The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-2909

FRACTURES;
CAUSES OF LOW VITAMIN D AND EFFECTS OF 25(OH) SUPPLEMENTATION IN PATIENTS ABOVE 50 YEARS

Dr. Nasir Zulfiqar[1], Dr. Hamid Mahmood[2], Dr. Ghazia Irfan[3], Ammara Waqar[4], Nadeem Iqbal[5]

1. Associate Professor 0f Surgery, Sir Syed institute of Medical Sciences, Karachi.
2. Professor of Bio Chemistry, Continental Medical College, Lahore.
3. PM&DC, Islamabad
4. PIQC, Lahore.
5. PIQC, Lahore.

Correspondence Address:
Dr. Hamid Mahmood
Professor of Bio Chemistry,
CMC, Lahore.
drhamidmahmood373@gamil.com

Article received on:
27/04/2015
Accepted for publication:
22/05/2015
Received after proof reading:
09/07/2015

ABSTRACT… To find out the effect in increase in serum 25(OH) vitamin D levels after supplementation with 1000 IU/day of vitamin D in patients with low vitamin D levels and other factors which may affect the increase in vitamin D levels. **Study Design:** Retrospective study. **Period:** January 2013 and June 2014. **Setting:** Ch. Rehmat Ali Trust Teaching Hospital in the Lahore. **Methods**: The study included patients > 50 years with a low-energy fracture and a vitamin D level < 25 nmol/l. **Results**: 85 patients were included, mean basal 25(OH) vitamin D level was 22 nmol/l. After a mean of 10 weeks, the mean increase in vitamin D was 49.5 nmol/l. Only 45.1% reached the target level of > 50 nmol/l. The increase was correlated with the basal level of vitamin D ($p < 0.05$), and the time interval between the two vitamin D measurements ($p < 0.05$) and was inversely related to body weight ($p < 0.05$), but was not related to age, gender or renal function. **Conclusions**: We found that the generally recommended dosage of 1000 IU of vitamin D per day resulted in suboptimal serum levels after ten weeks of treatment in more than half of the patients. The increase in vitamin D levels was higher in patients with low body weight and in patients with very low basal vitamin D levels. These data suggest that these patients should initially be treated with higher dosages of vitamin D. If not possible, vitamin D measurements should be performed after at least six months of supplementation with dosage adjustment.

Key words: 25-hydroxyvitamin D levels, vitamin D deficiency, low-energy fracture

Article Citation: Zulfiqar N, Mahmood H, Irfan G, Waqar A, Iqbal N. Fractures; Causes of low vitamin D and effects of 25(OH) supplementation in patients above 50 years. Professional Med J 2015;22(7):954-958.

INTRODUCTION

Vitamin D deficiency is common in elderly patients with a fracture caused by a low-energy trauma. Bours et al. found a vitamin D deficiency (< 50 nmol/l) in 64% of their patients, all with a recent fracture.[1] Severe vitamin D deficiency is associated with muscle weakness, bone pain, and an increased risk of falls and fractures.[2] In general, the supply of vitamin D mainly relies on exposure to the sun, body mass index (BMI) and skin colour.[3] The recent orthopedic guidelines on osteoporosis and fracture prevention advise a daily intake of 1000 IU cholecalciferol for people over 50 years of age and those suffering from osteoporosis. They additionally recommend a 25-hydroxyvitamin D level target value of at least 50 nmol/l.[4] However, several authors consider the optimum level to be > 75 nmol/l, since it is considered to be the minimum level to prevent falls.[5] Considering its impact on preventing falls and fractures, vitamin D supplementation is of great importance. No consensus has been reached on whether a post-treatment control level should be established when a mild or severe vitamin D deficiency has been diagnosed, or what the optimum daily dose of vitamin D supplementation should be in clinical practice.[2] Van den Bergh et al. recently proposed to establish a control 25-hydroxyvitamin D level after three months of supplementation and, if necessary, to adjust the recommended dose of cholecalciferol.[6] They based their proposal on the finding that, in a low-energy fracture patient population, the optimal level of > 50 nmol/l was often not reached with a daily dose of 1000 IU.[1] A meta-analysis showed that with a 25-hydroxyvitamin D basal level of < 50 nmol/l, vitamin D supplementation with 400 IU/day led to an average increase in vitamin D levels of 12 nmol/l.[5] So far, there have been few reports on the effect of a relatively low dose (400-1000 IU a day) of oral vitamin D supplementation on the increase of 25-hydroxyvitamin D levels in patients

