culture, and sensitivity; UCD: urine crystals detected; USS: ultrasound scan.

Table 2 highlights the daily trend of changes in laboratory parameters during the first 8 days of admission. By the 8th day, all clinical and laboratory parameters except for the albumin-adjusted plasma calcium (AAPC), the vitamin metabolites [25(OH)D; 1,25$(OH)_2$D], and intact parathyroid hormone (PTH) levels had normalized. He was discharged home on oral medications but continued weekly clinic visits for 8 weeks. By the 8th week of clinic follow-up, all laboratory parameters had normalized and he was counseled on the dangers of self-medication with unproven medications for COVID-19 (Table 3).

Table 2. *Trend of laboratory results in the first 8 days of admission.*

Investigations	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8(D)	Remark
Plasma sodium, mmol/L	139	136	137	137	136	138	137	136	Normal
Plasma potassium, mmol/L	3.3	3.5	3.6	3.5	3.7	3.5	3.8	3.6	Normalized
Plasma bicarbonate, mmol/L	34	33	32	33	30	29	28	27	Normalized
Plasma chloride, mmol/L	103	ND	ND	ND	ND	ND	ND	ND	-
Plasma urea, mmol/L	8.4	7.5	6.4	6.4	6.2	5.8	5.6	4.8	Normalized
Plasma creatinine, umol/L	110	105	99	90	84	77	68	63	Normalized
Plasma uric acid, mmol/L	0.40	0.30	0.40	0.20	0.30	0.40	0.30	0.20	Normalized
Total plasma calcium, mmol/L	3.2	3.2	3.1	3.1	3.0	2.9	2.7	2.4	Normalized
Free plasma calcium, mmol/L	2.1	2.0	1.8	1.7	1.5	1.4	1.3	1.1	Normalized
Plasma magnesium, mmol/L	0.7	ND	ND	ND	ND	ND	ND	ND	-
Plasma phosphate, mmol/L	1.9	1.8	1.7	1.6	1.5	1.2	1.1	1.1	Normalized
Plasma albumin, g/L	36.0	37	36	38	37	36	37	38	Normalized
AAPC, mmo/L	3.28	3.26	3.20	3.18	3.06	2.96	2.76	2.44	Normalized
Serum 25(OH)D, nmol/L	425	420	417	416	409	404	390	370	Still high
Serum 25$(OH)_2$D, pmol/L	230	222	213	210	210	207	201	180	Still high
Serum Intact PTH, ng/L	2.0	2.7	2.9	3.4	3.4	4.0	4.5	4.9	Still low
UCaER/24 hours, mmol/L	11.7	ND	ND	ND	ND	ND	ND	6.9	Normalized
Urinalysis/Urine MCS	UCD	UCD	UCD	UCD	UCD	UCD	UCD	NAD	-
Abdominal USS	Normal	ND	ND	ND	Normal	ND	ND	ND	-

D: discharged day; ND: test not done that day; NAD: no abnormality detected; AAPC: albumin-adjusted plasma calcium; PTH: parathyroid hormone; UCaER: Urine calcium excretion rate; MCS: urine microscopy, culture, and sensitivity; UCD: urine crystals detected; USS: ultrasound scan.

Table 3. *Trend of laboratory results during the 8 weeks follow-up after discharge from hospital.*

Investigations	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	Remark
Plasma sodium, mmol/L	136	138	137	139	136	135	136	136	-
Plasma potassium, mmol/L	4.0	4.1	4.0	4.1	3.9	4.0	4.1	4.0	-
Plasma bicarbonate, mmol/L	26	27	25	26	24	25	26	24	-
Plasma chloride, mmol/L	99	99	100	101	99	98	100	101	-
Plasma urea, mmol/L	3.9	4.1	4.0	4.3	4.2	4.1	4.0	4.6	-
Plasma creatinine, umol/L	64	62	59	61	60	61	63	62	-
Plasma uric acid, mmol/L	0.3	0.2	0.3	0.2	0.4	0.3	0.3	0.2	-
Total plasma calcium, mmol/L	2.3	2.4	2.3	2.3	2.4	2.3	2.2	2.3	-
Free plasma calcium, mmol/L	1.1	1.2	1.2	1.2	1.3	1.2	1.3	1.2	-
Plasma magnesium, mmol/L	0.7	0.6	0.7	0.8	0.6	0.7	0.6	0.8	-
Plasma phosphate, mmol/L	1.0	1.2	1.0	1.1	1.0	1.0	1.1	1.2	-
Plasma albumin, g/L	37	38	37	36	37	39	38	37	-
AAPC, mmo/L	3.36	2.44	2.36	2.38	2.46	2.32	2.24	2.36	Normalized
Serum 25(OH)D, nmol/L	365	330	305	284	273	261	245	232	Normalized
Serum 25$(OH)_2$D, pmol/L	170	166	164	159	151	145	124	116	Normalized
Serum Intact PTH, ng/L	5.2	5.9	6.3	6.7	7.3	8.1	12.6	17.4	Normalized
UCaER/24 hours, mmol/L	ND	ND	ND	ND	ND	ND	ND	Normal	-
Urinalysis/Urine MCS	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	-
Abdominal USS	ND	ND	ND	ND	ND	ND	ND	Normal	-

