RESEARCH ARTICLE

Inappropriate supplementation of Vitamin D can result in toxicity: a cross-sectional study of paediatrics population

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Abstract

Objective: To evaluate children with suspected or definite hypervitaminosis D with respect to prevalence, clinical manifestations and pharmacological aspects.

Method: The retrospective cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, and comprised medical records from January 1 to December 31, 2018, of children aged <18 years with 25-hydroxyvitamin D levels >50ng/ml. Clinical and pharmacological data was retrieved. Data was analysed using SPSS 23.

Results: Of the 118,149 subjects visiting the clinical laboratory during the study period, children tested for serum 25-hydroxyvitamin D levels were 16,316(13.8%) who had a median age of 9.78 years (interquartile range: 10.2 years). Children who registered for consultation were 2720(16.6%), and, out of them, 602(22%) had serum 25-hydroxyvitamin D >50ng/ml. The median 25-hydroxyvitamin D levels and age were 70.1ng/ml (interquartile range: 100ng/ml) and 3.1 years (interquartile range: 17.93 years), respectively, and 345(57.3%) of them were boys. Children supplemented with vitamin D were 197(33.1%) and 193(97.9%) of them were prescribed by physicians. Mega-doses were taken by 68(34.17%), while the remaining had used various combinations in syrup or tablet forms. Commonly prescribed mega-doses were 600,000IU 30((44.1%) and 200,000IU 31(45.5%) injections of vitamin D. The primary indications were pains/aches in 51(25.8%) cases, developmental delay 50(25.3%), and vitamin D deficiency 49(24.8%). The main symptoms of hypervitaminosis D or toxicity were abdominal pain 27(13.7%) and constipation 31(15.7%).

Conclusion: Children should be given vitamin D supplements with caution as prolonged supplementation and repeated mega-doses can result in toxicity which may cause serious consequences.

Keywords: Vitamin D deficiency, Vitamin D supplements, Hypervitaminosis D, Vitamin D toxicity.

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Introduction

Vitamin D insufficiency (serum 25-hydroxyvitamin D [25OHD] 15-29ng/ml) and deficiency (serum 25OHD <15ng/ml) is a common problem in the paediatric age group worldwide, with prevalence ranging 9-61% in the United States[1]. A study on Asian children showed that 51% had deficiency (<20ng/ml), and another 39% of children had vitamin D insufficiency (20-30ng/ml)[2]. The increased prevalence of vitamin D deficiency and subsequent increased awareness and potential benefits of vitamin D in combatting chronic diseases provoked a significant increase in prescribing pharmaceutical supplements, prolonged and disproportionate intake of which may lead to toxicity[3]. Furthermore, reports of increasing hypervitaminosis over time are now reported[4].

The 25OHD level of >100ng/ml is considered hypervitaminosis, whereas a level of >150ng/ml is toxic. There may be hypercalcaemia, hypercalciuria, hyperphosphataemia with very low or undetectable parathyroid hormone (PTH) activity being present[5]. The clinical manifestations of hypervitaminosis D are non-specific and include confusion or difficulty in concentration, apathy, recurrent vomiting, abdominal pain, constipation, polyuria, polydipsia and dehydration. In vitamin D-deficient areas, it has been noted that practitioners are more inclined towards prescribing vitamin D for body aches and pain of nonspecific nature[6]. The risk of vitamin D toxicity has been further increased by the practice of self-medication with over-the-counter (OTC) vitamin D supplements[7,8]. Bleizgys A et al. reported hypervitaminosis in 1169 (12.2%) cases and 72 of toxicity in children aged 0-9 years[9].

The recommended daily allowance (RDAs) of vitamin D defined by the American Institute of Medicine (IOM) differs for each age group. In infants, RDA is 400IU per day, in children >1 year of age, 600IU, for toddlers and adolescents 2000IU, while 1000IU and 1500IU have been

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recommended for infants <6 months and >6 months of age, respectively.[10,11] Administration of similar dosages to infants as given to children or adults and inconsistent monitoring during supplementation pose a significant risk of toxicity[12,13].

The severity of vitamin D toxicity and its adverse health effects needing a prompt diagnosis is not fully recognized. The only way to prevent this condition is by making healthcare providers aware about the toxic potential of vitamin D doses if prescribed in high doses. The cautious prescription of vitamin D supplements accompanied with close observation of people during supplementation is the key to preventing this condition[14].

The current study was planned to determine the frequency of vitamin D toxicity, the clinical features associated with toxicity, and to identify the pharmacological factors leading to hypervitaminosis D in paediatric patients.

