

## Effect of replacement therapy on clinical symptoms in patients with vitamin D deficiency

Kamal Abdul Naser<sup>1</sup>, Basheer Abdel Rahman<sup>2</sup>, Humaira Alam<sup>3</sup>, Muhammad Asim Rana<sup>3</sup>, Sameer Akbar<sup>1</sup>

From, <sup>1</sup>Department of Medicine and Endocrine, Royal Care Hospital, Akurana, Sri Lanka, <sup>2</sup>Department of Critical Care Medicine, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia, <sup>3</sup>Department of Hepatobiliary and Critical Care, Bahria International Hospital, Lahore, Pakistan.

**Correspondence to:** Dr. Kamal Abdul Naser, Department of Medicine and Endocrine, Royal Care Hospital, Akurana, Sri Lanka. Email: [mackanaser@gmail.com](mailto:mackanaser@gmail.com)

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### ABSTRACT

**Background:** 25(OH) D is an important component for human health. Vitamin D deficiency is a worldwide problem. Previous epidemiological studies have shown the association of this deficiency with development of other chronic disease that also increase the morbidity. So early detection of deficiency helps to plan intervention and treatment to avoid morbidity. **Objective:** To evaluate the association of vitamin D deficiency in individuals suffering with chronic diseases and the effect of replacement therapy on the clinical symptoms of vitamin D deficiency. **Method:** This study analyzed a total of 115 patients visiting the Diabetes and Endocrine Research Centre. Factors such as age, gender, duration of sun exposure and body parts exposed to sunshine were studied. The data was recorded on a questionnaire performa. Patients with 25(OH) D levels below 30ng/ml were considered to have insufficient levels. 48 patients who agreed for treatment were given standard loading and maintenance dose of vitamin D. 31 Patients reported back after 3 months of maintenance dose treatment. **Results:** The mean age of patients was 47.82±13.86 years. Duration of sunshine exposure was significantly low with p-value of 0.005. In our study, 112/115(97.3%) patients were found to have 25(OH) D level below 30ng/ml and 41/115 (21.5%) were severely deficient. 48(41%) patients agreed for replacement therapy. However, only 31 reported back with vitamin D level. In comparison to pretreatment records, there was significant improvement in vitamin D levels after 3 months of treatment. There was improvement with symptoms such as lethargy which improved in 11/17, whereas depression and body aches improved in 12/19 and 16/26 patients respectively. **Conclusion:** It is important to recognize the deficiency of vitamin D level in patient suffering from chronic diseases in order to avoid other co morbidities. So, this study can help to make policy in future about which population needs to be screened and what preventive precautions can be taken.

**Key words:** Cholecalciferol, chronic diseases, vitamin D3, vitamin D deficiency

Vitamin D is a fat soluble vitamin involved in bone mineralization. It can be ingested in diet as cholecalciferol (Vitamin D3) or ergocalciferol (Vitamin D2), but can also be synthesized in skin by exposure to sunlight [1]. Vitamin D deficiency can manifest at all ages. Common manifestations of Vitamin D deficiency are symmetric lower back pain, proximal muscle weakness, muscle aches and throbbing bone pain elicited with pressure over sternum or tibia [2]. However, epidemiological studies have shown low vitamin D level

associated with high risk of osteoporotic fractures and malignancy of breast, colon, ovary and prostate [3]. Common causes of vitamin D deficiency include diet low in vitamin D and reduced exposure to sunlight [4]. In adults, vitamin deficiency is defined as a serum 25-hydroxyvitamin-D level of less than 20ng/ml [50 nmol/L] and insufficiency is defined as serum 25-hydroxyvitamin D level of 20-30ng/ml (50-75nmol/L) [5].

Studies have reported that 25(OH) D deficiency status is an unrecognized entity is endemic in both children and

adults in the United States [6]. Despite the important role of sunlight in vitamin D synthesis, recent studies have shown that rate of vitamin D deficiency is still higher in the sunniest areas of the world including Middle East countries because of low exposure to sunlight due to cultural factors [7]. However, there is still debate how much vitamin D replacement is needed to correct severe vitamin D deficiency. Commonly applied strategy is to prescribe a loading dose of 50,000 IU of vitamin D orally once a week for 2-3 months or 3 times a week for 1 month [8]. Daily requirements of vitamin D is around 800-1000 IU, but larger doses required for deficient individuals [9]. Oral supplementation with 3000–5000 IU daily for 6–12 weeks can be used to replete stores followed by a maintenance dose of 1000–2000 IU per day. Vitamin D status should be assessed 3–4 months after commencing treatment as vitamin D is stored in fat and muscle and there is a lag time before normalization of serum concentrations [10]. The present study was conducted to see how patients suffering from chronic disease are also being affected by hypovitaminosis D and how they respond to vitamin D therapy.

