Vitamin D assessment and precision of clinical referrals: Insights gained from a teaching hospital in southern India

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ABSTRACT

Objective: Vitamin D deficiency is widely prevalent worldwide. This has led to a significant surge in referrals for vitamin D assessment in recent years. The cost-effectiveness and rationalization of this practice is uncertain. This study aimed to evaluate the referral pattern for vitamin D testing from a tertiary center in southern India.

Materials and Methods: This was a cross-sectional study done over a period of one year (2017). A total of 95,750 individuals, referred for vitamin D screening were included in this study. Details regarding referring departments and indications for referral were obtained from the computerized hospital information processing system (CHIPs).

Results: The study population exhibited a female preponderance (54.1%) with mean (SD) age of 40.3 (18.5) years. Overall, 44% were found to have vitamin D deficiency. Most of the referrals were from nephrology (15.4%), neurology (10.1%), and orthopedics (9.1%). Nevertheless, dermatology, the staff-clinic, and hematology which contributed to 3.3%, 1.7%, and 1.7% of referrals, had a higher proportion of vitamin D deficiency of 59.1%, 57.7%, and 64.6%, respectively. Although the most common indications for referral were generalized body aches (20.5%) and degenerative bone disorders (20.1%), the proportion of subjects with vitamin D deficiency referred for these indications were 46.1% and 41.6%, respectively. In contrast, chronic steroid use that accounted for 3.3% of the referrals had 59.1% of subjects who were deficient in vitamin D.

Conclusion: To ensure a rational approach to vitamin D testing, clinicians ought to use their discretion to screen those truly at risk for vitamin D deficiency on a case to case basis and avoid indiscriminate testing of the same.

KEY WORDS: Appropriateness of referral, chronic steroid use, cost-effectiveness, dermatology, nephrology, vitamin D deficiency, vitamin D referral

Introduction

Since the discovery of vitamin D in the early 20th century, its role in the maintenance of musculoskeletal health has been well studied and acknowledged. It has been estimated that 1 billion people worldwide suffer from a deficiency or insufficiency of vitamin D. Yet, there have been differences of opinion amongst various scientific authorities with regard to adequately defining the reference range, indications for testing, supplementation, and its implications on the extraskeletal manifestations of vitamin D insufficiency. Despite there being multiple reference ranges in vogue, the consensus range is 30-70 ng/mL. A serum level of 25-hydroxy vitamin D (vitamin D) lower than 20 ng/mL is considered to be suboptimal for skeletal health.
As vitamin D receptors are expressed in all body tissues, vitamin D deficiency also has extraskeletal manifestations.12-14 Deficiency of vitamin D may be associated with (in addition to its well-known musculoskeletal manifestations) myriad manifestations such as type I diabetes, rheumatoid arthritis, cardiovascular disease, multiple sclerosis, and infectious diseases.15 However, optimal serum 25-hydroxy vitamin D concentrations for extraskeletal health have not been established till date.9,10

Sunlight exposure [Solarultra-violet B radiation (wavelength = 290–315 nm)] and dietary supplements are the major sources of vitamin D in humans.11-13 Vitamin D synthesized from the skin and obtained from the diet is metabolized to 25-hydroxy vitamin D in the liver after which it is metabolized in the kidneys by the enzyme 25-hydroxy vitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxy vitamin D.12 Even though 1,25-dihydroxy vitamin D is the biologically active form of the vitamin, clinical correlation is better with serum levels of 25-hydroxy vitamin D or calcidiol.13 This has been attributed to extrarenal presence of the enzyme 1α-hydroxylase, which mediates the intracellular synthesis of 1,25-dihydroxy vitamin D in target cells, resulting in the specific effects of vitamin D on various cells and tissues.12

A high prevalence of vitamin D deficiency has been noted among the South Asian population. Numerous socio-cultural and economic factors, especially in India, limit the dietary intake of vitamin D and sunlight exposure needed to maintain optimal levels of 25-hydroxy vitamin D.13 A diet low in consumption of meat, fish, dairy products and eggs, rich in high extraction cereals, and reduced exposure to sunshine have been identified as determinants for vitamin D deficiency.14,15 The pleiotropic effects of vitamin D have led to an exponential increase in the number of tests carried out for the same. The cost-effectiveness of this practice is doubtful. There is no consensus in India with regard to indications for vitamin D testing. This leads to indiscriminate testing for the same by various medical practitioners. There is no data available till date about referral pattern for vitamin D assessment in the Indian context.

