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RESEARCH ARTICLE

NEED TO RELOOK AT THE POPULATION-SPECIFIC LEVELS OF VITAMIN D -A PILOT STUDY

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ABSTRACT

An alarming high prevalence of vitamin D deficiency in a tropical country like India, necessitates addressing certain important factors based on which hypovitaminosis D is diagnosed and treated. Though vitamin D deficiency is related to various clinical conditions ranging from simple myopathy to cancer; most of the studies done in Indian population report the deficiency based on the reference range of vitamin D in Western population and in addition, report no evident clinical symptoms or signs associated with the deficiency. This study therefore tried to relook at the vitamin D levels in apparently healthy subjects and observed that the vitamin D levels were in the deficiency range without any clinical findings related to hypovitaminosis D. It was concluded that it's high time to establish population specific reference ranges for vitamin D which would help in preventing unnecessary supplementation of vitamin D.

INTRODUCTION

In the recent years, vitamin D deficiency in India has gained much significance because of its high prevalence (50-90%). International Osteoporosis Foundation (IOF) has reported the prevalence of hypovitaminosis D in different age groups to be as high as 96% in neonates, 91% in healthy school girls, 78% in healthy hospital staff, and 84% in pregnant women in Northern India.[1,2] Similarly other studies have also reported high prevalence of vitamin D deficiency among pregnant women and their new-borns and also among apparently healthy post-menopausal women.[3,4]

Vitamin D deficiency is expected to be uncommon in tropical countries like India where there is abundant sunshine throughout the year. As per FAO/WHO expert committee, most of the countries located between 42°N & 42°S latitude experience abundant sunshine throughout the year. India is located between 8.4° and 37.6° Northern latitude and hence vitamin D deficiency is unexpected. However from the data available in the published literature, vitamin D deficiency is very common in India in all the age groups and both sexes across the country.[5,6,7]

It is important to note that studies which have reported the prevalence of vitamin D deficiency in India have followed the reference ranges of vitamin D based on Western population. In this scenario, establishment of reference range of vitamin D in Indian population gains eminence to verify the actual vitamin D status. Another striking fact observed is that vitamin D deficiency which is known to cause secondary hyperparathyroidism has been conspicuously absent in such patients as reported in some of the studies done in Indian population.[7, 8] This emphasizes the fact that there is a need for comprehensive assessment of the vitamin D status in the Indian population before diagnosing and treating vitamin D deficiency.

Hence this pilot study was taken up, which aims to determine the 25 Hydroxy vitamin D levels along with calcium, inorganic phosphorous and parathormone (PTH) levels in apparently healthy individuals in and around Mysore city.

MATERIAL AND METHODS

The study was approved by institutional ethical committee.

Source of data; 118 apparently healthy subjects were selected from the areas in and around Mysuru for this study. Sample size was calculated based on the reported prevalence of vitamin D deficiency of 50% with allowable error of 10%. Subjects were selected by simple stratified sampling method.

Inclusion criteria: The age group of the subjects was between 20-40 years. Subjects were divided into two groups based on the hours of exposure to sunlight. Group A (n=59): Duration of Sun exposure: 4-8 hrs. Group B (n=59): Duration of Sun exposure :< 4hrs.

Exclusion criteria: Present or past history of vitamin D supplementation, chronic liver disease, renal disease, or treatment with anti-tubercular, antiepileptic drugs, diabetes mellitus, autoimmune disease, gastrointestinal malabsorption and any form of cancer.

Methodology: Informed-written consent was obtained from all the subjects. An interviewer-administered questionnaire was used to collect the patient details. Height, weight was recorded and Body Mass Index (BMI) was calculated.

Under aseptic precautions, about 3 ml of blood was collected and subjected to centrifugation at 4000 rpm for 15 minutes. Serum separated was used for the estimation 25-hydroxy vitamin D {Although 1,25 $(OH)_2$ vitamin D is the active form, 25(OH) vitamin D gives a better idea of vitamin D status in the body because, 25(OH) vitamin D is major circulating form of vitamin D, with a circulating half-life of approximately 2–3 wk. 1,25$(OH)_2$vitamin D has a circulating half-life of approximately four hours and circulates at 1000 times lower concentration than 25(OH)vitamin D}[9], PTH, calcium and inorganic phosphate.