## MATERIAL AND METHODS

The present study was conducted at the Diabetes and Endocrine Research Centre of Royal Care Hospital, Sri Lanka. Data was collected retrospectively from a total in 115 symptomatic patients who visited the department from June 2017 to march 2018. All patients above 18 years of age, diagnosed Diabetic and hypertensive patients with clinical signs and symptoms of depression and mood disorders were included in study. Patients not willing to be a part of the study and those patients on corticosteroids, antiepileptic medications and those who were already on vitamin D supplements were excluded from the study. Informed consent was obtained prior to all the investigations and interventions. Variables such as age, gender, duration of sun exposure and body parts exposed to sunshine were studied. Patients with 25(OH) D levels below 30ng/ml are considered insufficient. The data was recorded on a questionnaire performa. After initial assessment, only 48 patients agreed for vitamin D replacement therapy, who were prescribed with Vitamin D replacement therapy for 3 months. Patients were started with loading dose of 200,000 IU for seven weeks or 400,000 IU for 2 weeks. Maintenance dose of 1000 to 2000 /day was given for 3months or 5000/week for 3 months. Post treatment vitamin D levels were also assessed in the same laboratory. All the collected data were tabulated and data was analyzed by using IBM SPSS version 19.

## RESULTS:

The present study was conducted to evaluate the effect of replacement therapy on clinical symptoms of patients with

vitamin D deficiency. A total of 115 patients visiting clinic of diabetes and endocrine research Centre ranging from age 18 years to maximum age up to 76 years were included in the study. The mean age of patients was 47.82 with a standard deviation of 13.86. Among 115 patients, 69 (46%) were females and 46 (24%) were males. Among the 115 patients, a total of 112(97.3%) were found to have vitamin D levels below the normal limits of 30ng/ml. Vitamin D levels between 20-30ng/ml were considered insufficient, Levels between 10-20 ng/ml was considered deficient <10ng/ml were considered severely deficient. In our study, 55 (47.8%) patients had deficient levels, 41 (21.5%) patients were severely deficient and only 16 (13.7%) patients had insufficient levels of vitamin D.

Relationship of variables such as gender, age, patient's body exposure areas and duration of sunshine exposure with Vitamin D deficiency were assessed. We found p value was not significant in this range of age group. So, it has been seen that vitamin D deficiency is not related to age ranging from 18 to 76 years of age. In our study population vitamin D level were found significantly deficient with P-value of 0.00. Among the 115 patients, face and hand up to wrist were exposed to sunlight in 56 (29%) patients, head and arms were exposed in 43 (22.3%) patients, face and arms, head and hand up to wrist were exposed in 7(3.6%) each patients and only 3(1.6%) patients were found fully covered. Exposure to sunlight was found to be significantly associated with vitamin deficiency (P= 0.02). with respect to duration of sunshine exposure, 82(42.9%) patients were exposed to less than 10 minutes of sunshine followed by 22(11.5%) people were found to be exposed by sunshine for 15-30 minutes. 8 (4.1%) patients were exposed to 30-60 minutes of sunlight, 2(1%) patients were exposed to 60-90 minutes and prolonged exposure to sunshine was noted in only 1(0.5%) patient. There was significant association of duration of exposure to sunlight with vitamin D deficiency.

In our study, only 48 patients out of 115 agreed for vitamin D replacement therapy. Clinical symptoms of vitamin D deficiency were evaluated in those who agreed for treatment. Depression was noted in 29 patients, followed by body aches in 26 patients, joint pain, anger in 24 patients each and lethargy was noted in 17 patients. The treatment was solely based on patient's preference, convenience and consent. Suggested route of administration of drug was either oral or intramuscular route. Oral route was selected by 38(79.2%) patients and 10(20.8%) patients preferred intramuscular injection. A loading dose of 200,000IU weekly for 4 weeks was administered in 29(60.4%) patients and 17(35.4%) took 400,000IU for 2 weeks. This was followed by a maintenance dose of 1000IU /day for 11(22.9%) patients, 2000 IU/day in 32(22.6%) and 5000 IU/week for 5(10.2%) patients for a period of 3 months. All patients were advised for a follow up visit after 3 months and Vitamin D level assessment was carried out. In the follow up visit, only 31 patients reported back and 17 (35.4%) patients were lost to

follow up. There was significant improvement in vitamin D levels when compared to pretreatment records. Table 1 depicts the pre and post treatment vitamin D levels in patients. In comparison with post treatment symptomatic improvements were seen. However these results were not statistically significant (Table 2, Figure 1).