ND: test not done that day; NAD: no abnormality detected; AAPC: albumin-adjusted plasma calcium; PTH: parathyroid hormone; UCaER: Urine calcium excretion rate; MCS: urine microscopy, culture, and sensitivity; USS: ultrasound scan.

3. Discussion

We have reported a 24-year-old male who had acquired VDT following self-medication with exogenous Vitamin D supplement (VDS) for unproven prophylaxis for COVID-19. He had presented acutely with features initially suggestive of acute abdomen. Based on a prompt medical history review and clinical examination coupled with broad investigations offered, he was diagnosed with VDT in association with various metabolic consequences without delay.

All metabolic consequences observed in the index case seem to be related to hypercalcemia. The evolution of hypercalcemia secondary to VDT has been adduced to the

increased activity of the more potent/active vitamin D [1,25$(OH)_2$D] [10, 11]. These findings have been documented in similar case reports [12-15].

Hypercalcemia of moderate-severe degree is often associated with multi-systemic effects which were apparent in the index case [10]. The renal, neuromuscular, central nervous system (CNS), gastrointestinal (GIT), and cardiovascular (CVS) features recorded in the index case have been linked to hypercalcemia in previous reports [11]. In the renal system, hypercalcemia can induce frequency of micturition by blunting vasopressin effect on the tubules leading to dehydration/polydipsia, precipitation of calcium crystals in the urine (crystalluria), and hypokalemia in association with metabolic alkalosis by inhibiting renal potassium reabsorption [10, 11]. Acute kidney injury (AKI) is a frequent manifestation of VDT as reported in the literature [12-15]. However, for unknown reasons, the index did not present with AKI. This may be related to the early presentation of the index case to the hospital.

Raised free ionized calcium can depress neuromuscular activities which could manifest as muscle hypotonia. Nausea and vomiting are manifestations of hypercalcemic effects on the CNS [10]. Hypercalcemia stimulates gastrin secretion and can induce peptic ulceration in the GIT which can present as acute abdomen associated with constipation and abdominal pain [10]. In the CVS, hypercalcemia can evoke hypertension by increasing peripheral resistance through vascular smooth muscle contraction [10, 11]. These varied clinical features were observed in the index which underscores the deleterious effect of VDT-induced hypercalcemia.

The diagnosis of VDT-induced hypercalcemia entails exploration of medical and drug history, undergoing a comprehensive physical examination, and carryings out relevant diagnostic investigations and also investigations geared toward its complications as was done for the index case. VDT due to supraphysiologic increase in serum 25(OH)D (hypervitaminosis D) as in the index case, leads to the increased serum level of active 1,25$(OH)_2$D, hypercalcemia, hypercalciuria, and suppressed level of PTH [10, 11]. These laboratory features can be deployed as diagnostic parameters for VDT-induced metabolic consequences.

The treatment of VDT-induced hypercalcemia depends on the severity of hypercalcemia and the presence or absence of clinical features. As previously documented, hyper-rehydration, use of loop diuretics, use of steroids, and the use of calcitonin or bisphosphonates are all targeted management protocols for moderate-severe symptomatic VDT-induced hypercalcemia which were meticulously applied in the management of the index case [10]. However, the VDS should be discontinued and all calcium-containing diets withdrawn before initiating medical interventions as was done for the index case [11].

4. Conclusion

Herein is a case of a 24-year-old undergraduate who self-medicated with a very high dosage of Vitamin D supplement for COVID-19 prophylaxis for 2 months without medical supervision. He developed VDT and manifested with varying degrees of clinical and metabolic derangements. However, all the observed clinical and the other metabolic derangements were all related to the effects of hypercalcemia.

He was admitted, managed accordingly, and discharged home in good clinical condition including during the follow-up periods.

Regulations and public health enlightenment of these unproven medications for COVID-19 prophylaxis should be prioritized to stem the deleterious effect of these agents. These measures will limit the current pandemic to a viral pandemic rather than a pandemic of drug misuse and overdose.

Consent

Written informed consent was obtained from the patient and it is available for review on reasonable request from the corresponding author.

Conflicts of Interest Statement

The authors declare that they have no competing interests.

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