In this study, we assessed the referral pattern and indications for vitamin D testing, the appropriateness of these referrals, and the prevalence of vitamin D deficiency in our institution, which is a tertiary care center based in southern India catering to a diverse population from India and overseas.

Materials and Methods

This study was conducted in the Christian Medical College and Hospital, Vellore (Tamil Nadu), a 2,858-bed multispeciality medical institution in Southern India, with an estimated 8500 patients seen in the outpatient department on a daily basis.

We identified patients referred for Vitamin D assessment during the time period from 1st January 2017 to 31st December 2017. Details of referring departments and indications for referral were obtained from the computerised hospital information processing system (CHIPS). Patients with inadequate documentation were excluded from the study. Vitamin D deficiency was defined as a 25-hydroxy vitamin D level of less than 20 ng/mL (<50 nmol/L); a level of 20–70 ng/mL was considered to indicate a sufficient vitamin D level. A vitamin D level in the range 20–30 ng/mL was classified as vitamin D insufficiency. Vitamin D deficiency was further stratified as mild (10–20 ng/mL), moderate (5–10 ng/mL) and severe (<5 ng/mL).16

The department of clinical biochemistry performed 5,364,396 tests in the year 2017 out of which 95,750 were for vitamin D testing (1.8%). Vitamin D assay is a competitive electro-chemiluminescence protein binding assay (ECLIA) carried out in a Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany) and was performed according to the manufacturer’s protocol. This assay uses vitamin D binding protein (VDBP), which binds to both 25-OH D3 and 25-OH D2 (80% cross-reactivity to D2 and 100% cross-reactivity to D3) instead of the antibody. This method has been standardized against LC-MS (liquid chromatography-mass spectrometry) method, which in turn has been standardized to the National Institute of Standards and Technology (NIST) standard. The analysis was performed within 24 hours of receiving the sample. Interday precision was 5.7% and 4.03% at mean concentrations of 21.3 and 40.4 ng/mL, respectively, using quality control material provided by Roche Diagnostics.

Statistical analysis was performed using SPSS, version 23.0 (Chicago, IL, USA). Continuous variables were expressed as mean (SD), and categorical variables as frequencies and proportions. Statistical significance was considered to be achieved at a P value of <0.05. This study received ethical approval from the institutional review board.

Results

Baseline characteristics: During the study period, a total of 95,750 patients were referred for assessment of Vitamin D levels. Details with regards to age, gender of the study patients, and referring departments are shown in Table 1. The study population had a mean (SD) age of 40.3 (18.5) years and exhibited a female preponderance (51795/95750; 54.1%). The mean (SD) 25(OH) vitamin D level of the entire cohort was 23.2 (11.8) ng/mL.

Referrals from specialty: Of the total number of patients catered to by each specialty in a year, the proportion of subjects referred for 25(OH) vitamin D testing were expressed as a percentage. As shown in Table 1, the majority of referred patients were from the departments of nephrology (15.4%), neurology (10.1%), orthopedics (9.1%), internal medicine (7.5%), and pediatrics (3.9%). Multiple specialties were grouped under the label “Others”, which included the critical care unit, ophthalmology, thoracic Surgery, neonatology, anesthesia, and others, which contributed to 2.4% of the referrals.

Indications for referral: Referred patients were further sub-classified on the basis of the underlying clinical diagnosis and indications for respective referrals. The most common indications for referral were generalized body ache (19663/95750; 20.5%), degenerative bone disorders such as cervical or lumbar
spondylosis or osteoarthritis (19227/95750; 20.1%) and neurological manifestations such as clinical features suggestive of a myopathy or a neuropathy (9877/95750; 10.3%). Another common indication, which was noted was that of a routine assessment (5455/95750; 9.2%).

