

Correction of Vitamin D Deficiency, Which Route Is Better ? A Randomized Controlled Trial in Hyderabad, Sindh, Pakistan

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Abstract: *Objective:* To compare the efficacy of oral vitamin-D versus injectable Vitamin-D supplementation in adults of Hyderabad. *Study Design:* randomized control trial, *Place and Duration of Study:* Sadder and Latifabad Hyderabad April 2016 to July 2016. *Methodology:* 285 adults were selected from clinics of Sadder and Latifabad Hyderabad, already diagnosed cases of vitamin D deficiency. Out of which 160 were females and 125 were males. All patients were included after obtaining written consent. Two groups were made after stratified randomization. Group A was kept on intramuscular (IM) therapy and group B was on oral therapy. Group A included 140 patients and group B 145 patients respectively. The dosage and frequency of vitamin D supplementation intramuscularly was 0, 4, 8 and 12 weeks and oral 20000 units per week. Serial vitamin D serum levels were done at 4th and 12th weeks. *Results:* The improvement at 4th week in Oral group was significantly greater than IM group ($p=0.02$) but the improvement in intramuscular group was significantly greater than Oral group at 12th week ($p=0.02$) *Conclusion:* vitamin D deficiency can be corrected by any route but intramuscular route is more preferable than oral route because of decreased side effects.

Key words: Vitamin-D oral • Route • Adults • Hyderabad

INTRODUCTION

Vitamin D deficiency is demonstrated in all ages of life and seems to be the commonest vitamin deficiency in the world [1]. Vitamin D is important in skeletal, bone health and maintenance of neuromuscular, endocrine and sexual functioning.

Because the signs and symptoms of vitamin D deficiency are subtle or nonspecific, it remains unrecognized and untreated for many years [2].

Oral supplementation of Vitamin D3 may be a safe alternative to sunlight and may be easy to achieve optimum levels [3].

Bile is needed for proper intestinal absorption of oral vitamin D supplementation. Vitamin D circulates in the blood in association with alpha globulin, disappears from plasma with a half-life of 19-25 hours and is finally stored in fat depots for a prolonged period.

Intramuscular Vitamin D is also derived from Arachis oil (flowering plant) in depot formulation in strength of 1 to 6 hundred thousand units. Compliance with oral therapy may be low; hence it is important to know which route of administration is better, oral or intramuscular.

Vitamin D < 30 ng/dL is a common laboratory finding in the world [4, 5] and its level can be affected by the society, demography, type of food consumption, tropical versus non-tropical. Over one billion people globally have low serum vitamin D levels [6].

The estimated low level of vitamin D in Pakistan ranges from 85–98%, as reported by various studies. Mansoor S *et al* done a study in Karachi, enrolled employees from a tertiary care center showed 90% of the employees having low vitamin D levels [6]. Another study showed 92% prevalence of vitamin D deficiency. Same reported prevalence also noticed in asymptomatic ambulatory patients to the endocrinology OPD in a tertiary care center in Karachi.

Researchers reported the prevalence of low levels of vitamin D in India in between 80–85% in groups of postmenopausal women and local hospital staff [7, 8].

High prevalence of Vitamin D deficiency and insufficiency was also reported in > 80% of healthy adults living in urban Tehran, Iran [9].

The correction of vitamin D deficiency improves the outcome of obesity and its associated insulin resistance [10].

Few studies have shown dose-response relationship between oral intake of vitamin D and subsequent serum levels of vitamin D [11].

Lawson *et al* [12] showed a high degree of association between iron deficiency anemia and vitamin D deficiency.

Observational studies have discovered the fact that decreased capacity for cutaneous vitamin D synthesis is associated with hypertension in winter season [13].

The route of supplementation is debatable throughout the world like a study presented at the 13th European Congress of Endocrinology (ECE) [14]. demonstrated that oral dosing protocol for vitamin D supplementation provides significantly greater recovery of 25-hydroxyvitamin D3 (25[OH]D3) levels than a single 3-month intramuscular (IM) injection of vitamin D in patients with vitamin D deficiency or insufficiency.

Vitamin D deficiency also predisposed greater adiposity through other metabolic effects, such as regulation of PTH and modulation of adipogenesis, [15] pathogenesis includes increased PTH lead to increase in free intracellular calcium into adipocytes which could enhances lipogenesis [16].

The rationale of this study is to demonstrate the effective route of supplementation of vitamin D in population of Hyderabad.

Methodology: Total of 285 adult patients (>18 years) of Vitamin D deficiency were selected by using 90% incidence of vitamin D deficiency from various studies with CI 95% and 5% margin of error. Patients were selected from the clinics of sadder and Latifabad towns of Hyderabad. Out of which 160(56.5%) were females and 125(44%) were males. The Participation was voluntary and a written informed consent was also obtained. A detailed history and clinical examination was done.

Patients having normal serum vitamin D level and who are on supplementation of vitamin D or calcium, having chronic GI disease like celiac, IBD or upper gut resection, renal or hepatic diseases, tuberculosis were excluded.

10 cc of blood was sent for vitamin D estimation by chemoemoulicent method to different laboratories of sadder and Latifabad. The level less than 20 was considered vitamin D deficiency. The patients were randomized into two groups A and B by simple random sampling.

Group A included 145 patients out of which 62 were males and 78 were females with a mean of 35.4 years \pm (5.7) and a sun exposure 3.2(\pm 1.9)hours/day.

Group B included 140 patients of 63 males and 82 females with a mean age 37(\pm 2.6) and a sun exposure of 3.9(\pm 1.6) hours /day.