**Table 1: Comparison of pre and post treatment vitamin D levels**

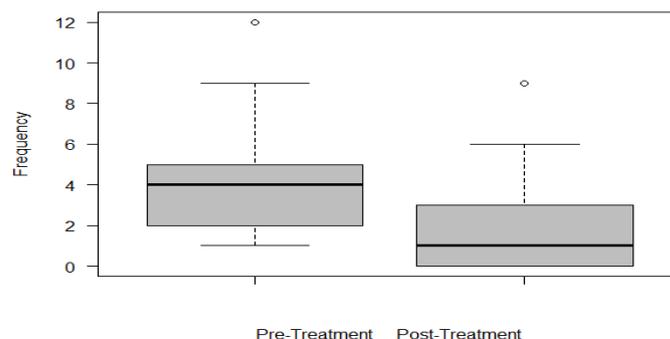
Vitamin D level	Pre treatment N=31	Post treatment N=31
>30ng/ml	2(6.4%)	3(6.3%)
20-29ng/ml	3(9.6%)	19(39.6%)
10-19ng/ml	16(51.6%)	8(16.7%)
<10ng/ml	10(32.2%)	1(2.1)
P value		0.00

## DISCUSSION

The present study was conducted to find the relationship between chronic diseases and vitamin D deficiency and the effect of replacement therapy in such patients. Patients who were suffering from Diabetic and hypertensive patients with clinical signs and symptoms of depression and mood disorders were included in study and these patients were found to have pronounced vitamin D deficiency (97.3%). The results of our study are in correlation with other studies conducted in different regions, patients with poor glycemic control were found to have 84% deficient levels as compared to good diabetes control patients [11]. Similarly another study detected high prevalence of vitamin D deficiency in patients with viral hepatitis [12].

In our study we found that significant association between sunlight exposure and vitamin D deficiency. This was in accordance with a study by Binkely N et al, who also noted significantly low levels of 25(OH) D in patients who were exposed to adequate sunlight [13]. Elspeth E and colleagues [14] in their study found that decreased sun exposure limits the synthesis of vitamin D, moreover they

found that sun exposure time is increased four to five times in naturally dark skinned people than white skin tone individuals. Similarly, we also noted that sun exposure time in our study population was less than 10 minutes in 42.9% population, although they require prolong sun exposure because of their dark skin tone. The main reason for low 25(OH) D production was time of exposure and it was significantly low in our study. Moreover our study population were dark skinned people. As it's also proven in previous studies dark skinned people suffered from more vitamin D deficiency because of poor absorption of UV.



**Figure 1: Comparison of symptoms in patients before and after treatment**

Yilmaz et al [15] in their study detected significant improvement in nonspecific musculoskeletal pain, level of depression, lethargy and quality of life with vitamin D replacement therapy. Our study also showed improvement of clinical symptomatology including lethargy, depression, anger, body aches and nonspecific joint pains. Upon administration of Vitamin D replacement therapy and follow up after 3 months, significant number of patients improved from severe deficiency levels to insufficiency levels, but still they were not restored to sufficient levels.

**Table 2: Clinical symptoms seen in affected population willing for treatment before and after treatment:**

Symptoms	Pre treatment	P-value (Pre treatment)	Improved (Post treatment )	Not Improved (post treatment)	P-value (Post treatment)
Body aches	26	0.04	16	10	0.42
Joint pain	24	0.41	14	10	0.17
Anger	24	0.02	8	16	0.43
Depression	29	0.55	12	16	0.42
Lethargy	17	0.87	11	6	0.39

Although there is no clear guideline to check the serum level after repletion, but the goal is to achieve a minimum level of 30ng/ml. in case if the values don't reach

sufficient levels, a second eight week course of ergocalciferol should be prescribed. The probable cause for not reaching the normal levels could either be non-

adherence to therapy or malabsorption. In case of malabsorption, consultation with gastroenterologist should be considered. After replenishing serum 25-hydroxy vitamin D levels, maintenance dosage of Cholecalciferol should be instituted at 800-1,000 IU per day along with supplemental sources [2].

With the above mentioned doses vitamin D replacement therapy is normally a safe treatment. It has been found vitamin D intoxication has been associated only with intakes of 50,000 to 1 million IU/d over the course of months or years [5]. So, it's yet to decide in our population about duration of therapy to prevent intoxication. Our study was conducted in a single center with a small sample size which is a limitation of the study. We further recommend this study in a larger population in a multicenter unit. Along with the variables used in our study other factors such as life style patterns, nutritional habits and sunshine exposure especially in places with cold climate can also be evaluated.

## CONCLUSION

Vitamin D deficiency is associated with chronic diseases. Currently, Vitamin D levels are below the recommended levels in worldwide population. Therefore as one of the preventive measures, mass awareness campaign should be started on media. In addition to the therapeutic measures, food fortification with vitamin D supplementation should be done. Regular follow up visits during the maintenance phase and evaluation of the serum Vitamin D levels are also equally important while treating such patients.

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