Materials and Methods

The cross-sectional study was conducted at Aga Khan University (AKU), Karachi. Karachi is the largest city of Pakistan with ample sunlight throughout the year. The integrated laboratory information system extracted data of serum 25OHD performed at the AKUH clinical laboratory from January to December 2018. Initial results of only paediatric patients aged <18 years were included, while repeat results were excluded. All identifiers were removed, and study identifications (IDs) were generated in order to maintain confidentiality. Exemption was obtained from the institutional ethics review committee.

Serum 25OHD had been analysed using Liaison immunoassay analyser (Diasorin Diagnostics, Italy) by electrochemiluminescence immunoassay methodology. For quality control purposes, three-level controls were analysed, while samples collected from the College of American Pathologists (CAP) were analysed thrice a year for proficiency testing. The assay was linear over an analytical measurement range of 4-150ng/ml with inter-assay precision or coefficient of variation 20%. The cut-offs of 25OHD for suspected high (≥50ng/ml), hypervitaminosis D (≥100ng/ml) and toxicity (≥150ng/ml) used were based on IOM recommendations[10,11]. Medical records of children registered at AKUH for clinical consultation (both inpatients and outpatients) who had serum 25OHD levels >50ng/ml were reviewed for demographic details, clinical features of vitamin D intoxication, biochemical laboratory, radiological findings and pharmacological risk factors of vitamin D intoxication. Medical record files were reviewed manually for extracting clinical and supplementation history, while laboratory and radiological histories were extracted from the electronic medical records.

Data was analysed using SPSS 23. The normality of quantitative variables was assessed using Kolmogorov-Smirnov normality test. For categorical variables, frequencies and percentages were calculated, while median and interquartile range (IQR) were calculated for numerical data. The data was stratified according to age, 25OHD status, use of vitamin D supplement, indications of prescription and symptoms.

Results

Of the 118,149 subjects visiting the clinical laboratory during the study period, children tested for serum 25OHD levels were 16,316(13.8%) (Figure), who had a median age of 9.78 years (IQR: 10.2 years). Children who registered for consultation were 2720(16.6%), and, out of them, 602(22%) had serum 25OHD >50ng/ml. The median 25OHD levels and age in this group were 70.1ng/ml (IQR: 100ng/ml) and 3.1 years (IQR: 17.93 years), respectively, and 345(57.3%) of them were boys.

Children supplemented with vitamin D were 197(33.1%) and 193(97.9%) of them were prescribed by physicians. The primary indications were pains/aches in 51(25.8%) cases, developmental delay 50(25.3%), vitamin D deficiency 49(24.8%), recurrent chest infections 28(14.2%), failure to thrive 23(11.6%), rickets 17(8.6%), short stature 6(3%), bowing legs 5(2.5%), accidental fracture 3(1.5%), others 23(11.6%). The 'others' category included pubertal issues, seizures, liver disease, thyroid disease, diabetes, leukaemia, Down Syndrome and migraine. Medical records showed that serum 25OHD levels were checked in only 82(41.6%) of the 197 subjects before initiating supplements with median 25OHD levels of 15ng/ml (IQR: 5015ng/ml).

Mega-doses were taken by 68(34.17%), while the remaining had used various combinations in syrup or tablet forms. The median age for the supplementation group 3.7 years (IQR: 9.3-1.9 years) was higher than for the no supplementation group 2.8 years (IQR: 6.3-1.6 years) (p=0.006). Age distribution for vitamin D supplements showed that most 116(59%) were aged 5 years (Table 1).

Commonly prescribed mega-doses were 600,000IU 30(44.1%) and 200,000IU 31(45.5%) injections of vitamin D. The 600,000IU supplements were mainly administered intramuscularly 24(80%) and rest were given orally. Dose 200,000IU was administered orally to 17(55%) and the rest were given intramuscularly.

Overall, 193(97.9%) subjects were prescribed by physicians. The median cumulative dose for vitamin D

