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Evaluation of Effectiveness of Use of Oral Vit D Supplements in Documented Vit D Insufficient or Deficient Patients- A Study in North Bihar

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ABSTRACT

Vitamin D is a group of fat soluble secosteroids responsible for a variety of physiological functions and mostly in respect to calcium homeostasis in the body. The major source of Vit D is from sunlight with a few other dietary sources. As Vit D is synthesised in the body it is being considered as a hormone more than a vitamin and has been found to have a role in prevention of various chronic illnesses like Diabetes, Cardiovascular disease.. The aim of the study was to determine the effectiveness of Oral Vit D supplements in patients with documented Vit D deficiency or insufficiency.

Method: *Patients(20-70years, both gender) attending outdoors of Darbhanga Medical College and hospital over a period of 6 months(1 january 2017-31st june 2017) with nonspecific complaints of myalgia, joint pain fatigue were screened for serum Vit D levels and patients who were deficient or insufficient were given oral supplements and levels repeated at 6 and 12 weeks. The statistical significance of improvement was measured by paired student t test.*

Results: *Most of the patients demonstrated clinical and biochemical improvement after 6 weeks of therapy($p<0.01$) and all patients achieved normal levels after 12 weeks of therapy($p<0.001$). The gender basis evaluation of the Vit D deficiency turned out not in favour of women who were more deficient as compared to age matched male counterpart and people>60 years were more deficient.*

Conclusion: *A majority of Vit D deficient people may be asymptomatic. Therefore a keen eye and high index of suspicion is necessary providing a role for screening in patients with non specific complaints and being a routine in people with bone diseases. Oral supplementation is both cost effective and feasible with good patient compliance and hence is an effective method to replinish stores.*

INTRODUCTION

Vitamin D refers to a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, phosphate, and zinc and multiple other biological effects. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalcife-rol) and vitamin D_2 (ergocalciferol). Vitamin D from the diet or skin synthesis is biologically inactive; enzymatic conversion (hydroxylation) in the liver and kidney is required for activation. As vitamin D can be synthesized in adequate amounts by most mammals exposed to sufficient sunlight, it is not an essential dietary factor, and so not technically a vitamin. Instead it could be considered as a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then produces effects via

a nuclear receptor in multiple different locations. Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 25(OH)D) are measured in serum to determine a person's vitamin D status.

Vit D deficiency contributes to the development of various diseases. Vit D is essential for Calcium metabolism and hence deficiency is an important contributing factor in bone pathologies and fractures. However,low vitamin D has been associated with an increased risk of diabetes mellitus, cardio-vascular disease, certain cancers, cognitive decline, autoimmune disorders and pregnancy complications. Commonest presentation being bone pain, myalgias and generalised weakness.

It has been estimated that worldwide one billion people have Vit D deficiency. In india more than 90% of apparently healthy Indians have subnormal Vit D levels. According to the endocrine society, levels <20ng/ml are considered deficient, 20-29ng/ml as insufficiency and levels above 30ng/ml as sufficient.

Primary source of Vit D in our country is exposure to sunlight. Secondary sources include dietary intake of foods naturally rich in vitamin D such as salmon, codliveroil, sundried mushrooms or vitamin D fortified foods. In our country, availability, acceptability and cost of these dietary products limits their widespread use by the general population. Hence pharmacological supplementation(mostly oral) is one of the most effective ways to prevent and correct Vit D deficiency is susceptible or proven deficient individuals. The serum Vit D level is directly proportional to the dose of oral Vit D and inversely proportional to the initial serum levels of Vit D.

The **Aim of the present study** is to determine the effectivity of oral supplementation of vitamin D(in any form) amongst patients with deficiency or insufficiency within 12 weeks with a mid course evaluation of response at 6 weeks.

METHODS

This was a prospective, open label, non comparative, dose response study of oral Vit D preparations in deficient or insufficient individuals. The study was conducted over a period of 6 months (1st January 2017- 30th June 2017). The primary objective was to reconfirm and establish the effectiveness of oral supplementation of Vit D in deficient or insufficient patients. Study was conducted in the Medicine Department of Darbhanga Medical College and Hospital (a Government medical college in north of Bihar).

Study population included adults,20-70 years of age, of both genders attending the outdoors of Darbhanga Medical College and hospital during the study period with non specific complaints of lethargy, myalgia and bone pain, generalised weakness with levels of Vit D <30ng/ml (insufficient) or with <20ng/ml (deficient) Patients with known hypersensitivity to Vit D oral preparations, hyperparathyroidism, growth hormone deficiency, malabsorption, kidney stones, uncontrolled hypertension and diabetes mellitus were excluded. Patients fulfilling criteria were included in the study after acquiring informed consent.

