Vitamin D Toxicity in A Pediatric Toxicological Referral Center: A Cross-Sectional Study from Iran

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Abstract

**Background:** Vitamin D is an essential element for body health whose supplements are generally administered to prevent vitamin D deficiency. Since these supplements are available at homes, vitamin D toxicity may happen in children.

**Methods:** All children younger than 12 years who presented to the pediatric emergency department of Loghman Hakim Hospital, Tehran, Iran with history of ingestion of vitamin D supplements more than 1500 IU/day were enrolled. Patients’ demographic data, on-presentation signs and symptoms, laboratory findings, treatments given, and outcome were evaluated.

**Result:** Fifteen patients presented during the study period. Their mean age was 46.53 ±10.14 months and 12 (80%) were girls. All of them had unintentionally ingested vitamin D. Mean ingested dose was 406700.7±227400.1 IU. In eight patients (53.3%), 25 Hydroxyvitamin D level was more than 100 ng/mL. One patient experienced hypercalcemia while all of them were asymptomatic and discharged without complications. There was no significant difference between patients with and without high levels of 25 OH vitamin D regarding lab tests, toxicity course, and outcome.

**Conclusion:** It seems that acute vitamin D toxicity is a benign condition in our pediatric population which may be due to high prevalence of vitamin D deficiency in Iran.

Introduction

Vitamin D is a fat-soluble pro-hormone. The major source of vitamin D is its skin synthesis by sun-light exposure(1, 2). Also, some foods such as mushrooms may contain small amounts of vitamin D(3, 4). This vitamin has a crucial role in the health of the musculoskeletal system. Furthermore, vitamin D has beneficial effects on cardiovascular, respiratory, and immune systems(4-12).

Due to various issues including heavy clothing, air pollution, reduced exposure to direct sunlight, inadequate nutrition, and lack of access to vitamin D-rich foods especially among children, vitamin D deficiency is a common health problem in our country. Thus, consumption of vitamin D containing supplements is encouraged in Iran during the recent years making them more available and prone to unintentional poisonings in children although the frequency of poisoning with these supplements is still low compared to other poisonings in them(13-17). Vitamin D toxicity may also happen as a result
of inappropriate dose administration by physicians or errors in manufacturing or unlicensed vitamin D preparations (18-22).

Daily recommended dose of vitamin D supplements is reported to be 400 IU in infants, 600 IU in people younger than 70 years of age, and 800 IU in people over 70 (23-25). Since studies in this regard are lacking in children, we aimed to assess all children with vitamin D toxicity referring to a tertiary referral center of toxicology during a year.

Materials And Methods
In a retrospective descriptive cross-sectional study performed in Loghman Hakim Hospital between March 2018 and March 2019, all children younger than 18 years who presented to the pediatric emergency department with the history of vitamin D supplements ingestion of more than 1500 IU in a single occasion were enrolled in this study. Written informed consents were taken from the patients’ parents before case enrolment. After taking history and physical examination, blood tests were performed six hours post admission.

All demographic data (age, sex, weight, amount of vitamin D ingested), vital signs (blood pressure, heart rate, dehydration signs), symptoms on presentation (nausea, vomiting, abdominal pain, loss of appetite, irritation, headache, constipation, polyuria, polydipsia, fever, and growth retardation), laboratory findings (25 OH vitamin D, serum calcium, phosphate, alkaline phosphatase, urea, creatinine, urine Ca/Cr), treatments given (close observation, hydration, steroid, bisphosphonate), and outcome (recovery, death) were recorded and analyzed using statistical package for social sciences (SPSS) version 18.

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.1216).

Results
Fifteen patients presented during the study period. Their mean age was 46.53 ±10.14 months (range; 24 to 60 months). Twelve patients (80%) were girls (male/female ratio was 1:4).

All of them had unintentionally ingested oral 50000-IU vitamin D pearls. Mean ingested dose of vitamin D was 8.13±4.54 pearls (range; 3 to 18 pearls) or 406700.7±227400.1 IU (range; 150000 to 900000
IU). One patient had serum calcium level of 12.5 mg/dL. She had ingested ten 50000 IU vitamin D pearls. After six hours of hydration, her serum calcium was normal. Patients' information is mentioned in Table 1.