Prevalence of vitamin D deficiency: In the study cohort, 42157/95750; 44% were found to have vitamin D deficiency. Mild, moderate, and severe Vitamin D deficiency was noted in 3245/95750 (33.9%), 9212/95750 (9.6%), and 509/95750 (0.5%) of the patient cohort, respectively. The prevalence of vitamin D deficiency was significantly higher among females than among males [26326/51795 (50.8%) vs 19247/43955 (45.8%); P < 0.001]. Of the 9078 pediatric referrals, some form of vitamin D deficiency was seen in about 4409/9502; 46% of the children. Amongst the 2750 postmenopausal women, vitamin D deficiency was noted in 1057/2570; (38.4%) patients. The mean (SD) age of the postmenopausal cohort was 61.5 (15.2) years. The prevalence of vitamin D deficiency stratified by

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**Table 1: Departments referring patients for a vitamin D assay**

| Department                              | Proportion of subjects referred per department n (%) | Gender n (%) | Age in years (SD) | Vit D <20 ng/mL n (%) |
|-----------------------------------------|-----------------------------------------------------|--------------|------------------|-----------------------|
| Internal Medicine                       | 17,656 (7.5)                                        | Male 6755 (7.1) | 44.4 (12.7)      | 7993 (45.3)           |
| Orthopaedics                            | 14,456 (9.1)                                        | Female 10,901 (11.3) | 46.8 (13.2)      | 5867 (40.6)           |
| Paediatrics                             | 9502 (3.9)                                          | Male 5728 (6.0) | 9.0 (8.7)        | 4409 (46.4)           |
| Neurology                               | 9249 (10.1)                                         | Female 4008 (4.2) | 33.3 (20.9)      | 4111 (44.4)           |
| Nephrology                              | 6740 (15.4)                                         | Male 3880 (4.1) | 47.4 (14.4)      | 3582 (53.1)           |
| Endocrinology                           | 6230 (6.6)                                          | Female 2509 (2.6) | 48.1 (12.6)      | 2710 (43.5)           |
| Gastroenterology                        | 4107 (4.8)                                          | Male 2565 (2.7) | 41.8 (13.8)      | 1879 (45.8)           |
| Pulmonary Medicine                      | 3388 (6.3)                                          | Female 1836 (1.9) | 46.4 (14.9)      | 1492 (44)             |
| Dermatology                             | 3123 (3.3)                                          | Male 1444 (1.5) | 30.7 (15.9)      | 1847 (59.1)           |
| Rheumatology                            | 2994 (6.5)                                          | Female 1679 (1.8) | 1090 (36.4)      | 543 (19)              |
| Geriatrics                              | 2248 (8.9)                                          | Male 919 (1.0) | 42.6 (12.9)      | 1090 (36.4)           |
| Physical Medicine and Rehabilitation    | 2198 (8.1)                                          | Female 1083 (1.1) | 66.2 (8.0)       | 841 (37.4)            |
| Oncology/Radiotherapy                   | 1894 (2.7)                                          | Male 1018 (1.1) | 42.2 (14.0)      | 1034 (47)             |
| Surgery                                 | 1831 (0.9)                                          | Female 354 (0.4) | 51.5 (12.5)      | 655 (35.6)            |
| Gynaecology/Reproductive Medicine       | 1402 (0.83)                                         | Male 469 (0.5) | 44.0 (13.7)      | 918 (50.1)            |
| Cardiology                              | 1142 (1.1)                                          | Female 3 (0.0)  | 40.8 (11.4)      | 742 (52.9)            |
| Doctors/Students/Staff Clinic           | 1100 (1.7)                                          | Male 484 (0.5) | 52.3 (14.5)      | 554 (48.5)            |
| Community Medicine Clinic               | 1068 (2.5)                                          | Female 744 (0.7) | 34.4 (12.1)      | 635 (57.7)            |
| Haematology                             | 777 (1.7)                                           | Male 359 (0.4) | 709 (0.7)        | 489 (45.8)            |
| Otorhinolaryngology                     | 678 (0.7)                                           | Female 382 (0.4) | 33.5 (20.0)      | 424 (54.6)            |
| Others                                  | 3967 (2.4)                                          | Male 289 (0.3) | 45.0 (13.9)      | 315 (46.5)            |