Patients enrolled were planned to receive weekly dose of 60,000 IU of oral Vit D(tablets capsules,sachets or liquid formulations). All patients enrolled were evaluated in details clinically and biochemically. Initial Vit D levels were recorded and patients were followed up at six weekly intervals of 6 and 12 weeks. Vit D levels were assessed in all three visits as well as patients were assessed on grounds of resolution of symptoms for which the patient had presented, tolerance, improvement in quality of life and general improvement symptomatically. Also patients were asked for long term follow up to determine effects of Vit D on other long term chronic disease parameters.

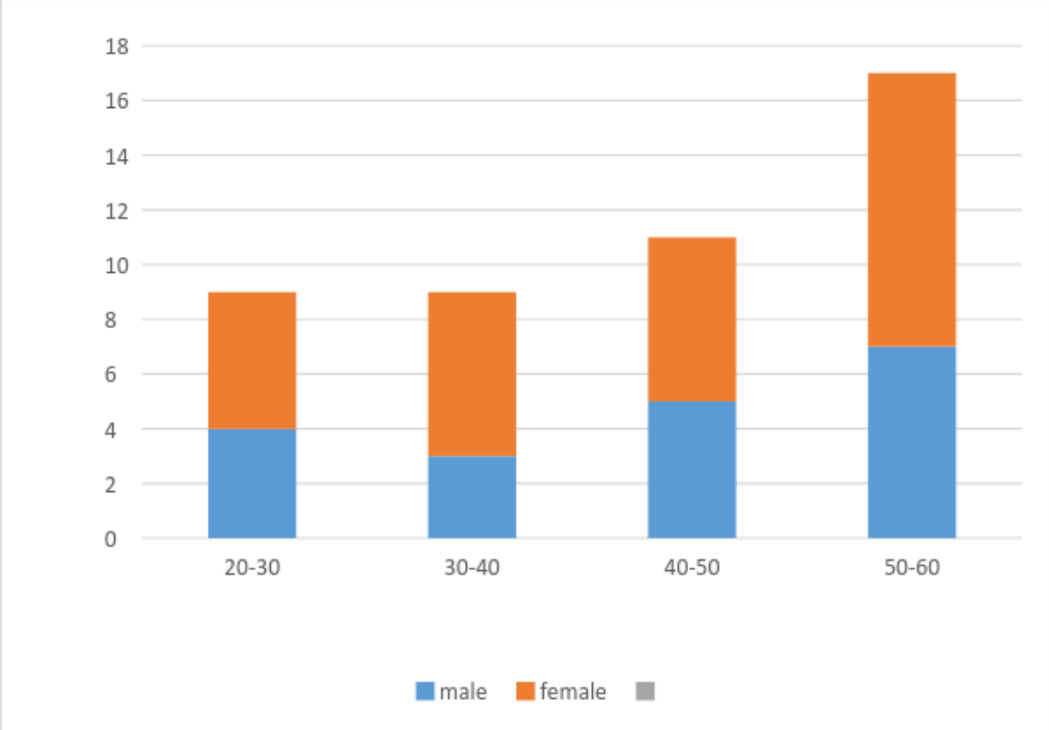
Sample size was 80 subjects (a population of 100 with a 95% confidence level and confidence interval of 5). Paired student t test was used to determine the statistical significance of the difference between the baseline and follow up visits. A p value of <0.05 was considered statistically significant.

No ethical committee issues were raised during the study.

RESULTS

A total number of 80 patients were selected randomly for inclusion in the study who fulfilled the inclusion criteria, out of whom 45(55%) were females and 35 mere males (45%). Total of 9(11.25%) patients were in the age group 20-30 years, while 34(42.5%) were above 60 years. 27 (33.75%) were obese, 18(22.5%) were overweight whereas rest were within the normal BMI range. As per exclusion criteria patients with significant co-morbidities were not included in the study.

Age/Gender	20-30	30-40	40-50	50-60	60-70
Male	4	3	5	7	16
Female	5	6	6	10	18



Highest prevalance of deficiency was found in the age group of 60-70years. 46(57.5%) patients (mostly women or people over 60 years of age) had lesser exposure to sunlight.