> 50 years with a (low-energy) fracture.

RESEARCH QUESTIONS

The objective of this study was to examine the following research questions:

A: What is the increase of the 25-hydroxyvitamin D level after supplementation with a daily dose of 1000 IU of cholecalciferol for 10 weeks in patients with a severe vitamin D deficiency (< 25 nmol/l) and a low-energy fracture?

B: What percentage of patients will reach the minimum target value of 50 nmol/l?

C: Which factors affect the increase of the 25-hydroxyvitamin D level? Factors that were expected to influence this increase were body weight, BMI, renal function, gender, age, season and 25-hydroxyvitamin D basal level.

METHODS/ PATIENTS

Since 2013, the Ch Rehmat Ali Trust Hospitals screen all patients over 50 years of age with a low-energy fracture (except in fingers, toes and metatarsal bones) at the fracture-osteoporosis .Outpatient clinic for the presence of osteoporosis/ osteopenia, by means of DEXA and X-rays of the lumbar and thoracic vertebrae. All patients were asked to complete a questionnaire on known risk factors for osteoporosis/osteopenia. In addition, relevant laboratory tests are run, including a measurement of the 25-hydroxyvitamin D level. Serum 25-hydroxyvitamin D levels were determined on a high-performance liquid chromatography (HPLC) column with two mobile phases (Chromosystems, Munich, Germany) after a purification step. Data on serum 25-hydroxyvitamin D levels were collected retrospectively. The patients with a serum 25-hydroxyvitamin D level < 25 nmol/l were referred to the rheumatologist to further investigate the cause of their severe vitamin D deficiency. For the purposes of this study, patients were not allowed to take supplements containing any vitamin D < 3 months prior to their first vitamin D measurement. All patients were prescribed a supplement of 1000 vitamin D IU/day (12 received 880 IU/day).

For all patients included in this study, a second measurement of the 25-hydroxyvitamin D level was done during their visit to the rheumatologist. Exclusion criteria for this study were: a known malabsorption syndrome, primary hyperparathyroidism, hyperthyroidism, an eGFR < 40 ml/min, any reasonable doubt on the intake of vitamin D and lack of a second vitamin D measurement after treatment.

DATA ANALYSIS

Standard descriptive statistical methods were used. To determine the association between two continuous variables, a linear regression was calculated with the correlation coefficient (r) and p-value for the beta of the independent variable. A T-test was used to calculate the association between a continuous variable and a binomial variable, and for a multiple category variable, the ANOVA test for an 'overall' p-value was used; to further explore the associations we computed Tukey multiple comparisons paired p-values and a p-value for linear trend.

RESULTS

Between January 2013 and June 2014, 85 patients who met the inclusion criteria for this study and had a 25-hydroxyvitamin D level < 25 nmol/l were seen at the fracture-osteoporosis outpatient clinic. Ninety Three patients had both an evaluation by the rheumatologist and a second 25-hydroxyvitamin D measurement. After exclusion of eight patients (see table I for the reasons), 85 patients were included in the final evaluation. An overview of the basal characteristics of the patients is provided in table II. The baseline 25-hydroxyvitamin D level had an inverse correlation ($r = -0.241$, $p = 0.0291$) with body weight but, due to missing data on height, not with BMI. From the 85 patients included, a second 25-hydroxyvitamin D measurement was performed after a mean period of 9.8 (SD 5.3) weeks. All patients showed a highly variable increase in 25-hydroxyvitamin D level, with an average increase of 48 nmol/l (SD 21; range 8-101).