**Table 1- Vitamin D dose and biochemical features in individual patients**

| cases | Vit D dose (<50000 IU) | Ca (mg/dl) | 25 OH vit D (ng/ml) |
|-------|------------------------|------------|---------------------|
| 1     | 10                     | 12.5       | 10                  |
| 2     | 3                      | 10.5       | 35.5                |
| 3     | 4                      | 9.5        | 48.3                |
| 4     | 5                      | 8.7        | 55                  |
| 5     | 8                      | 10.2       | 56                  |
| 6     | 4                      | 10.5       | 65                  |
| 7     | 8                      | 10.5       | 97.28               |
| 8     | 17                     | 8.9        | 102                 |
| 9     | 3                      | 10.4       | 104                 |
| 10    | 6                      | 9.7        | 107                 |
| 11    | 10                     | 10.4       | 111                 |
| 12    | 7                      | 10.1       | 120                 |
| 13    | 9                      | 10.2       | 120                 |
| 14    | 18                     | 9.8        | 138                 |
| 15    | 10                     | 9.3        | 500                 |

Eight (53.3%) cases had 25 OH vitamin D levels more than 100 ng/mL. Mean serum 25 OH vitamin D was 113.33±113.59 (range; 10 ng/mL to 500 ng/mL). There was no significant difference between variables in patient with and without high level of 25 OH vitamin D. The most important data is mentioned in Tables 2 and 3.

**Table 2- Lab parameter features in patients (Mean±SD).**

| group            | 25OH vit D (ng/ml) | Ca (mg/dl) | P (mg/dl) | ALK-P (U/L) | Cr (mg/dl) | Urea (mg/dl) | Ca/Cr Urine ratio |
|------------------|--------------------|------------|-----------|-------------|------------|--------------|-------------------|
| 25OH vit D <100 ng/ml | Mean 52.44         | 10.34      | 4.8       | 478.0       | .38        | 26.7         | .20               |
|                  | Std. Deviation 26.74 | 1.16       | .72       | 31.11       | .30        | 10.79        | 23.7143           |
| 25OH vit D >100ng/ml | Mean 162.86       | 9.85       | 4.73      | 546.0       | .63        | 23.7143      | .17               |
|                  | Std. Deviation 136.71 | .53        | .581      | 38.5        | .14        | 6.12955      | .19               |
| Total            | Mean N=7 111.3     | 10.08      | 4.75      | 526.6       | .56        | 24.60        | .18               |
|                  | Std. Deviation N=15 | 113.59     | .88       | 47.43       | .21        | 7.28         | .18               |

**Table 3- Demographic features in patients (Mean±SD).**

| group          | AGE (month) | Vit D dose (<50000 IU) | BP systolic (CmH2O) | HR Beat/min | Weight (Kg) |
|----------------|-------------|------------------------|---------------------|-------------|-------------|
| 25OH vit D <100ng/ml | Mean 46.29  | 6.0                    | 97.85               | 109.71      | 16.5        |
|                | Std. Deviation N=7 | 12.82 | 2.64 | 6.36 | 5.05 | 3.40 |
| 25OH vit D >100ng/ml | Mean 46.75 | 10.0                  | 96.25               | 99.37       | 15.81       |
|                | Std. Deviation N=8 | 8.04 | 5.18 | 7.90 | 8.63 | .59 |
| Total          | Mean N=15   | 46.53                  | 8.13                 | 97.0        | 104.2       |
|                | Std. Deviation | 10.14 | 4.54 | 7.02 | 8.76 | 2.29 |
None of them had abnormal signs and symptoms; 46.3% were observed for eight hours and received activated charcoal. In addition, 53.3% were hospitalized and treated by activated charcoal and fluid therapy. All cases were discharged without any complications. All patients were taking vitamin D regularly. We recommended them to discontinue consumption of vitamin D supplements and keep low vitamin D diet at least for one month and recheck 25 OH vitamin D levels. Unfortunately, most of the patients did not refer for follow-up check-ups.

**Discussion**

Although upper tolerable intake level is various in different age groups, maximum tolerable and safe dose of vitamin D is 1000 IU/day in infants younger than 6 months, 1500 IU/day in children older than 6 months, and 10000 IU/day in adults(24-27).