Out of 80 patients 54(67.5%) patients had insufficient levels of Vit D (<30ng/ml) whereas 26(32.5%) patients were Vit D deficient (<20ng/ml). The average level of Vit D in the population was 20.03ng/ml at base line level with standard deviation of 5.69(+/-). 64 patients (80%) showed increase to normal ranges of Vit D after 6 weeks of therapy whilst all patients achieved normal ranges of Vit D after 12 weeks of oral therapy(100%). The average value of Vit D at 6 weeks after intervention was 30.85 ng/ml with a standard deviation of 2.51(+/-). The level of increase in Vit D levels was an average of 10.82 ng/ml with oral supplementation within 6 weeks which was statistically significant with a p value <0.01(paired student t test, t=4.48 and standard

error= 2.19). At the end of 12 weeks the average blood levels of Vit D for all the patients enrolled in the study was 33.63 ng/ml with a standard deviation of 2.37(+/-). The rise in serum Vit D level of 13.60ng/ml was statistically significant with a p value of <0.001(paired student t test, t value at 12 weeks=5.02 with standard error of 2.50)

	Number of patients	Mean(ng/ml)	Standard deviation
Initial Vit d levels	80	20.03	5.69
After 6 weeks therapy	80	30.85	2.51
After 12 weeks therapy	80	33.63	2.37

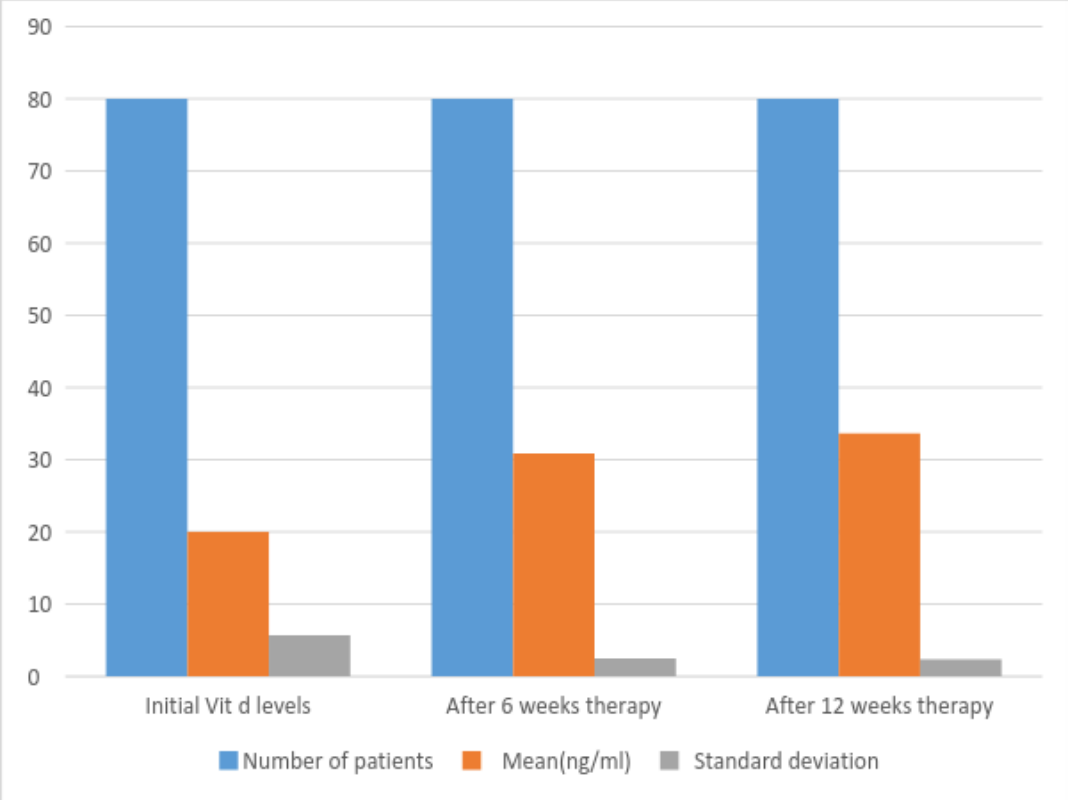


Fig: Mean serum Vit d levels at baseline, after 6 and 12 weeks of therapy respectively

Overall tolerance of the oral preparations were reported to be good by patients as well as clinician (researcher). Seven patients(8.75%) developed nausea and mild abdominal discomfort with the preparations but none were serious enough to warrant active intervention or drop out from the study.

DISCUSSION

Vitamin D deficient state has become one of the most prevalent and under diagnosed medical conditions in the world. Recent evidence suggests that lack of adequate sun exposure is the most important factor for this global pandemic as very few foods naturally contain vitamin D (wild caught salmon and UV exposed mushrooms). Analysis in children and adults indicate that dietary sources are grossly inadequate in providing the Recommended Dietary Allowances (RDA) for vitamin D. In our population, cutaneous production of vitamin D is further limited by increased melanin content of skin or sun avoidance by use of sunscreens, extensive clothing cover due to socio-cultural practices or staying indoors for most of the day. Also aging has frequently been reported to be associated with lower levels of Vit D levels in circulation as has been proposed that the capacity of the epidermis to synthesise Vit D and the expression of Vit D binding protein is compromised by aging.

