Original Article

PARADIGM SHIFTS IN VITAMIN D TESTING AND DIAGNOSIS: A DECADE-LONG OBSERVATIONAL STUDY

Hafsa Majid, Nawazish Zehra, Lena Jafri, Muhammad Abbas Abid, Siraj Muneer, Aysha Habib Khan

Aga Khan University, Karachi Pakistan

ABSTRACT

Objective: Awareness about vitamin D deficiency has linearly increased over the years. Lack of clear guidelines regarding optimum dosage and inadvertent use of higher doses can lead to toxicity. This study was done to evaluate the changes in trends of vitamin D testing and status of serum levels of 25-hydroxy vitamin D (25-OHD) submitted for analysis to a large-volume reference laboratory.

Material and Methods: An observational study was conducted at the section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University. Data analysis of serum 25-OHD tests from January 2010 to December 2019 was performed. The patients were categorized as deficient, insufficient, optimal, hypervitaminosis or toxic based on 25-OHD values. Data was analyzed using Microsoft Excel version 16.

Results: Total 903,282 tests were analyzed during the 10 years' period Mean age (SD) was 40.7 (16.5) years, with 35.8% males. The 25-OHD testing since 2010 to 2019 increased by 62.3% in adults and 66.6% in children. The mean 25-OHD levels improved from 18.8 ng/ml in 2010 to 24.5 ng/ml in 2019 in adults, while no change in mean 25-OHD levels was noted in children.

Conclusion: Testing and status of vitamin D improved with increased mean vitamin D levels and a decline in deficiency over 10 years. Our study calls for developing local guidelines for vitamin D-deficiency management, and taking caution when prescribing supplements, as vitamin D intoxication is concurrently increasing in the population.

Key Words: 25OHD, Deficiency, Toxicity, Pakistan.

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INTRODUCTION

Being a sun-drenched and hot weather country, it is assumed that the deficiency of vitamin D would be almost nonexistent in Pakistan; but the reality is different from the hypothesis. The prevalence of Vitamin D Deficiency (VDD) is high in south-east Asia [1]. In the 2018-National Nutrition Survey, the prevalence of VDD among children was 62.7% (10.1% severe and 31% deficient), and in adults was 79.7% (25.7% severe and 54.0% deficient) [2]. Consideration of vitamin D supplementation was one of the recommendations made to prevent VDD but an area of great controversy in our setup lies in the strategies for correcting VDD. Newer strategies and recommendations have been put forward for dietary and supplemental use of vitamin D and calcium in the light of existence of pandemic of VDD and in osteoporosis management but no consensus is present on a single strategy [3]. Hence, practice patterns of physicians in treating VDD vary widely in the country.

Vitamin D intoxication resulting from supplementation has been reported rarely in the past, but now occur more frequently [4]. Unpublished data from our center has revealed that over the counter and prescribed supplementation and faulty preparations or errors of labeling, are being reported and now an increasing number of patients have been reported with vitamin D toxicity. In addition, patients may improperly ingest high maintenance doses with or without physician recommendation [5]. Replacement of vitamin D for maintaining sufficient bone health is crucial; but a balance between optimal and toxic levels is obligatory. To avoid sub-optimal treatment of VDD as well as toxicity, serum vitamin D should be tested on a regular basis, and doses to be adjusted accordingly. However, it is uncertain if all physicians perform biochemical testing to assess the status of 25-hydroxy D (25-OHD) prior to vitamin D replacement.

According to the Endocrine Society, serum vitamin D levels above 100ng/ml are considered as hypervitaminosis D, whereas serum levels above 150ng/ml are associated with Vitamin D intoxication [6]. In this study, we aimed to evaluate the changes in trends of vitamin D testing and status of serum levels of 25-hydroxy vitamin D (25-OHD) submitted over a decade to a large-volume reference laboratory.

Correspondence: Dr Hafsa Majid, Section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan.

Email: **hafsa.majid@aku.edu**

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MATERIAL AND METHODS

A retrospective, observational study was conducted at the Section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan. Laboratory data of patients tested for 25-OHD from January 2010 to December 2019 was retrieved from the Integrated Laboratory Management System (ILMS). Only initial test results were included in analysis for subjects while results of repeat testing for 25-OHD were excluded. The study was exempted by the Aga Khan University Ethics Review Committee (ERC ID: 3930-Pat-ERC- 15).

