

TUBERCULOSIS AND VITAMIN D DEFICIENCY IN KERALA, INDIA

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ABSTRACT

Background

Vitamin D deficiency was considered to be uncommon in India till recently. Following an original observation of Vitamin D deficiency in patients with Tuberculosis, a controlled study was done to verify that.

Methods

Vitamin D levels in patients with recently diagnosed active Tuberculosis and matched healthy controls were compared. 25 Hydroxy vitamin D₃ level was estimated utilizing a sensitive RIA technique, Adequacy of dietary intake of vitamin D and adequacy of sunlight exposure was studied in the two groups.

Results

The mean value of 25 hydroxy Vit D₃ in patients with tuberculosis was 10.7ng/ml in comparison to the apparently control group who had a mean value of 19.4ng/ml, and the difference was statistically significant ($p < 0.005$)¹. The study was done in 1999 and the results were published in 2002¹ and the present article is a relook at the original data, since at that time there was no consensus on normal values of Vitamin D. Since the lowest value got in the control group was 9ng/ml,¹ a Vitamin D level of 9ng/ml was arbitrarily taken as normal. Even with that value there were 16 patients out of 35 who had values well below the lower limit of 9ng/ml¹. As per current guidelines the optimal level of vitamin D is 30- 60ng/ml⁷, and on applying that to the original data got in 1999, it is observed that all the patients with Tuberculosis had values less than 30ng/ml and therefore had vitamin D deficiency, and more than 90% of the asymptomatic apparently normal controls also had Vitamin D deficiency.

Conclusions

Vitamin D deficiency was present in all patients with active Tuberculosis. Since it has a role in Cell Mediated Immunity it could be one of the causes for the infection. Deficiency was noted in 90% of the apparently healthy controls even though the level was higher as compared to the patients. The population studied was a representative sample of Kerala and presumably whole of India, the results indicate the possibility of widespread deficiency in the apparently healthy population in India in spite of adequate sunlight exposure. Considering the role of Vitamin D in Cell Mediated Immunity and the protective effect of it in several other diseases, the article highlights the importance of improving the nutrition and if required even supplementing Vitamin D by food fortification, rather than hoping to get vitamin D from sunlight exposure alone.

INTRODUCTION

Though vitamin D belongs to the class of vitamins, it is unique because it is also synthesized in the body and functions as a hormone. Besides having a crucial role in calcium homeostasis and bone mineral metabolism, it is known to be involved in biological functions like cell differentiation, inhibition of cell growth and immunomodulation.^{1,2,3,4} Vitamin-D is an important effector of macrophage functions

and thus could be having an important role in limiting growth or survival of intracellular pathogens like Mycobacterium Tuberculosis, Salmonella and all viruses.^{2,3,4,5} The role of Vitamin D in preventing several malignancies is increasingly being recognized. Recent evidences link vitamin D deficiency to diseases like Diabetes, Hypertension, infections, autoimmune disorders and cancer.^{8,9} Vitamin D modifies gene expression in the tissues where it acts by binding to specific receptors (VDR) and has several known actions and several more hitherto unknown to us.^{2,3,4,8}

Being a tropical country it was firmly believed that Vitamin D deficiency did not exist in India. Following an original observation made in 1993 in a 14 year old boy with skeletal Tuberculosis in whom there was documented Vitamin D deficiency, it was hypothesized that it could be a cause rather than the effect.¹ Subsequently several cases of Tuberculosis were observed to have of vitamin D deficiency. To prove the significance of the observed association a controlled study was undertaken in 1999 to look for Vitamin D deficiency in cases of active Tuberculosis.¹

MATERIALS AND METHODS

There were 35 cases of, recently diagnosed pulmonary and extra pulmonary tuberculosis. Comparison was done with 16 healthy controls who were age and sex matched. Their clinical characteristics, dietary intake of vitamin D and biochemical characteristics including serum vitamin D levels (25 Hydroxy Vit D₃) were compared.¹ The blood samples of patients were taken before starting anti-tuberculous treatment. Cases excluded were those who were otherwise prone for vitamin D deficiency like malabsorption, liver or renal disorders and those on drugs which can reduce Vitamin D levels or antagonize its actions.¹ Those who were predisposed to develop tuberculosis due to other obvious causes also were excluded (HIV infection, Diabetes, on immunosuppressive treatment, severe Protein Energy malnutrition).¹ Their clinical details including symptoms of hypovitaminosis D were recorded.¹ Adequacy of sunlight exposure was assessed based on whether or not the subjects spent at least ten hours a week outdoors in daylight. Dietary assessment regarding adequacy of Vitamin D intake was assessed based on analysis of the dietary intake using a food chart standardized by the Central Food Research Institute, Mysore.^{1,10} Investigations to confirm the diagnosis of Tuberculosis, Calcium, Phosphorus and serum protein levels were done.¹ All the samples were analyzed in duplicate for 25 OH Vit D₃ using a sensitive RIA technique.¹