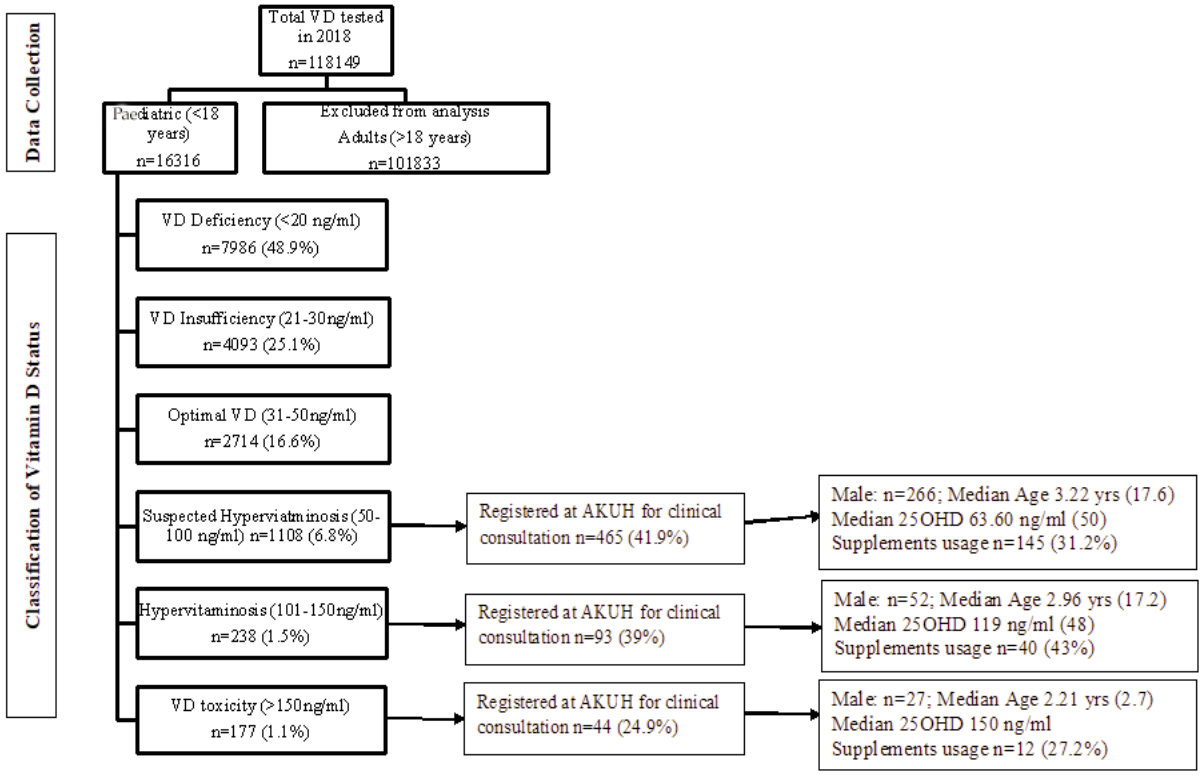

Figure: Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study.[24]

Table-1: Age distribution of patients with serum 25OHD >50 ng/mL (n=197)..

Age Categories n=197	) n	On Vitamin D supplements Mega dose* or syrups	oral tablets ng/ml	Serum Vitamin D levels ng/ml Median (IQR)
1-5 years	116	29	87	84.2 (99.7)
5-10 years	36	17	19	77.2 (99.9)
11-18 years	45	22	23	63.2 (99.9)
Total	197	68	128)	76.2 (99.9)

25OHD: 25 hydroxyvitamin D, IQR: Interquartile range.
*Patients were on 200,000 and 600,000 units 25OHD supplements.

Table-2: Distribution of the subjects based on duration of vitamin D supplementation (n=197).

Duration of Vitamin D supplementation	n (%)	Cumulative Vitamin D consumed (IU) Median (IQR)	Serum Vitamin D levels (ng/ml) Median (IQR)
<1 month	3 (1.5)	800000 (2700000)	101 (79.3)
1-3 months	58 (59.3)	132000 (1220400)	86.5 (99.7)
3-6 months	68 (34.4)	146000 (725200)	71.7 (99.9)
6-9 months	8 (4)	292000 (745200)	79.1 (55.8)
≥1 year	31 (15.6)	146000 (2385600)	64 (99.6)
Once	29 (14.7)	600000 (1387000)	83.9 (98.5)

25OHD: 25 hydroxyvitamin D, IQR: Interquartile range, IU: International units.

supplements taken by the patients was 200,000IU (IQR: 2996400IU). The median time of supplements intake was 6 months (IQR: 23.97 months). The patients took mega-dose supplements mostly once 29(42.6%), while vitamin D supplements in oral drop or tablet forms were mostly used for <6 months (Table 2).

In children who were prescribed vitamin D supplements, the main clinical features at presentation were abdominal pain 27(13.7%), constipation 31(15.7%), decreased appetite 6(3%), vomiting, difficulty in concentration and polyuria 2(1%) each, and apathy 1(0.5%). The rest had no symptoms at the time of presentation. Median serum calcium in subjects with serum 25OHD levels >50ng/ml was 9.8mg/dl (IQR: 7.2mg/dl. Serum calcium levels were high in 11(16.9%) children. Among children with hypercalcaemia, 1(0.5%) was symptomatic having abdominal pain.

Discussion

The growing awareness of the beneficial effects of vitamin D in various diseases has led to increased prescriptions by physicians that can lead to toxicity [14,15]. Due to a wide therapeutic index, it may happen at excessively high doses and if the supplements are taken for prolonged periods[16,17].