The status of vitamin D was categorized as VDD (≤20 ng/ml), insufficiency (21-30 ng/ml), sufficiency (31-100 ng/ml), hypervitaminosis (101-150 ng/ml) and toxicity (≥151 ng/ml). Serum 25-OHD levels were measured by Liaison Auto analyzer (Diasorin Diagnostics, Italy) using an electro-chemiluminescence immunoassay method. Three levels of manufacturer-provided controls were run with each batch for internal quality control, while for proficiency testing, samples received from College of American Pathologist (CAP) were analyzed on periodic basis. The analytical measurement range for the assay was 4 to 150 ng/ml and inter-assay precision was approximately 20% CV (functional sensitivity).

The statistical analysis was performed using the Microsoft Excel 2016. Normality of the data was assessed, mean and standard deviation of age, 25-OHD and frequency of gender were derived. Frequencies of patients with VDD, insufficiency, desirable range, hypervitaminosis and toxic 25-OHD levels were also calculated.

RESULTS

During ten years' period from 2010 to 2019, a total of 903,282 tests of 25-OHD were performed. The mean age of the subjects was 40 ±16.5 years, with 35.8% being male. Of these patients, 14.6% (n=131,440) were younger than 18 years. Over time, a rise of 62.3% in 25-OHD testing (39,366 tests in 2010 to 104,924 tests in 2019) was observed in adults and a rise of 66.6% (6,427 tests in 2010 to 19,225 tests in 2019) in children. The mean 25-OHD levels in adults and children over the ten-year period are shown in Table-I.

Cumulative prevalence of deficiency, insufficiency, sufficiency, hypervitaminosis and toxicity in adults was 57.4%, 20.9%, 19.6%, 0.79% and 0.23%, respectively. In adults, an increase in subjects with sufficiency (18.18% to 23.4% total cases) and a decrease in toxicity (0.24% to 0.19% total cases) of 25-OHD levels, VDD (68.5% to 48.9% total cases) and hypervitaminosis D (1.39% to 0.19% total cases) was observed, as shown in Figure-I (a) and (b).

While in children, cumulative prevalence of deficiency, insufficiency, sufficiency, hypervitaminosis and toxicity was 55.5%, 19.9%, 20.0%, 1.73% and 1.13%, respectively. In children, an increase in subjects with sufficiency (17.1% to 20.6% total cases), while a decrease in toxic (1.19% to 0.8%) 25-OHD levels, VDD (60.8% to 52.8% total cases) and hypervitaminosis D (1.8% to 1.3% total cases) was observed, as shown in Figure-I (c) and (d).

Table-I: Comparison of yearly trends of Mean 25-OHD levels in adults and pediatrics population reported from a high-volume clinical lab of Pakistan.

Year	25-OHD levels	
	Adults n=771,842	Children n=131,440
2010	18.8 ± 17.7	24 ± 26
2011	20.6 ± 20.9	24.9 ± 27.4
2012	20.9 ± 20.5	24.8± 26.4
2013	20.8 ± 18.7	24.6 ± 25.2
2014	22.0 ± 18.8	25.8 ± 24.9
2015	21.7 ± 17.5	23.7 ±20.8
2016	22.0 ± 16.7	23.7 ± 20
2017	24.2 ± 18.0	24.7 ± 19.9
2018	24.8 ± 17.3	25.0 ±20.0
2019	24.5 ±16.9	24 ± 19.2

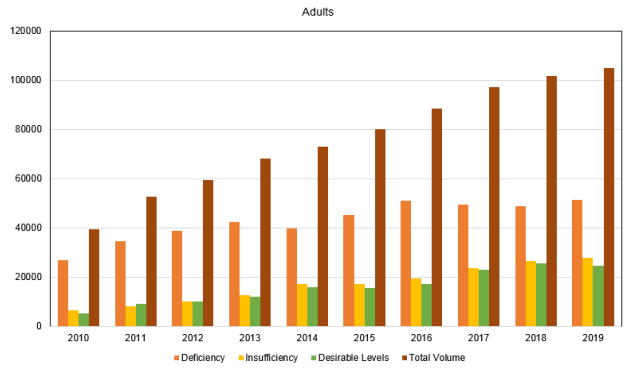

Figure-I (a): Status of Vitamin D deficiency, insufficiency, desirable range in adults tested for 25-OHD from 2010 to 2019.