Only 37 patients (45.1%) reached a 25-hydroxyvitamin D level of > 50 nmol/l. There was an inverse correlation between the increase

in vitamin D levels and body weight (r = -0.225, p = 0.0417). We also found an inverse correlation between the individ (r = -0.235, p = 0.0337). When comparing different subgroups by their basal vitamin D level, the group that had the lowest basal values (0-10 nmol/l, mean increase 73 [SD 28]) clearly showed a stronger increase than both the middle (11-20 nmol/l, mean increase 48 [SD 22]) and the highest (21-25 nmol/l, mean increase 46 [SD 19]) groups [p for trend = 0.0298). The degree to which the level increased was not related to gender, BMI (missing data), age, season (April to October versus November to March) or renal function.

Statistical analysis showed a significant positive correlation between the increase in 25-hydroxyvitamin D level and the number of days that passed between the first and second measurement (r = 0.246, p = 0.0260). Even after three months of vitamin D supplementation, a plateau phase was still not reached.

Patients	N
Patients with a vitamin D level < 25 nmol/l who met inclusion criteria	134
Patients seen by rheumatologist + second vitamin D measurement	90
Exclusion following consultation by rheumatologist:	8
Reason for exclusion: Doubts about vitamin D intake Intolerance for vitamin D Crohn's disease Primary hyperparathyroidism eGFR <40 ml/min missing data	 1 2 1 1
Final study population	85

Table-I. Study patient population

Patient characteristics	Mean values (SD)#
Male n (%)	32 (39%]
Age (years)	68.2 (10.7)
Body weight (kg)	72.8 (16.4)
Male n (%)	75 (91%)
BMI* (kg/m2)	25.6 (4.1)
25-OH vitamin D level (nmol/l)	21.2 (6.1)
Calcium (normal values 2.10-2.50 mmol/l; unadjusted)	2.36 (0.12)
Creatinine (normal values 62-106 µmol/l)	70.4 (18.1)
Alkaline phosphatase (normal values 0-120 U/l)	99.2 (34.2)
# except for gender and race; * missing data for 49 patients	

Table-II. Patient basal characteristics (n = 85)

DISCUSSION

In our study, male and female population with a mean age of 68.2 years and severe vitamin D deficiency (average value 21.2 nmol/l), after supplementation with 1000 IU/day of vitamin D, we observed a mean increase of 49.5 nmol/l after an average of 10 weeks. These results are in concordance with those found by Chel et al.,[7] who reported a mean increase of 34.9 nmol/l after two months and 44.9 nmol/l after four months after supplementation with 600 IU/day of vitamin D in nursing home patients (mean age 84 years). In patients with various rheumatic diseases and a mean age of 68 years, vitamin D levels increased from 25.[8] to about 60 nmol/l after at least six months of treatment with vitamin D 1000-1000 IU a day.[8]

After supplementation with 1000 IU/day, Lips et al. observed a larger increase in the 25-hydroxyvitamin D level (namely from 23.7 nmol/l to 80 nmol/l) after three months in elderly patients (> 80 years) living in nursing homes or old peoples' homes, who likely had a better compliance.[9] Gallagher et al. recently reported in a placebo-controlled study with healthy post-menopausal women (mean basal vitamin D level 38.2 nmol/l) that after three months of supplementation with 1000 IU vitamin D a day, a vitamin ual 25-hydroxyvitamin D basal level and the increase in 25-hydroxyvitamin D levels. D level of > 50 nmol/l was reached in 97.5% of the cases.[10] These results obviously cannot be translated to clinical practice in fracture patients who are for the most part older and have lower basal vitamin D levels. In daily practice, it is a clinically relevant question to ask whether the generally recommended dosage of 1000 IU vitamin D per day is sufficient for elderly patients with a recent fracture and a severe vitamin D deficiency.[11] We are not aware of any other reports on the increase of vitamin D levels after supplementation in elderly fracture patients with very low basal vitamin D levels.