**Table 2: Indications for referral for vitamin D assay**

| Indication for referral | Number of patients [n (%)] | Number with Vit D <20(%)|
|-------------------------|----------------------------|------------------------|
| Chronic infections       | 280 (0.3)                  | 131 (46.8)             |
| Chronic kidney disease  | 6299 (6.6)                 | 3408 (54.1)            |
| Chronic steroid use     | 3123 (3.3)                 | 1847 (59.1)            |
| Community nutritional assessment | 311 (0.3) | 131 (42.1)             |
| Critically ill patients | 317 (0.3)                  | 168 (53.0)             |
| Degenerative bone disorders | 19227 (20.1) | 7992 (41.6)            |
| Dental disorders        | 34 (0.04)                  | 18 (52.9)              |
| Generalised body ache   | 19663 (20.5)               | 9058 (46.1)            |
| Inflammatory polyarthritis | 2994 (3.1) | 1090 (36.4)            |
| Malabsorption assessment | 4529 (4.7) | 2101 (46.4)            |
| Metabolic bone disorders | 5284 (5.5) | 2461 (46.6)            |
| Metastases/Pathological fracture | 1894 (2.0) | 655 (34.6)             |
| Myopathy/Neuropathy     | 9877 (10.3)                | 4409 (44.6)            |
| Paediatric nutritional assessment | 9078 (9.5) | 4221 (46.5)            |
| Post-transplantation    | 2750 (2.9)                 | 1057 (38.4)            |
| Post-transplantation    | 1257 (1.3)                 | 629 (50)               |
| Pulmonary disorders     | 3388 (3.5)                 | 1492 (44)              |
| Routine assessment      | 5455 (5.7)                 | 2773 (50.9)            |
| Total                   | 95750                      | 43641 (45.6)           |
the other indications is shown in Table 2. The distribution of vitamin D sufficiency, insufficiency, and deficiency were studied across different age groups. This is demonstrated in Figure 1. It was found that the proportion of subjects with vitamin D sufficiency was more in the elderly age group as compared to the younger age group ($P < 0.05$).

Appropriateness of referrals: This was analyzed with respect to each specialty and the indication for these referrals. Thus, although the greatest number of referrals for vitamin D testing were from nephrology (15.4%), neurology (10.1%), orthopedics (9.1%), internal medicine (7.5%), and pediatrics (3.9%), the relative proportion of vitamin D deficiency ($<20 \text{ ng/mL}$) present in these units were 3582/6740 (53.1%), 4111/9249 (44.4%), 5867/14456 (40.6%), 7993/17656 (45.3%), and 4409/9502 (46.4%), respectively. Interestingly, the departments of Dermatology, the staff clinic, and Hematology that contributed to 3.3%, 1.7%, and 1.7% of referrals, had a prevalence of vitamin D deficiency of 1847/3123 (59.1%), 635/1100 (57.7%), and 424/777 (54.6%), respectively. Similarly, although the common indications for referral were generalized body ache (20.5%), degenerative bone disorders (20.1%), and neurological manifestations (10.3%), the proportion of subjects with vitamin D deficiency referred for these indications were 9058/19663 (46.1%), 7992/19227 (41.6%), and 4409/9877 (44.6%), respectively. In contrast chronic steroid use that accounted for 3.3% of the referrals, had 1847/3123 (59.1%) of subjects who were deficient in vitamin D. Moreover, about 5.7% of the referrals were for “routine assessment,” and vitamin D deficiency was prevalent in 50.9% of these subjects.

Referrals from different states and overseas: In keeping with the referral pattern to our centre, 58.5% of referrals for vitamin D testing were jointly from the states of Tamil Nadu and West Bengal (49594/84777). Among the referrals from overseas, 95% were from the region of Bangladesh (10468/10973). The referrals from a few Indian states and neighboring countries are shown in Figure 2a and b.