In the current study, the frequency of suspected hypervitaminosis, i.e. 25OHD level >50ng/dl, was found to be 9.3%, and out of these, 39.5% patients were registered at the AKUH for clinical consultation. Definite hypervitaminosis D and intoxication were found in 1.5% and 1.1%, respectively. This frequency is much less than 7.2% hypervitaminosis D (25OHD >100mg/dl) found among the paediatric population in a study conducted in India[4]. In another study at a toxicology centre in Tehran, 15 cases brought to the emergency department over a period of one year, had ingested >1500IU of vitamin D in a single dose, and mean dose of vitamin D ingestion was 406701±227400IU. Four out of the 15 patients were suspected of having vitamin D toxicity, seven had definite hypervitaminosis and one had intoxication[18]. A US study reported that the frequency of subjects with 25OHD levels >50ng/ml and >100ng/ml was 8.4% (n=1714) and 0.2% (n=37), respectively. Out of all the subjects tested between January 2002 and December 2011, 3.8% were children aged <18 years[19].

The results for self-medication with readily available vitamin D supplements was considerably much less than expected in the current study, as 97.9% of the supplements were prescribed by physicians mainly for the complaints of unspecified body-aches, developmental delay, failure to thrive, etc. Similar findings were reported earlier[20]. The common manifestations of hypervitaminosis D reported in the current study were abdominal pain, constipation, decreased appetite and vomiting, while polyuria was noted only in a few children. All the features except for persistent hypertension are comparable to the symptoms noted in literature.[20,21] Another study conducted in Turkey reported that children with vitamin D intoxication presented with symptoms, such as vomiting, anorexia, weight-loss, dehydration, polyuria and constipation[22].

In the current study, vitamin D supplementation could only be ascertained in 33.1% subjects (n=197). One reason for this can be that the patients were being followed up elsewhere. Children in the study were prescribed 200,000IU of mean cumulative dose of vitamin D supplements (range: 3600 to 30,00,000IU) for 8-24 weeks. Moreover, all of the prescribed preparations were cholecalciferol, as the ergocalciferol preparations are less readily available in Pakistan. Physicians use mega-doses because of their easy availability in markets, compliance issues in long-term treatment and low cost.

Furthermore, the lack of awareness regarding the deleterious effects of vitamin D supplementation can also be a cause. Vitamin D supplementation, when given within recommended doses, rarely lead to intoxication. Studies have reported that doses as little as five times the RDA can cause vitamin D intoxication in the paediatric age group[16,22].

Acute intoxication as a result of mega-dose and parental dosing errors have been reported[18,20]. Therefore, at the time of prescription, physicians should inform parents about the symptoms of intoxication. Ideally, clinical, radiological and biochemical investigations should be carried out before prescribing mega-doses for treating vitamin D deficiency. Currently, this practice is not being followed, as the cost of the treatment, medical consultation or laboratory investigations is paid out-of-pocket by the patients and the mega-dose cost is considerably less than the laboratory or radiological investigations. Hence, there is a need to develop a clinical proforma that may identify patients at risk of developing intoxication if given mega-dose supplements.

The dosage of vitamin D and calcium for the treatment of nutritional rickets or vitamin D-deficient rickets recommended by the Global Consensus group is at least 2000IU/day of vitamin D2 or D3 in those aged <12 months, 3000-6000IU/day in those aged 1-12 years, and 6000IU/day in those aged >12 years for 3 months. Single high dose of vitamin D can be given in areas with limited resources[23]. Alternatively, stoss therapy can also be given, which recommends 50,000IU for those aged 3-12 months, 150,000IU for children aged 1-12 years, and 300,000IU for children aged >12 years. Oral administration is the preferred route in stoss therapy as it causes rapid correction of 25OHD levels and daily intake of at least 500mg/day of calcium as supplements or through diet is also advised[23].

The limitations of the current study include the unavailability of data related to serum calcium and parathyroid hormone levels for all the subjects, and the indication for serum 25OHD testing was unknown. Another important limitation was that the study could only identify that one-third of the patients had received supplements. It was probably because the patients were being followed up elsewhere. Moreover, the sub-

specialties of the physicians prescribing supplements was not known. Also, dietary factors, such as consumption of fortified milk intake, dairy products, calcium intake and sunlight exposure, could not be assessed. Finally, subjects who manifested symptoms of hypercalcaemia were not followed up till the final outcome.

Conclusion

Varying clinical practices of physicians prescribing vitamin D supplements were noted, indicating the need to develop contextual guidelines. The prescription of excess vitamin D on clinical grounds without radiological evidence or serum 25OHD levels measurement led to unnecessary treatment that resulted in high vitamin D levels in the subjects.

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Conflict of Interest: None.

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