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COMPARISON OF VITAMIN D REPLACEMENT STRATEGIES WITH HIGH-DOSE INTRAMUSCULAR OR ORAL CHOLECALCIFEROL: A PROSPECTIVE INTERVENTION STUDY

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ABSTRACT:

Objective: To ascertain the frequency of correction of vitamin D deficiency (VDD) with single or multiple doses of oral (PO) and intramuscular (IM) administration of 2 high-dose preparations of vitamin D_3 (VD_3).

Methods: This was a prospective intervention study conducted in an ambulatory care setting. One hundred participants with VDD (25-hydroxy vitamin D [25-OHD] <20 ng/mL) were randomized to receive a dose of 600,000 or 200,000 IU of VD_3 via a PO or IM route. The main outcome measure was serum 25-OHD levels at 2, 4, and 6 months after the intervention.

The same dose was repeated in participants if 25-OHD remained <30 ng/mL at 2 and 4 months.

Results: At 2 months, VDD was corrected in 93.8% of participants in Group 1 (600,000 IU IM); 83.3% in Group 2 (600,000 IU PO), 87.5% in Group 3 (200,000 IU IM), and 70.6% in Group 4 (200,000 IU PO). The mean changes from baseline in vitamin D levels at 2 months were 29.6 ± 13.7, 19.8 ± 12.3, 18.3 ± 10.6, and 13.7 ± 7.8 ng/mL in Groups 1, 2, 3, and 4, respectively. The mean levels remained significantly higher from baseline in all groups at all time points during the 6 months of observation. The mean 25-OHD level achieved in Group 1 was significantly higher than all other groups at 6 months.

Conclusion: Two months after the intervention, VDD was corrected in more than 70% of participants with a single dose of either 600,000 or 200,000 IU given PO or IM. **(Endocr Pract. 2015;21:1125-1133)**

Abbreviations:
ALT = alanine transaminase; **IM** = intramuscular; **iPTH** = intact parathyroid hormone; **IQR** = interquartile range; **25-OHD** = 25 hydroxyvitamin D; **PO** = oral; **VD_3** = vitamin D3 (cholecalciferol); **VDD** = vitamin D deficiency; **VDI** = vitamin D insufficiency.

INTRODUCTION

Vitamin D deficiency (VDD) has resurfaced as a significant public health problem in recent years. About 40 to 100% of U.S. and European elderly males and females are deficient in vitamin D (1,2). In Pakistan, VDD is highly prevalent despite adequate sunshine throughout the year (3-6). Vitamin D insufficiency (VDI) and VDD are when serum levels are <30 ng/mL and <20 ng/mL, respectively (1,2). According to reports from adult ambulatory care patients and healthy volunteers from centers in Karachi and Lahore, the prevalence rates of VDD and VDI range from 84 to 99% and 57 to 86%, respectively (3-6).

Safe and adequate correction of VDD is an area of active interest. This is a complex issue as there is no universally accepted regimen, particularly with high-dose preparations. Moreover, controversies exist in practices and recommendations. Despite recent recommendations and guidelines, some of the important unanswered questions regarding vitamin D replacement include its preferable form (ergocalciferol or cholecalciferol), administration route (oral [PO] or parenteral), fixed or titrated dosing strategy, and lower daily or higher intermittent doses (7-9). There is also wide interindividual variability in the

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dose-response relationship, and factors such as the initial 25 hydroxyvitamin D (25-OHD) concentration, patient weight, adequacy of the dosing, variability in absorption, and inaccurate 25-OHD analysis contribute to this variability (10).

Recently, concerns about the safe upper level of vitamin D have been raised, and a reverse "J-" or "U-" shaped relation has been described for 25-OHD level and mortality (11,12). Increasing numbers of patients are being reported with vitamin D toxicity because of excessive intake resulting from misinterpretation of prescription, manufacturing errors, and inappropriate prescription of excessive vitamin D doses for vague musculoskeletal complaints without monitoring 25-OHD concentrations (13,14).

In Pakistan, the issue is further complicated as until recently oral vitamin D supplementations were only available in combinations with calcium supplements at the maximum dose of 400 IU. Two depot intramuscular (IM) preparations are widely used; they contain 200,000 or 600,000 IU vitamin D_3 (VD_3). As there are no recommendations regarding the dosing interval for these mega doses, practice among physicians varies widely, with the conservative being 600,000 IU IM or PO every 3 months to a very aggressive regimen of 600,000 IU IM weekly for up to 12 weeks. As a result, it is not an uncommon occurrence to see patients with vitamin D toxicity (15).