RESULTS

The value of 25 hydroxy Vitamin D₃ in the study subjects ranged from 1-30ng/ml with a mean value of 10.7ng/ml. The control group had Vitamin D levels ranging from 9-58ng/ml and a mean value of 19.4ng/ml, and the difference was

statistically significant ($p < 0.005$).¹ Vitamin D level of 9ng/ml was the lowest value observed in the apparently healthy controls and that was arbitrarily taken as normal as there was no consensus on normal values at the time of doing the study in 1999.¹ Even with that value there were 16 patients out of 35 who had values well below the lower limit of 9ng/ml.¹ Sunlight exposure was adequate in 72% of the cases, only 28 % had, if at all, inadequate exposure to sunlight. Vitamin D levels in the ambulant (adequate sunlight exposure) and house bound groups were not significantly different and inadequacy of sun exposure was not the primary cause for Vitamin D deficiency. But the diets of 54% of the patients were deficient in Vitamin D containing food items. Symptoms of hypovitaminosis D like proximal muscle weakness were present only in 20% of the cases and that too in those with levels below 5ng/mL.¹ Even with less than 1ng/mL of 25 hydroxy Vitamin D, there were no symptoms to suggest deficiency in a 30 year old female, who looked normal but for the mono arthritis of ankle joint due to Tuberculosis^{1,6} (Table 1, patient No 13). The serum Calcium, Phosphorus and Alkaline phosphatase were in the normal range in all patients and controls.¹

DISCUSSION

When the study was done in 1999, there were only scattered reports from India on vitamin D deficiency and it was considered nonexistent and there was no consensus on the normal levels of vitamin D. The healthy controls had a mean value of 19.4 ng/ml with a range of 9 to 58ng/ml (Table 2). Since there were no population data from the study region on normal levels of 25 OH Vitamin-D, a value less than 9 ng/ml, which was the lowest level in the controls, was taken as definite deficiency. The mean value in the patients with Tuberculosis was 10.7ng/ml with a range of 1-30ng/ml (Table 1). Now it is clearly known that any value less than 30ng/mL indicates deficiency, and the normal range is taken as 20-100ng/ml and the preferred range of normal value is 30-60ng/ml.⁷ Intoxication with vitamin D is possible only if the level is above 150ng/mL⁷ (Table 3).

Applying those values to the original data got in the study done in 1999 (table 2), there was only one patient, out of the 35 with Tuberculosis, who had 25 Hydroxy D₃ level of 30ng/mL and even that was less as compared to the preferred range, indicating that all patients with Tuberculosis had Vitamin D deficiency.⁷ Only three patients out of 35 had values above 20 ng/mL and the mean value of 10.7 ng/ml indicated severe deficiency in those with tuberculosis. Among the apparently healthy controls only six of them had Vitamin D level of 20ng/ml and above (table 2). More than 25ng/ml was seen in just two of the controls and above 30 ng /ml only in one. Though the sample size was small, the study done in 1999 itself throws light on the possibility of wide spread and significant deficiency of vitamin D in the population studied which was representative of Kerala and hence could be representing the

Table 1: 25 Hydroxy D3 levels in patients

Study subjects with Tuberculosis	Age	Sex	Religion	Level of 25 OH D3(ng/ml)	Study subjects with Tuberculosis	Age	Sex	Religion	Level of 25 OH D3(ng/ml)
1	13	F	H	21.0	19	17	F	M	10.0
2	22	F	M	9.6	20	23	F	M	8.5
3	33	F	M	8.2	21	28	M	H	11.0
4	35	F	M	8.2	22	40	M	H	13.5
5	46	M	M	30.0	23	27	M	H	6.6
6	20	M	H	5.8	24	50	M	M	7.0
7	18	F	M	4.6	25	18	F	H	2.0
8	60	M	H	18.0	26	20	M	M	2.5
9	38	M	M	5.8	27	28	F	H	20.0
10	55	M	H	12.0	28	50	M	H	5.4
11	58	F	H	13.5	29	55	M	H	23.0
12	40	F	H	12.0	30	65	M	H	10.0
13	30	F	H	<1.0	31	21	F	M	12.0
14	54	M	H	3.7	32	29	F	H	18.0
15	32	F	H	9.5	33	69	M	H	13.5
16	36	F	M	7.0	34	28	F	M	5.0
17	40	N	H	14.0	35	20	M	C	17.0
18	56	F	M	8.5					

M= Male, F= Female; Religion M= Muslim, H= Hindu

Table 2: 25 Hydroxy D3 levels in Control Samples (in ng/ml)

Sr No	Age	Sex	Religion	Vit D level	Sr No	Age	Sex	Religion	Vit D level
1	31	M	M	17.0	9	30	M	H	26
2	45	M	H	58.0	10	40	M	H	15
3	65	F	M	20.0	11	25	M	H	12
4	42	F	M	9.5	12	14	M	M	14
5	53	F	H	9.0	13	24	F	M	17
6	19	M	M	22.0	14	28	M	M	22
7	21	F	M	14.0	15	28	M	H	17
8	35	F	H	18.0	16	45	M	H	20

Table 3: Normal levels of Vitamin D⁷

Reference Range of 25 Hydroxy Vitamin D		
<20ng/ml	20-100ng/ml	>150ng/ml
Deficiency	Preferred Range 30-60ng/ml	Intoxication

whole of India, in spite of being a sunny country.