Group A included 140 patients who received dose 20,0000 U injection intramuscularly monthly and group B represented 145 patients received dose of 20000 U orally per weekly. Serial vitamin D estimation was done at 4th and 12th weeks. During treatment all patients were assessed for side effects of vitamin D supplementation either by oral or intramuscular injection like pain, dyspepsia, metallic taste, vomiting, bony pain and vertigo.

RESULTS

A total 285 patients were included in the study, which were divided in two groups A and B. For group comparison two-sample t-tests was being used.

BMI of group A was 34 (3.6) and group B 32(4.1) (P value<0.07) Shown in Table 1.

Baseline line serum vitamin D was 18.2-3.5 and 17.6-4.7(P value <0.06), While 23.5-2.0 and 28.7-2.6 (P value<0.02) and 33.7-1.3 and 28.4-1.5(P value<0.02) after 4 weeks and 12 weeks in group A and B respectively. Shown in Table 2

Both Oral and injectable forms of vitamin-D were effective but injectable form was shown to be statistically significant during 1st 4 weeks, while oral therapy was statically more significant after 4 weeks of therapy shown in Table 3.

Table 01: Demographic variable of 285 patients of vitamin D deficiency

| Variables | Group A | Group B | P value |
|----------------------------|-------------------|------------------|---------|
| Male | 62 | 63 | |
| Females | 78 | 82 | |
| Age(years) | 35.4 (\pm 5.7) | 38 (\pm 2.6) | |
| Sun exposure(hours /day) | 3.2(\pm 1.9) | 3.2(\pm 1.6) | |
| BMI | 34 (\pm 3.6) | 32(\pm 4.1) | <0.07 |
| Exercise (20 minutes /day) | 22.3(\pm 11.2) | 25.3(\pm 6.9) | <0.06 |

Table 2: Vitamin D levels after supplementation of vitamin D

| Weeks | Group A | Group B | P value |
|----------------------|-------------------|-------------------|---------|
| Initial dose | 18.2 (\pm 3.5) | 17.6 (\pm 2.6) | <0.01 |
| 4 th week | 23.5 (\pm 2) | 28.7 (\pm 1.5) | <0.02 |
| 12 th week | 33.7(\pm 1.3) | 28.9(\pm 1.5) | <0.02 |

Table 3:Side effects of two groups received vitamin D supplementation (%)

| Side effects | Group A | Group B | P value |
|----------------|---------|---------|---------|
| Dyspepsia | 23 | 60 | <0.07 |
| Pain | 70 | 46 | <0.08 |
| Metallic taste | 40 | 45 | <0.06 |
| bony pain | 25 | 35 | <0.06 |
| Vertigo | 10 | 30 | <0.04 |
| Vomiting | 15 | 40 | <0.02 |

DISCUSSION

This randomized controlled trial was conducted in different towns of Hyderabad and Pakistan. The rationale was that vitamin D deficiency is a very common in our region in all age groups despite of good nutrition, sunlight and exercise. It has been a debate that which route is preferred so that 285 patients were included in this study, which were divided in two groups, group A taken vitamin D supplementation by intramuscular and group B by oral route.

BMI of group A was 34 (3.6±) and group B 32(±4.1), baseline serum vitamin D was 18.2 (±3.5) and 17.6 (±4.7) P value <0.06.

While serum vitamin D was 23.5 (±2.0) and 28.7(±2.6) P value<0.02 after 4 weeks and 33.7(±1.3) and 28.4(±1.5) P value<0.02 after 12 weeks in group A and B respectively.

Vitamin D is tolerated by both oral and intramuscular routes. Terrence *et al.* [17] shown a single intramuscular dose of vitamin D, increase in the serum 25(OH)D levels at the end of 12 months was 26% compared to an average rise of 28% reported by but it is in contrast to our study where steady increase in vitamin D which was significant as shown in Table 3.

Another study compared the different formulation of vitamin D supplementation like Single intramuscular dose (600,000 IU) of vitamin D, a lower daily oral dosage (2,000 IU daily) for four weeks in the form of 25 ml syrup daily and small frequent intramuscular doses (20,000 IU) five times in two weeks. They have not found any significant difference between the three groups in the increase in the serum calcium concentration or the serum phosphorous concentration and serum vitamin D levels [18].

Intramuscular injections was shown to be statistically better in correction of deficiency of vitamin D during 1st 4 weeks, while oral therapy was statically more significant after 4 weeks of therapy. Our study is match able to Both Davie *et al* [19] and Weisman *et al* [20] showed that with oral dosing, there was a relatively rapid peak in serum 25 (OH) D concentrations, with concentrations falling progressively afterward. When doses were administered intramuscularly, there was a longer-lasting response in terms of serum D levels. While in some cases it took more 2 months for the peak concentration to be achieved as shown by Heikinheimo *et al.* [21].

Incomplete or failure to compliance to take oral tablet has been associated with difficulty swallowing combined vitamin D/calcium tablets, gastrointestinal side-effects [22].

It is quite similar in our study where 60% were having dyspepsia, 45% flushing of face, 46% pain and 45% metallic taste made difficult for patients to continue with oral supplementation.

Serial doses of vitamin D more than 200,000 IU/month appeared to be most effective in treating vitamin D deficiency, such as that in the study of Ilahi *et al* [23]. The frequent dosage is also shown in our study that we have given supplementation 4 weeks apart and did not prefer the mega dose.

CONCLUSION

In vitamin D deficiency, monthly supplementation by intramuscular route is better option than weekly oral supplementation. In the majority of the patients Vitamin D levels significantly reached optimal levels. Although both administration routes are effective and appear to be safe, IM application is more effective in increasing 25(OH) D levels and balance performance.

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