There are relatively few studies with these mega doses; an Italian group has published a series of studies to evaluate the effects of a single dose with a maximum follow-up of 4 months (16-18). We strongly feel that information regarding the effectiveness and safety of correction of VDD with mega-dose preparations is insufficient. Therefore, we performed this study to evaluate the optimal dose and dosing interval needed to correct the VDD with PO and IM administration of 200,000 and 600,000 IU VD_3 preparations.

METHODS

A randomized clinical trial was conducted from November 2011 to July 2012 at the Section of Endocrinology and Metabolism at the Aga Khan University Hospital, Karachi, Pakistan. The trial was registered at clinicaltrial.gov (NCT01430793).

Participant Selection

Healthy volunteers and patients with diabetes visiting the endocrine clinic of the Aga Khan University Hospital with 25-OHD levels <20 ng/mL measured within the previous month were selected. Participants who had received vitamin D injection in the last 3 months, serum calcium ≥10.5 mg/dL, chronic liver disease or alanine transaminase (ALT) level 3 times higher than the normal limit, chronic kidney disease or serum creatinine >2.0 mg/dL, and with known malignancy were excluded from the study. Written, informed consent was obtained from all participants. The protocol was approved by the Ethics Review Committee of the Aga Khan University, Karachi, Pakistan.

Study Intervention

The study participants were randomly assigned into 4 groups of 25 volunteers to receive either IM or PO VD_3 at 600,000 or 200,000 IU per the following group allocation: Group 1: 600,000 IU IM, Group 2: 600,000 IU PO, Group 3: 200,000 IU IM, and Group 4: 200,000 IU PO. The IM dose was given as deep intragluteal injections in the clinic by a nurse. For the oral doses, elixirs of 5 mL were compounded by the pharmacy from the injectable preparation in a dosing syringe, and water was offered after dose ingestion. The dose was taken in the clinic under the supervision of the research officer. For the 200,000 IU dose, we used a brand "Indrop D" manufactured by Bouchara Recordati Laboratoires (Levallois Perret, France), and for the 600,000 IU dose we used the brand of VD_3 manufactured by Shanghai Pharmaceutical Industry Corporation Limited (Shanghai, China). If the participants in a group failed to achieve a 25-OHD level >30 ng/mL at 2 or 4 months, the same dose of VD3 was given via the same route at that time point. The second dose and date of administration was recorded.

All participants were prescribed 1 g/day elemental calcium. Biochemical analyses of serum for calcium, albumin, phosphorus, creatinine, ALT, and intact parathyroid hormone (iPTH), and urine for calcium and creatinine were performed prior to dosing to establish baseline levels.

Main Outcome Measure

Serum measurements for 25-OHD levels and calcium and urine for calcium and creatinine were repeated after 2, 4, and 6 months following the initial mega dose of VD3 to assess the adequacy of vitamin D replacement and monitor for the development of hypercalcemia or hypercalciuria. Serum PTH was measured at baseline and 6 months.

Biochemical Analysis

25-OHD testing was performed at the Clinical Laboratory of Aga Khan University, Karachi, Pakistan, which in addition to an internal quality control and quality assurance plan, participates in the College of American Pathologist proficiency testing program. To standardize the sample collection procedure, venous blood and urine (spot/random) samples were collected in the morning between 0800 and 1100 hours. Serum and plasma were separated immediately after phlebotomy. Plasma, serum, and urine samples remained frozen at –78°C until analysis.

Routine analytes included total serum and urinary calcium, serum inorganic phosphorus, serum magnesium, serum albumin, serum ALT, serum and urinary creatinine. Serum and urine samples were analyzed on ADVIA 1800 (Siemens Medical Solutions Diagnostics, Tarrytown NY).

Albumin-corrected calcium and urinary calcium to creatinine ratios were calculated for each participant at baseline and 2, 4, and 6 months.

Plasma iPTH was measured by a solid-phase, 2-site chemiluminescent enzyme-labeled immunometric assay on Immulite (Siemens Medical Solutions Diagnostics). The assay's analytic sensitivity was 3.0 pg/mL with an intra-assay precision of 4.2 to 5.7%, an interassay precision of 6.3 to 8.8%, and a reference range of 16 to 87 pg/mL.