Vitamin D concentration is measured by 25- hydroxy vitamin D level because it has longer half-life compared to 1,25 OH vitamin D(24, 28). Although there are different ranges of 25 OH vitamin D levels in several studies, the optimal level of 25 OH vitamin D is 30-100 ng/mL. Based on the normal range provided by the kit manufacturer, 25OH vitamin D less than 10 ng/mL is deficient, while levels 11-30 ng/ml, 31-100, and over 100 ng/mL are insufficient, sufficient, and vitamin D toxicity, respectively(29). The most important laboratory findings in vitamin D toxicity are high levels of 25 OH vitamin D and hypercalcemia(28).

Patients with vitamin D toxicity may be asymptomatic or have signs or symptoms including nausea, vomiting, dehydration, abdominal pain, loss of appetite, irritation, headache, constipation, polyuria, polydipsia, fever, and growth retardation. In fact, most of the patients’ symptoms are compatible with serum calcium level. Differences between symptoms and laboratory parameters in patients may be related to gastrointestinal absorption, vitamin D binding protein, vitamin D storage, and diet(18). All of our patients were asymptomatic and it might be due to upper tolerable intake level differences in various groups and high prevalence of vit D deficiency among Iranian children. Also further studies need to do in this regard.

Vitamin D deficiency is estimated to be approximately 35% in boys and 65% in girls in Iranian pediatric population. Vitamin D insufficiency rate is reported to be 31%. It shows that vitamin D
deficiency is a critical health problem among Iranian children. Recently, the prevalence of vitamin D toxicity has increased because of more availability of its supplements (30, 31).

This study is one of the first ones about vitamin D toxicity in Iranian children. Although there are various studies in this field from around the world, most of them have been performed on adults. It describes all cases of pediatric vitamin D toxicity that had referred to a major center for treatment of poisoned children in Tehran, Iran within a year.

All of our patients were between 24 and 60 months of age and had unintentionally ingested pearl form (50000 IU) of vitamin D. In fact, accidental poisoning in this age is more common. In the majority of studies, poisoning happens more frequently in boys, but in this study, poisoning was more common among girls (32, 33). This cannot be generalized to the whole population because our study is only a case series in one center during a year.

Some studies have demonstrated higher frequencies of symptoms and hypercalcemia in their patients compared to ours reporting hypervitaminosis D in adults and a few children, whereas in this study more than half of our cases (53.3%) had high levels of 25-OH vitamin D and just one had hypercalcemia without any symptom who was treated by hydration. It may be as a result of high prevalence of vitamin D deficiency in Iranian children or be due to early laboratory parameters assessment mandating re-checking of the lab tests in consecutive hours post admission (16, 34-40).

We found only one study that had reported a patient with vitamin D intoxication in Iranian children. Faraht reported a 50-day-old girl in Imam Reza Hospital, Mashhad, Iran, with respiratory distress and hypotonia who had plasma creatinine of 1.4 mg/dL, BUN of 11 mg/dL, serum calcium level of 18.3 mg/dL, and 25-OH vitamin D of 75ng/mL which was higher than normal range. It was due to the constant usage of premature formula with high dose of vitamin D drop supplement (800 units /day) (41).

Although there is not any reliable data on vitamin D toxicity among Iranian children, Spiller et al have reported there were 25397 human exposures to vitamin D in USA in 2000-2014. It explains that between 2005 and 2011, vitamin D toxicity increased 1600%. There was 0.02% morbidity without mortality (42). These results indicate that we need further researches in this field and vitamin D
toxicity and vitamin D supplement intake should be more cautiously evaluated in children (38, 43-45).

Conclusion
It seems that acute vitamin D toxicity is a benign condition and has a good prognosis in Iranian pediatric population maybe due to high prevalence of vitamin D deficiency in Iranian children. Owning to insufficient and limited studies among children, we need more studies in this regard.

List Of Abbreviations
Vitamin D: Vit D
25-Hydroxy vitamin D: 25OH vitamin D
International Unit: IU
Blood urea nitrogen: BUN
milligrams per deciliter: mg/dl
Nanograms per milliliter: ng/ml
Alkaline phosphatase: ALK-P
Calcium: Ca
Phosphor: P
Heart Rate: HR
Blood Pressure: BP

Declarations
Ethics approval: This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.1216).

Consent for publication: Not applicable
Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.
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