Discussion

This cross-sectional study is the first of its kind, to assess the referral patterns and indications for vitamin D testing in a large number of subjects from a teaching hospital in southern India. Over a period of one year, there were about 0.1 million referrals for vitamin D testing. Vitamin D deficiency is reported to be a public health issue and there has been a 6-25 fold rise in the incidence of vitamin D testing[17] Whether such rampant screening of vitamin D levels is warranted or truly indicated is a matter of much speculation.

In the present study, of the 95,750 individuals referred for testing, the majority were female, with a mean age of 40 years. This is probably reflective of the increased health seeking behavior of young women in the Indian subcontinent. Moreover, the majority of Indian women are confined to the constraints of their homes and are more liable to experience the symptoms of vitamin D deficiency than their male counterparts. This was exemplified in our study, which showed a significantly higher proportion of vitamin D deficiency among female subjects as compared to males. Another justification to screen for vitamin D deficiency in women in the reproductive age group is that, ensuring vitamin D replete status in the mother, reduces the incidence of neonatal hypocalcemia, craniofacial, seizures, and results in improved postnatal growth.[18] The finding of higher proportion of vitamin D sufficiency among the elderly age group is reflective of greater numbers of these subjects being treated with cholecalciferol (13).
Most referrals were from the department of nephrology, followed by neurology, orthopedics, internal medicine, and pediatrics. Most patients presenting to the department of nephrology have end-stage renal disease causing disturbances in parameters of bone and mineral metabolism. Thus, vitamin D is often tested in most of these patients and is justified. In our centre, end-stage renal disease due to diabetic nephropathy accounts for more than 70% of the subjects presenting to the department of nephrology, whereas a small proportion is contributed by renal disease secondary to collagen vascular disease. Internal medicine, being a broad specialty, attends to numerous common ailments and infections, and caters to a large majority of patients from across the country. This probably explains the greater proportion of subjects being referred for vitamin D testing. Among “chronic infections” tuberculosis and HIV account for the majority (≥90%) of cases in this center. The department of orthopedics similarly provides services for several bone related complaints, fractures, tumors, and degenerative conditions. Therefore, many bone mineral-related parameters and vitamin D levels are often investigated.

Vitamin D levels in children assume importance in the context of prevalent bony deformities associated with rickets and nutritional deficiencies. Other pediatric diseases where vitamin D testing becomes relevant include malabsorption, inherited and refractory forms of rickets, inflammatory bowel disease, chronic liver disease, and chronic kidney disease. Yet, the west has witnessed a drastic increase in the diagnosis of vitamin D deficiency among young children. This trend may have tremendous economic implications. Thus, although screening for vitamin D deficiency in children may be indicated for the conditions listed above, indiscriminate testing is probably not warranted. The department of neurology referred a tenth of their patients for vitamin D testing. Vitamin D is involved in the reduction of oxidative stress in the nervous system, and vitamin D deficiency is implicated in the pathogenesis of various neurodegenerative conditions such as multiple sclerosis, Parkinson’s disease, and Alzheimer’s disease. Besides these, testing for vitamin D deficiency may also be indicated in individuals on long-term antiepileptics, which is known to be associated with vitamin D deficiency.

However, although the highest referrals were from the above said departments, the proportion of vitamin D deficiency was greatest in dermatology, the staff clinic, and the department of hematology. As vitamin D synthesis occurs in the skin, it is expected that subjects with various skin diseases would indeed be deficient in vitamin D. The staff clinic caters to the staff (medical, paramedical, and nonmedical staff) employed at our hospital. As their work and job description mostly involves indoor work, it is not surprising that a significant proportion of them are vitamin D deficient. Patients admitted under hematology have various malignant and nonmalignant disorders, and usually have a prolonged hospital stay especially those initiated on different chemotherapeutic regimens. There are reports of deficient circulating levels of 25(OH) vitamin D among subjects diagnosed to acute lymphoblastic leukemia and non-Hodgkin’s lymphoma, and this was associated with a shorter survival in these individuals. Thus these departments may be encouraged to refer higher numbers of their respective patients for vitamin D testing. The department of pulmonary medicine accounted for about 6% of referrals for vitamin D testing, where most cases (about two-thirds) included subjects with obstructive airway disease (35%) and interstitial lung disease (30%).