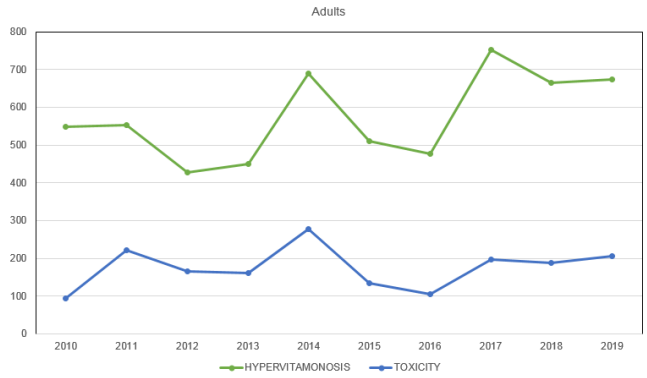

Figure-I (b): Status of hypervitaminosis and toxicity in adults tested for 25-OHD from 2010 to 2019.

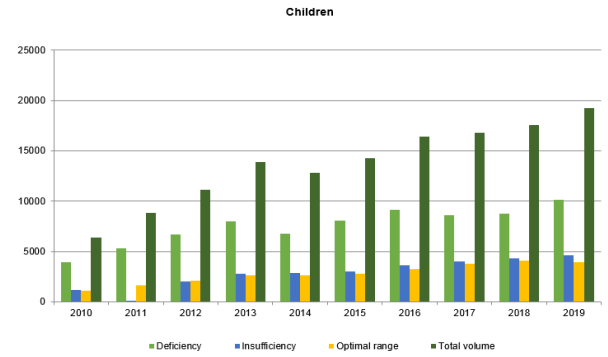

Figure-I (c): Status of Vitamin D deficiency, insufficiency, desirable range in children tested for 25-OHD from 2010 to 2019.

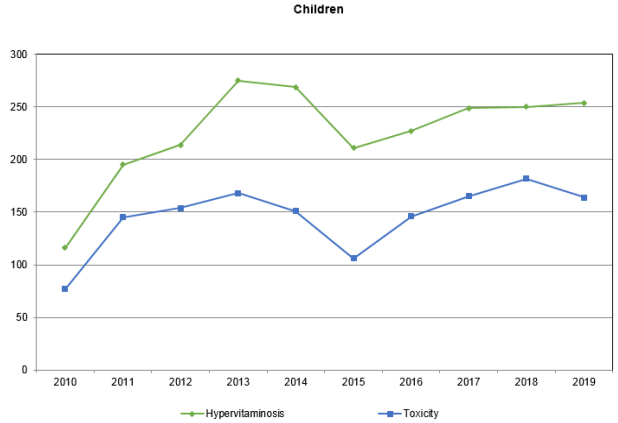

Figure-I (d): Status of hypervitaminosis D and toxicity in children tested for 25-OHD from 2010 to 2019.

DISCUSSION

Vitamin D is important for bone health and deficiency of the crucial element has detrimental effects on bone and different parts of the body. A balanced intake of vitamin D is the necessity of the time [7]. Research has highlighted the consequences of vitamin D deficiency, but the prevalence of hypervitaminosis D and vitamin D intoxication, and its subsequent consequences, is a neglected area [5]. As awareness regarding the vitamin D increases, its supplementation and inadvertent use also increases in the same proportion [8-11]. This study reports rising numbers of hypervitaminosis D and vitamin D toxicity and declining numbers of vitamin D deficiency from 2010 to 2019 in both adults and children.

In this study, we report an increase in testing in children by 66.6%, and in adults by 62.3%. This increase is in line with trends observed globally. Woodford *et al*. reported a drastic increase in vitamin D testing within the North Umbria Healthcare National Health Service Foundation Trust over 8 years, with <100 tests in 2007 to 22,871 tests performed in 2016 [12]. Similar data presented from Australia where testing increased from <500 tests in 2006 to almost 6000 tests in 2011 [9]. Similarly, vitamin D testing increased 25-fold from 2004-2010 in Ontario, Canada, while a sixfold increase in such tests was seen in UK between 2007 and 2010 [10,13].