In our study, the patients with the lowest 25-hydroxyvitamin D basal levels showed the highest increase after supplementation. This is in concordance with results previously reported in the literature on this subject.[2] In the present study, no plateau phase was reached after three months of supplementation. Vieth et al. showed that healthy volunteers (mean age 41 years)

taking 1000 IU/day of vitamin D reached a plateau phase of vitamin D after three months, with vitamin D levels increasing from 40.7 to 68.7 nmol/l.[12] However, in a study with elderly subjects, Lips et al. reported on a plateau phase after 6-9 months of supplementation.[9] A control measurement of Vitamin D should therefore be conducted after at least three months of supplementation[3] or, in our opinion, perhaps preferably after six months. Fewer than half (45.1%) of our patients reached the generally advised 25-hydroxyvitamin D target value of 50 nmol/l (after ten weeks). We do realize that this threshold of 50 nmol/l is arbitrary and that some advocate higher target levels such as 75 nmol/l.[6] As expected, a level of > 75 nmol/l was reached in only a minority of our patients (12.2%). We do agree that the follow-up time was probably too short to reach a new plateau level of vitamin D.

Despite that, it seems likely that the generally used and recommended dosage of vitamin D of 1000 IU/day is too low and that treatment should perhaps consist of a higher, possibly loading, dose,[6,8] especially in cases of severe deficiency and obesity.[5] Van Groningen et al. found an increase of vitamin D from 20.5 to 74.8 nmol/l after eight weeks following a loading dose of vitamin D (total dosage 100,00-200,000 IU) in vitamin D-deficient adults. The target levels of vitamin D of 50 and 75 nmol/l were reached in 76% and 48%, respectively.[13] These figures are obviously higher than in our study. Of course, it may also be considered to adjust the dosage of vitamin D supplementation according to the basal vitamin D levels.

We identified an inverse correlation between body weight and basal vitamin D levels. Indeed, it is already known that obese subjects have lower basal vitamin D levels because they have a larger distribution volume.[13,14] It has been demonstrated in recent literature that also the increase in the 25-hydroxyvitamin D level negatively correlates with body weight and/or BMI.[11,15] Indeed, in our only slightly obese patients (BMI 25.4), we found a negative correlation between body weight and the increase in vitamin D levels. We did not find such a correlation between this increase and BMI due to a large quantity of missing data on height.

The most important limitations of our study are its retrospective format and the follow-up time < 10 Weeks, which is too short to reach a new plateau level of vitamin D. In addition, there was no information on dietary intake of vitamin D and compliance of intake of vitamin D medication. The study's strengths are: it reports on a clinically relevant question in daily practice and that it was investigator driven without any financial support.

CONCLUSIONS

In conclusion, we have shown that after a dose of 1000 IU/day of vitamin D, only 45.1% of the elderly fracture patients with a severe vitamin D deficiency reached the advised 25-hydroxyvitamin D level of > 50 nmol/l after an average of ten weeks. The increase in vitamin D level had an inverse correlation with basal vitamin D levels and body weight, and was expectedly associated with the duration of supplementation. Based on our data and data from the literature, we propose taking a second measurement of the vitamin D level after at least six months of supplementation, with dosage adjustment.

REFERENCES

1. Bours SPG, van Geel TACM, Geusens PPMM, et al. **Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture.** J Clin Endocrinol Metab. 2011; 96:1360-7.

2. Rosen CJ. **Vitamin D insufficiency.** N Engl J Med. 2011; 364:248-54.

3. Dawson-Hughes B, Mithal A, Bonjour J-P, et al. **IOF position statement: vitamin D recommendations for older adults.** Osteoporosis Int. 2010; 21:1151-4.