25-hydroxy vitamin D and PTH were estimated by Electrochemiluminesence immunoassay (ECLIA) using Roche e601 immunoassay analyser. Calcium was estimated by using Arsenazo III method, and inorganic phosphate was estimated by phosphomolybdate method, using fully automated Toshiba TBA 120 chemistry analyser.

Statistical analysis: Data collected was entered in MS Excel 2010 and analysed using SPSS version 22.Descriptive statistical measures like mean, SD was applied. Inferential statistics tests like Pearson's correlation was applied to correlate PTH, calcium, inorganic phosphate and vitamin D. Correlation and differences were interpreted as statistically significant at P <0.05.

RESULTS

In our study, the mean age of the subjects was 28.38±5.88 years. The mean vitamin D levels was 14.64 ± 7.38 ng/ml and the mean PTH levels was 40.79±16.18 pg/ml. There was significant correlation between vitamin D and calcium, skin complexion, BMI. However there was no correlation between vitamin D and inorganic phosphate, PTH, smoking, alcoholism, diet, socioeconomic status.

There was a statistically significant difference noticed in the mean vitamin D levels between males and females and also between fair skinned individuals and dark skinned individuals (Table1).

Table 1 Mean Vitamin D levels distribution with respect to gender and skin complexion (Total subjects n==118)

	Gender	Mean ± SD
25 OH Vitamin D (ng/ml)	Males (n=77)	15.19±7.34
	Females(n=41)	13.61±6.97
	Skin Complexion	**Mean ± SD**
	Fair(n=22)	16.86±6.78
	Medium(n=67)	15.06±7.66
	Dark(n=29)	11.53±6.64

The subjects were further divided into 2 groups based on the duration of sun exposure into two Groups: Group 1 & Group 2. The demographic details of the subjects under the 2 groups are shown in Table 2. There was statistically significant difference in the mean vitamin D & PTH levels between the two groups (P <0.05). However there was no significant difference in calcium and inorganic phosphate levels. (Table 3)

Table 2 Demographic data of subjects with respect to two groups

Sl No	Parameters	Group 1 (n=59)	Group 2 (n=59)
1.	Males	39	38
2.	Females	20	21
3.	Mean age (years)	30.49± 5.98	26.27±5.05
4.	Smokers/Nonsmokers	07/52	09/50
5.	Alcoholics/Non alcoholics	07/52	13/46
6.	Diet: Vegetarian/Mixed	07/52	12/47
7.	BMI (kg/m^2)	21.88±3.94	22.15±3.30

Table 3 Biochemical parameters among the two groups.

Parameters	Groups	Mean ± SD	p<0.05 (Significant)
25 OH Vitamin D (ng/ml)	Group 1	15.91± 7.71	Significant
	Group 2	13.24±6.98	
Parathormone (pg/ml)	Group 1	35.34±16.42	Significant
	Group 2	46.23±14.22	
Calcium (mg/dl)	Group 1	9.65± 0.47	Not significant
	Group 2	9.67± 0.558	
Inorganic Phosphorous(mg/dl)	Group 1	3.90±0.76	Not significant
	Group 2	3.56±0.57	

DISCUSSION

Vitamin D3 (cholecalciferol) is synthesized endogenously from 7-dehydrocholesterol when skin is exposed to ultraviolet B radiation, hence referred as "sunshine vitamin". Exposure to UVB (280 – 310nm) sunlight accounts for more than 80% of vitamin D synthesized in the body.[8] Considering the above fact and the geographical location of India (between 8.4° and 37.6° Northern latitude), vitamin D deficiency is highly unexpected.[6]