A decrease in vitamin D deficiency status over ten years was observed in this study. Vitamin D status is consistently improving globally, likely due to fortification of different food products, especially milk, with vitamin D as well as supplementation [14]. Institute of Medicine (US) recommends that appropriate exposure of sun during different seasons of the year, along with nutritional sources, can improve the vitamin D levels from deficient or insufficient to an optimal range [15]. In Pakistan, with increasing awareness about vitamin D, people are now more inclined to buy fortified food products. Even though this fortification started in last 5 years, however, vitamin D fortified food products including oil, ghee and milk are now easily available in local markets [16].

In the present study, the mean serum 25-OHD levels improved from 13.8 ng/ml in 2010 to 24.5 ng/ml in 2019 in adults and observed a decline of 19.6% in VDD over the 10-year's period. Similarly, a study conducted in Ireland reported that mean serum vitamin D levels improved from 14.46 ng/mL in 1993 to 22.96 ng/mL in 2013 [17]. We report an 8% decline in VDD in children while then mean 25-OHD levels remained similar.

Though a decline in the mean of frequency for hypervitaminosis and toxicity was noted in both adults and the pediatric age group with an overall increase in the number of tests, toxicity was noted in 95 adult individuals in 2010 and 206 in 2019, and hypervitaminosis was noted in 549 individuals in 2010 compared to 675 in 2019. Similarly, 77 children presented with toxic vitamin D levels in 2010, which increased to 64 in 2019, and 116 children had hypervitaminosis in 2010 compared with 254 children in 2019. Contrasting findings are reported by a cohort by Sharma LK *et al*. of 5,527 patients with an increase in hypervitaminosis D from 1.48% in 2011 to 7.82% in 2016 [18]. Another study from Mayo Clinic, US reported an increasing incidence of >50 ng/mL serum 25-OHD levels from 9 to 233 cases per 100,000 person-years from 2002 to 2011 [19].

Although we report a large increase in the number of cases with hypervitaminosis and toxicity, however, the overall percentage remains low due to the increased number of testing. This could be due to increased awareness about VDD, leading to a surge in vitamin D supplementation by self-medication and physicians' prescription, and also the consumption of fortified food. Another cause of vitamin D intoxication is the over-the-counter availability of vitamin D supplements, including megadose supplements.

Patients are prescribed vitamin D for nonspecific complaints such as body aches, joint-related problems, fatigue, malaise, etc. Many a times, parents give children multiple doses of vitamin D supplements without physician's prescription, which can lead to toxicity [20].

Limitation of the study was that levels of serum calcium, plasma parathyroid hormone and other biochemical markers of bone health were not available for all subjects. Large, population-based studies should be conducted, and serum and urinary calcium, other bone health markers and radiologic studies should be assessed in patients with hypervitaminosis and vitamin D toxicity to better understand its clinical impact.

CONCLUSION

The vitamin D testing has been increased over last decade. Overall vitamin D status improved over this period whereas the numbers of cases with hypervitaminosis D and toxicity are also increased. These findings necessitate the development of that country-specific guidelines for management of VDD. Education regarding harmful effects of self-medication and possible intoxication should be provided to masses. Physician education regarding careful dosing and practicing caution while prescribing mage-doses is essential. Prescribing supplements only when necessary alongwith regular monitoring is also essential and these guidelines will be beneficial for physicians as well as their patients.

AUTHOR CONTRIBUTION

Hafsa Majid: Conceived the idea, designed the study, analyzed results, wrote the first draft of the manuscript and take full responsibility of the manuscript.

Nawazish Zahra: Organized and curated the data, wrote the manuscript.

Lena Jafri: Reviewed and made critical revisions to the final draft.

Siraj Munir: Collected the data, drew graphs and tables and reviewed the final manuscript.

Muhammad Abbas Abid: Analyzed results and reviewed the final draft.

Aysha Habib Khan: Supervised the study and critically reviewed the manuscript for intellectual content.

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