There could be three possible reasons for the deficiency in the population. 1) Poor intake of vitamin D containing food items was the primary cause and not decreased sunlight exposure. It therefore implies that we need to get both sunlight as well as a balanced diet for adequacy of vitamin D. This is possible by consuming a vegetarian diet with a combination of “Cereals + Pulses + Vegetables + fruits” in the right proportions everyday (non-vegetarians could take egg, fish or meat instead of the pulses). Though there are no data to support, it is a common

observation that very few people know what constitutes a balanced diet, and some beliefs and wrong concepts about diet prevent many from taking dietary items which contain Vitamin D. There are only very few who regularly get all these in their diet due to lack of awareness about what constitutes a balanced diet. Even if they are made aware of and motivated many have no access to a balanced diet due to poverty. 2) Reduced cutaneous biosynthesis of vitamin D could be another reason, due to the increased melanin in skin which could be interfering with ultraviolet light mediated vitamin D synthesis.¹¹ 3) To compound the problem further it could be possible that the poor intake of vegetables, which is a very common issue in most people of our country, and the resultant Magnesium deficiency might lead to reduced Parathyroid hormone (PTH) secretion and the consequent reduction of 1 hydroxylation of vitamin D,¹² since PTH is needed for this

step in Vitamin D biosynthesis

Social significance of the data: The study suggests that Vit D deficiency is very common in the population studied which is representative of the People of Kerala and could be indicating similar situation in the rest of the country. Vitamin D deficiency could be the tip of the iceberg of nutritional deficiency, which initiates or perpetuates diseases like Tuberculosis and possibly even progression to AIDS in the HIV infected people. It is intriguing to ask the question -why HIV and Tuberculosis are maximum in India, Africa and other developing countries alone. The results of the study support the already known link between Tuberculosis and malnutrition. Similar could be the case of HIV also since it is a common observation that those with advanced AIDS have severe malnutrition as well, and it could be a cause rather than the effect. Besides, there are several examples of persons living with HIV for long periods if they follow a healthy diet and lifestyle. Randomized controlled studies are not feasible for establishing the link between all aspects of nutrition and diseases. The observations suggest that Tuberculosis control programme, to succeed, may need to incorporate dietary intervention and education of the people on the need for balanced diet. This observation is particularly relevant since, even relatively affluent section of society do not consume a balanced diet which contains adequate protein, vegetables and fruits, but consume all kinds of fast foods, junk foods and many of them are exposed to overeating, sedentary habits, alcohol and tobacco smoking. It is also interesting to note the recently recognized role of Vitamin D in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, other infectious diseases, and cardiovascular disease⁸. Clinicians in India are witnessing an increase in lifestyle disorders, autoimmune disorders and malignancies. This could be because already malnourished people are now getting exposed to wrong lifestyle habits (thrown open by promotion of consumerism. The role of vitamin D in cancer prevention is becoming more obvious and needs special mention⁹. It is reported that raising the minimum serum 25(OH)D level to 40 to 60 ng/mL would prevent breast, prostate and colorectal cancers.⁹ There are no risks from intake of 2000 IU per day of vitamin D₃, or from a population serum 25(OH)D level of 40 to 60 ng/mL.^{9,10} There could thus be a need for nationally coordinated action to substantially increase intake of vitamin D and calcium.

CONCLUSIONS

Vitamin D deficiency was observed in all patients with active Tuberculosis. There is definite relationship between Vitamin D deficiency and Tuberculosis. Vitamin-D deficiency could be a cause of Tuberculosis rather than the effect of it. Even apparently healthy people have vitamin D deficiency. The lower levels of vitamin D are due to reduced intake and not due to reduced sun exposure. Vitamin D deficiency occurs without any symptoms, if at all any symptoms are present it indicates

severe deficiency (<5ng). Serum calcium and phosphate are not sensitive to screen for deficiency. The drawbacks of the study were the small sample size, and the disparity between the number of patients and controls which was inevitable then due to lack of resources for the study[#].

RECOMMENDATIONS

There is an urgent need to improve the diet and other health conditions of the people including the necessary reforms to make provision for balanced diet to all. Now we have adequate proof for widespread Vitamin D deficiency, fortification of foodstuffs like oil or wheat-flour also may be tried till such time that all sections of the society have provision for taking balanced diet regularly.

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