4. Richtlijn Osteoporose en Fractuurpreventie, **derde herziening (2001).** Utrecht: Nederlandse Vereniging voor Reumatologie.

5. Bisschoff-Ferrari H**. What is an adequate vitamin D level and how much supplementation is necessary?** Best Pract Res Clin Rheumatol. 2009; 23:789-95.

6. Bergh van den JPW, Bours SPG, van Geel TACM, Geusens PP. **Optimal use of vitamin D when treating osteoporosis.** J Clin Endocrinol Metab. 2011; 96:1360-7.

7. Chel V, Wijnhoven HAH, Smit JH, Ooms M, Lips P. **Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents.** Osteoporosis Int. 2008; 19:663-71.

8. Sainaghi PP, Bellan M, Nerviani A, et al. **Superiority of a high loading dose of cholecalciferol to correct hypovitaminosis D in patients with inflammatory/ autoimmune rheumatic diseases.** J Rheumatol. 2013; 40:166-72.

9. Lips P, Wiersinga A, van Ginkel FC, et al. **The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects.** J Clin Endocrinol Metab. 1988; 67:644-50.

10. Gallagher JC, Sai A, Templin II, T Smith L. **Dose response to vitamin D supplementation in postmenopausal women.** Ann Int Med. 2012; 156:425-37.

11. Bisschoff-Ferrari HA, Willett WC, Orav EJ, et al. **A pooled analysis of vitamin D dose requirements for fracture prevention.** N Engl J Med. 2012; 367:40-9.

12. Vieth R, Chan P-KR, MacFarlane GD. **Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level.** Am J Clin Nutr. 2001; 72:288-94.

13. Van Groningen L, Opdenoordt S, van Sorge A, Telting D, Giesen A, de Boer H. **Cholecalciferol loading dose guideline for vitamin D deficient adults.** Eur J Endocrinol. 2010; 162:805-11.

14. Lee P, Greenfeld JR, Seibel MJ, Eisman JA, Center JR**. Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index.** Am J Med. 2009; 122:1056-60.

15. Saliba W, Barnett-Griness O, Rennert G. **The relationship between obesity and the increase in 25 (OH) D levels in response to vitamin D supplementation.** Osteoporosis Int. 2012; 24:1447-54.

PREVIOUS RELATED STUDY

Hafiz Muhammad Rafique, Sardar Ali, Azeem. FRAGILITY HIP FRACTURES (Original) Prof Med Jour 16(2) 298-301 Apr, May, Jun, 2009.

Irfan Zafar Haider, Tahir Ahmad Khan. CLAVICLE FRACTURES; INCIDENCE A TWO YEARS STUDY (Original) Prof Med Jour 17(2) 325-327 Apr, May, Jun 2010.

Noor Akbar Sial, Abid Rashid, Ajmal Yasin. SUPRACONDYAR HUMERUS FRACTURES; OUTCOME OF OPEN REDUCTION AND PERCUTANEOUS CROSSED PIN FIXATION (Original) Prof Med Jour 18(1) 147-153 Jan, Feb, Mar 2011.

Tariq Mahmood, Ajmal Yasin, Arshad Ali Cheema, Rasul Ahmad Chaudhary. COMMINUTED FRACTURES OF SHAFT OF FEMUR; BRIDGE PLATE VERSUS INTERLOCKING NAIL IN LOW VELOCITY GUN SHOT INJURIES. (Original) Prof Med Jour 16(3) 351-356 Jul, Aug, Sep, 2009.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Nasir Zulfiqar	Clinical findings	
2	Dr. Hamid Mahmood	Clinical assay	
3	Dr. Ghazia Irfan	Data collection	
4	Ammara Waqar	Data evaluation	
5	Nadeem Iqbal	Thesis writing	