Diagnosing vitamin D deficiency is of utmost importance due to its wide ranging calcitropic (calcium homeostasis) to pleotropic effects (cell differentiation, T cell proliferation and immune regulation). The basis of calcitropic effects are as follows: vitamin D aids in increasing the intestinal absorption and mobilizing the calcium from the bones; and on the other hand, pleotropic effects of vitamin D have been attributed to the presence of VDR receptors in tissues such as heart, kidneys, lungs, liver, pancreas, intestine, brain, muscle and other immune tissues and discovery of CYP27B1 enzyme in various tissues. Because of these properties, vitamin D has the ability to stimulate the tissues to deal effectively with the physiological & pathological stimuli and therefore individuals with vitamin D deficiency are at increased risk of developing varied disorders involving different organs such as diabetes, hypertension, cardiovascular diseases, neurological diseases, and various types of cancers.[10,11]

Most of the studies which have reported high prevalence of vitamin D deficiency in India are based on the vitamin D reference ranges of Western population: <20 ng/ml -deficient, 20-30 ng/ml -insufficient and > 30 ng/ml – sufficient[12]and in addition have attributed the vitamin D deficiency to various other causative factors such as inadequate sun exposure due to socio-cultural practices, decreased calcium intake, increased skin pigmentation, amplified air pollution, use of sunscreens etc[3].

In our study, we found that the mean vitamin D levels were in the deficiency range when the above mentioned Western population reference range was considered. We further tried to assess the effect of sun-exposure among the subjects. It is found that sun exposure for 30 minutes over arms and face without application of sunscreen is adequate for the synthesis of vitamin D.[5] We observed that vitamin D levels in both the groups which were based on the duration of sun exposure, were in the lower range. All these subjects were healthy without any clinical symptoms, with normal levels of serum calcium and inorganic phosphorous. Further it was noticed that there was no secondary increase in PTH levels as anticipated in Vitamin D deficiency. Similarly, studies have reported vitamin D levels did not show any significant difference even with inadequate sun exposure and decreased dietary intake of calcium.[3]

Based on the above findings, it can be inferred that lower vitamin D levels in certain population when compared to Western population, might be due to gradual adaptation through natural selection over a long period of time and the requirement of vitamin D might have reduced gradually.

Hence, lower ranges might be optimal in certain population, which has been attributed to genetic factors & adaptive mechanisms such as: [7,9,10,13,14]

- possible differences in vitamin D metabolism in different population
- 25(OH)-24 hydroxylase activity was found to be upregulated in Asians resulting in a decrease in serum 25-OH vitamin D
- calcium absorption was found to be more effective in dark skinned individuals
- persons with low 25(OH)-D show efficient conversion to its active forms 1,25$(OH)_2$ Vitamin D
- studies have shown that that VDR bind more effectively in Eskimos when compared to other population, and therefore an example of adaption to environment and lower ranges.

Labelling a person as vitamin D deficient based on the reference range of western population can result in unnecessary supplementation which is expensive and might also lead to toxicity. This impending toxicity could be due to vitamin D supplementation for prolonged periods or consumption of single mega dose which can be due to increased synthesis of vitamin D metabolites such as 25(OH) vitamin D; 24, 25 $(OH)_2D_3$, 25,26$(OH)_2D_3$, 25-OH-26,23 lactone etc. Increased vitamin D metabolites bind with vitamin D receptors in the target cells and cause exaggerated gene expression.[9,15]

The need of the hour is

- To redefine population specific reference range of vitamin D.
- In addition to laboratory results, clinical and radiological findings should be taken into consideration before starting the vitamin D supplementation.
- Large scale multi-centric studies to establish nationwide standard levels for Vitamin D.

Limitations: Our study admits quite a few limitations such as: smaller sample size, no comparison between urban and rural population, usage of sunblock by the subjects, seasonal variation of vitamin D.

CONCLUSION

The present study showed that vitamin D levels were in the deficiency range irrespective of duration of sun exposure. The subjects even with lower vitamin D levels did not have any clinical symptoms or any secondary increase in parathormone levels as expected in vitamin D deficiency, which implies the need for further research. This pilot study thereby acts as a prelude for further larger studies so as to establish population specific reference range for vitamin D.

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