Title of Study: Practices of Vitamin D Supplementation leading to Vitamin D toxicity: Experience from a Tertiary care center of a Low Middle Income Country

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STUDY PROPOSAL

INTRODUCTION:

High prevalence of vitamin D deficiency (VDD) is well recognized in Pakistan but is in fact a global problem (1). Recommendations and strategies have been put forward for food fortification, dietary and supplementation intake of vitamin D and calcium but there is wide variation and no consensus on any one of the strategy (2, 3). Practice patterns of physicians in treating VDD vary world widely due to lack of clear guidelines on optimum doses of Vitamin D, and availability of different preparations in countries worldwide. Replacement of vitamin D for maintaining sufficient bone health is necessary but achieving balance between optimal and toxic levels is equally important. For this serum vitamin D should be tested regularly, and doses adjusted accordingly. International Osteoporosis Foundation recommends that serum 25-hydroxy vitamin D (25OHD) levels should be measured after 2-3 months of vitamin D replacement (3). However very few physicians perform biochemical testing to assess the status of 25OHD prior to or after vitamin D replacement (4).

The trend of prescribing vitamin D preparations for nonspecific body, leg and backaches in vitamin D deficient endemic areas and self-medication with over the counter vitamin D supplements has increase significant risk to the development of Vitamin D toxicity and since 2010 reports of Vitamin D toxicity are being increasingly published (5, 6).

Supplementation is reported as the most frequent cause of high vitamin D levels (7). Unprescribed and prescribed supplementation and faulty preparations or errors of labeling of vitamin D formulations, or inadvertent use such administration of high doses of vitamin D in infants or children for complaints such as delayed teething, 'late walking', and 'knock-kneed gait' are reported (8). In addition, since mega dose preparations of vitamin D are available as an over the counter medication, subjects may improperly ingest high or frequent doses (9).

According to the American Academy of Pediatrics, serum 25OHD levels above 100ng/ml are considered as hypervitaminosis D, whereas serum levels above 150ng/ml are associated with Vitamin D intoxication. The importance of vitamin D toxicity has been underestimated and under recognized. In a report from our center, hypervitaminosis and toxicity was reported in 6.6% (n=148) and 3.2% (n=72) of children out of 2,249 children under 1 year of age tested for vitamin D. These finding shows that there is inadvertent use of higher doses of Vitamin D resulting in toxicity. Replacement of Vitamin D for maintaining sufficient bone health is necessary but achieving balance between optimal and toxic levels is equally important. There is rarity of data from our country about vitamin D toxicity. This study is designed to evaluate the frequency of subjects identified with hypervitaminosis and toxicity of vitamin D and will assess the use of supplementation as a reason of high vitamin D levels.

OBJECTIVE:

To determine the frequency of hypervitaminosis and vitamin D toxicity in subjects being tested at the clinical laboratory of AKU and assess the use of supplementation as a reason of high vitamin D levels.

MATERIALS AND METHODS:

Study Design: Cross sectional study

Setting: Section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital Karachi.

Study duration: One year after the approval of Ethical Review Committee.

Sample size: Subjects tested for 25OHD from April 2020 to March 2021.

Inclusion criteria: All subjects tested for 25OHD from April 2020 to March 2021 will be included.

Exclusion criteria: For subjects with repeated 25OHD testing during the study period, only the initial result will be included while all the repeat analysis will be excluded.

Sampling Technique: Purposive Sampling

DATA COLLECTION PROCEDURE:

Laboratory data of subjects tested for 25OHD from April 2020 to March 2021 will be retrieved from integrated laboratory management system. Frequency of subjects with toxicity of vitamin D will be estimated. The cutoffs for Vitamin D toxic levels are >150ng/ml.

Clinical details of all subjects with 25OHD levels >150ng/ml will be collected on a structured clinical history forms, including demographics, biochemical details, drug or supplementation history of calcium and vitamin D.

For subjects registered at AKU for clinical consultation the medical records will be reviewed. While for outside referral subjects and for subjects whose relevant clinical history is not available in medical records, clinical history will be collected by telephonic interview after verbal informed consent. Co-Principal Investigator (Co-PI) will obtain the verbal consent (if age ≥18)/assent (if age 7-17) from the subject and parental consent (if age less than 18 years) for telephonic interview in Urdu in simple language. Co-PI will also explain about the study, need of the study and request them to participate. Once they give their consent/assent; their clinical details will be collected on a structured clinical history forms.

DATA ANALYSIS:

The statistical analysis will be performed using the Microsoft Excel 2016. Subjects will be categorized into two age groups: <18 years (pediatric) and ≥18 years (adult). Frequencies of subjects with VD toxicity will be derived and their correlates will be evaluated in the both the age groups. Demographics (age and gender), calcium status of subjects, indications, formulation strengths, frequency, duration, cumulative and daily dose of supplementation will be generated.

Descriptive statistics median (interquartile range, IQR) will be calculated for numerical data while frequency (percentage) for categorical data.

REFERENCES:

1. Khan AH, Iqbal R, Naureen G, Dar FJ, Ahmed FN. Prevalence of vitamin D deficiency and its correlates: results of a community-based study conducted in Karachi, Pakistan. Arch Osteoporos.7(1-2):275-82.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
3. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21(7):1151-4.
4. Deluca HF, Prahl JM, Plum LA. 1,25-Dihydroxyvitamin D is not responsible for toxicity caused by vitamin D or 25-hydroxyvitamin D. Arch Biochem Biophys.505(2):226-30.
5. Taylor PN, Davies JS. A review of the growing risk of vitamin D toxicity from inappropriate practice. Br J Clin Pharmacol. 2018.
6. Shea RL, Berg JD. Self-administration of vitamin D supplements in the general public may be associated with high 25-hydroxyvitamin D concentrations. Ann Clin Biochem. 2017;54(3):355-61.
7. Khan AH, Majid H, Iqbal R. Shifting of vitamin D deficiency to hypervitaminosis and toxicity. J Coll Physicians Surg Pak. 2014;24(7):536.
8. Alshahrani F, Aljohani N. Vitamin D: deficiency, sufficiency and toxicity. Nutrients.5(9):3605-16.
9. Lowe H, Cusano NE, Binkley N, Blaner WS, Bilezikian JP. Vitamin D toxicity due to a commonly available "over the counter" remedy from the Dominican Republic. J Clin Endocrinol Metab.96(2):291-5.