US Endocrine Society recommends that serum 25 (OH) D levels of 30 ng/ml (vitamin D sufficiency) should be attained for children and adults to optimize the probability of good health and avoid other risk associated with Vit D deficient status. Furthermore, it is now acknowledged that previously recommended Vit D intake of 200 IU/day in the American recommended intakes or 400 IU/day in the WHO report are grossly inadequate. Thus, RDA of 600-800 IU is recommended to maintain adequate levels of Vit D. In our country, Indian Council of Medical Research (ICMR) recommends a daily supplement of 400 IU/day of vitamin D

This was an individual initiated study in a government set up. Patients(n=80) receiving any form of oral supplementation of Vit D showed significant($p<0.01$) rise in Vit D levels within 6 weeks of supplementation for most of the population(80%) and levels maintained at 12 weeks of therapy for them and also everyone achieved desired Vit D levels at 12 weeks of therapy($p<0.001$).

The most common formulation for oral administration is in the form of tablets (*n*=40, 50%) and capsules (n=24, 30%). Though alfacalcidiol and calcitriol are commonly available as tablets and capsules; cholecalciferol is in the form of granules in sachets (*n*=16,20%). Other dosage forms include syrups and softgel capsules. Though oral administration in the form of drops is commonly recommended for infants and children, adolescents and adults are usually prescribed tablets, capsules or granules for supplementation. Vitamin D preparations also contain various other minerals/vitamins such as magnesium, cupric, boron, methylcobalamin, vitamin E, vitamin K, vitamin C, pyridoxine, folic acid, beta-carotene, glutamic acid, manganese, omega 3 and docosapentaenoic acid. Tablets and capsules contain 10 IU (0.25microg) -10000 IU (25 mg) of vitamin D and are usually administered on a daily basis. Sachets of cholecalciferol containing granules of vitamin D amount to 60,000 IU of vitamin D are administered weekly. The approximate average cost of 1 sachet weekly was 20 INR, therefore at 6 weeks was 120 INR and at 12 weeks was 240 INR.

Prevalence of Vit D deficiency was higher in the age group>50 years(aging being a contributing factor to deficiency as discussed earlier) and amongst women(probably due to lesser exposure to sun owing to socio-cultural practices or more use of sun protectives or active avoidance of sun exposure) though a significant number of asymptomatic but deficient patients were found in the 20-30 age group.High body fat percentage or higher BMI have been associated with smaller increases in Vit D levels in response to therapy. However this study revealed no differences in response rates across BMI,gender, age and method of supplementation. All forms of supplementation were well tolerated and no significant adverse effects were encountered during the study. Vit D levels were corrected in all patients who received 12 weeks of supplementation therapy (n=80,100%)and symptoms of non specific myalgia, bone pain or lethargy significantly improved amongst the study population leading to improvement in quality of life assessed by a questionnaire at the baseline and at the end of the study.

Vit D preparations are reported to be reasonably safe for children and adults and doses upto 10000 IU/L can be tolerated per day without significant alterations in urinary and serum calcium levels. However, in rare cases, vitamin D toxicity can cause hypercalcemia, hyperphosphatemia, nephrocalcinosis, and soft tissue calcification, thus contributing to high risk of mortality. None of these were however encountered during the course of the study.

CONCLUSION

Vit D is essential for maintaining the Calcium homeostasis in the human body and also serves a magnitude of other functions. Recent studies suggest its role in immunity, protection against chronic diseases like Diabetes, Cardiovascular diseases, COPD and deficiency as a predisposing

factor to even diseases like Tuberculosis. The prevalence of deficiency is quite high and even may be amongst asymptomatic patients. Symptoms even if present are mostly nonspecific and hence deficiency is often missed. Patients with prolonged myalgia nonspecific lethargy not attributed to any other cause and not resolving with treatment may be screened for vit d deficiency and should be routinely screened in the aged, post menopausal women, patients with non traumatic fractures and poor bone health. Correction of Vit D levels are easy and cost effective with good patient compliance, hence the loophole lies with the diagnosis. A high index of suspicion with good awareness can reduce the number of cases missed and help in reducing the prevalence levels. The study confirms the feasibility and ease of diagnosis and correction of Vit D levels with limited resources and catering to mostly a lower socioeconomic strata of the society(which is also the limitation of this study as the sample size is not varied across all socioeco-nomic groups and can have selection bias).

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