Furthermore, the most common indications for testing were generalized body aches and degenerative bone disorders, constituting about two-fifths of the referrals for vitamin D testing. Degenerative bone disease commonly includes hip or knee osteoarthritis and noninflammatory spondyloarthropathy. The prevalence of vitamin D deficiency in individuals referred for these indications was 40% for degenerative bone disorders and 45% for generalized body aches. In a study by Turner et al., involving 267 subjects with chronic pain, vitamin D deficiency was found to be an under-recognized source of nociception in these patients. Thus, ensuring adequate vitamin D stores in this group of individuals might help in improving response to other pain modulating therapies. Although chronic steroid use accounted for just about 3.3% of the total referrals, the prevalence of vitamin D deficiency in this group was 59.1%. A National Health and Nutrition Examination Survey (NHANES) review (2001–2006) demonstrated that the odds of developing vitamin D deficiency in chronic steroid users were two-fold higher than in nonsteroid users. This also calls for greater screening among chronic steroid users for vitamin D deficiency. About 5.7% of the referrals underwent vitamin D testing as a part of general assessment, and of these, 50.9% were found to have deficient vitamin D levels. Routine screening of asymptomatic individuals is not indicated. Thus, the impact of vitamin D supplementation on their health functional status needs further exploration.

In this study, about two-fifths of the subjects from India and overseas had some degree of vitamin D deficiency. In keeping with the referral pattern to our center, more than half of the subjects who underwent vitamin D testing were from the states of Tamil Nadu and West Bengal, and about 95% of the overseas referrals were from Bangladesh.

A formal cost-effectiveness analysis has not been done in this study. In patients presenting with nonspecific aches and pains, where the likelihood of harboring a sinister disease condition is very remote, we may err of empirically treating with cholecalciferol. Empircal treatment in such cases is justified as vitamin D deficiency is widely prevalent, the cost of vitamin D testing is high (INR 1500) and the margin of therapeutic safety is reasonable. Given the fact that the prevalence of vitamin D deficiency is high, it is prudent to consider aggressive food fortification strategies to address this problem as the exorbitant costs involved preclude testing in many. Moreover, food fortification will go a long way in tackling the problem in the community especially among postmenopausal women and elderly men who stand a high risk of age related bone loss.

This descriptive study on the trends in vitamin D referral is the first of its kind from India. The strength of this study lies in the fact that it is probably the only study in the world that analyzed a large cohort of almost 0.1 million subjects referred for vitamin D testing. The limitation of the cross-sectional design of this study may have underestimated the true prevalence of vitamin D deficiency.
study is duly acknowledged by the authors. The key points that stand out in this study are that vitamin D deficiency is a public health problem, which may present to multiple specialties in a tertiary care centre. Its manifestations may be subtle; however, it might be prudent to screen children at risk, women in the reproductive age group, subjects with chronic dermatological conditions, hematological diseases, chronic steroid users, postmenopausal women at risk for osteoporosis, and hospital staff who are constrained to work indoors. Indiscriminate testing for vitamin D levels in asymptomatic individuals is questionable as this may result in higher costs, unnecessary burden on laboratory personnel and uncertain benefits.

**Conclusion**

This Indian study evaluated the referral pattern and indications for vitamin D testing in patients referred from different specialties in a tertiary care centre. Although the present study represents cross-sectional data from a tertiary care centre in southern India, it may be rightly presumed that practicing physicians may go overboard with testing for 25(OH) vitamin D.

Until there are clear-cut guidelines in place for directing the indications for vitamin D assessment, clinicians should use their discretion to screen those truly at risk for vitamin D deficiency, without overlooking less common indications such as chronic steroid use and chronic dermatological disorders. This will ensure a more pragmatic and rational approach to 25(OH) vitamin D assessment, better channeling of resources, and greater cost effectiveness.

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**Conflicts of interest**

There are no conflicts of interest.

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