Serum levels of total 25-OHD were assayed using direct competitive chemiluminescence immunoassays on a LIASON autoanalyzer (DiaSorin Inc, Stillwater, MN). Within-run and total coefficient of variations were 2.9 to 5.5% and 6.3 to 12.9% respectively.

Statistical Analysis

Data analysis was done using SPSS version 18.0 (SPSS Inc, Chicago, IL). Continuous variables with normal and nonnormal distributions were reported as mean, SD and median (inter-quartile range [IQR]), respectively. Between-group differences at baseline were assessed by 1-way analysis of variance (ANOVA). The differences between groups and their change (2 and 6 month) from baseline were assessed by repeated measures ANOVA. The statistical analyses for the differences and correlations in the levels of 25OHD, iPTH, calcium, and phosphorous before and after VD_3 supplementation were made using paired *t* tests and Pearson correlation tests. Statistically significant difference was considered when at $P \leq .05$.

RESULTS

Baseline Characteristics and Initial Intervention

One hundred participants were initially enrolled in the study and were randomized in 1 of the 4 groups (n = 25/each). The assigned study intervention, follow-up, and number of participants are depicted in Fig 1. The baseline characteristics of the 4 groups are reported in Table 1. No differences in the baseline characteristics were noted in participants among the groups or between sexes within the groups.

Mean 25-OHD Levels After Initial and Follow-Up Interventions

There was a significant increase in 25-OHD levels after the initial intervention. The mean change from baseline in vitamin D levels at 2 months was 29.6 (13.7) ng/mL in Group 1, 19.8 (12.3) ng/mL in Group 2, 18.3 (10.6) ng/mL in Group 3, and 13.7 (7.8) ng/mL in Group 4. The number of participants who received single or repeat dose(s) at different time points is presented in Table 2.

Table 3 shows the mean levels of 25-OHD in all participants and those who received single or multiple doses of VD_3. The overall mean 25-OHD levels remained significantly elevated from baseline in all groups at all time points ($P<.05$). This significant increase was also observed in participants who received a single dose at baseline and those who received repeat dose(s) at different time points. Mean serum 25-OHD level, in all participants and in participants who received single or repeat doses, remained approximately 10 ng/mL higher in Group 1 than the other groups at 6 months. In terms of statistical significance, the mean 25-OHD level in Group 1 remained significantly higher than all other groups at the 6-month visit ($P<.001$). In participants who received a single dose, the Group 1 participants achieved a significantly higher mean level when compared with Group 4 at 6 months ($P = .034$).

Serum 25-OHD levels remained only 2 to 5 ng/mL apart without any statistically significant difference among the participants of the other 3 groups at the 3 observation periods (2, 4, and 6 months) despite differences in doses and administration route.

Correction of VDD after Initial Intervention

A single dose of VD_3 corrected the VDD in 15/16 participants in Group 1, 17/19 in Group 2, 14/16 in Group 3, and 12/17 in Group 4 at 2 months. Figure 2 shows the percentages of participants in whom 25-OHD levels rose above 20 and 30 ng/mL at 2 months. A significantly higher number of participants in Group 1 had corrected VDD and VDI at 2 months than all other groups. Similarly, significantly higher percentages of participants in Groups 2 and 3 showed corrected VDD and VDI at 2 months when compared with Group 4 ($P<.0001$).

Correction of VDD at 6 Months and Effect of Follow-Up Interventions

The percentages of participants in whom 25-OHD level remained greater than 20 ng/mL at 6 months is shown in Figure 3. The participants are divided into overall participants and those who received single doses. Mean levels of 25-OHD remained >20 ng/mL in a significantly higher number of participants in Group 1when compared with the other groups ($P<.0001$). A single IM dose of 600,000 IU maintained the 25-OHD levels >20 ng/mL in 83% of participants at 6 months.

The groups were also compared on the basis of total cumulative dose received and mean levels of VD_3 achieved at 6 months (Table 4). No significant differences in mean 25-OHD levels were found with various cumulative doses within each group at 6 months. However, the levels tended to be higher in participants with higher cumulative doses. Group 1 again performed significantly better than Group 2 with the same doses at 6 months ($P = .042$).

Correlation of Vitamin D with Serum Calcium, PTH, and Urinary Calcium to Creatinine Ratio

We did not find significant changes in serum calcium, phosphorus, urinary calcium to creatinine ratio, or PTH levels when comparing baseline and 6-month measure-

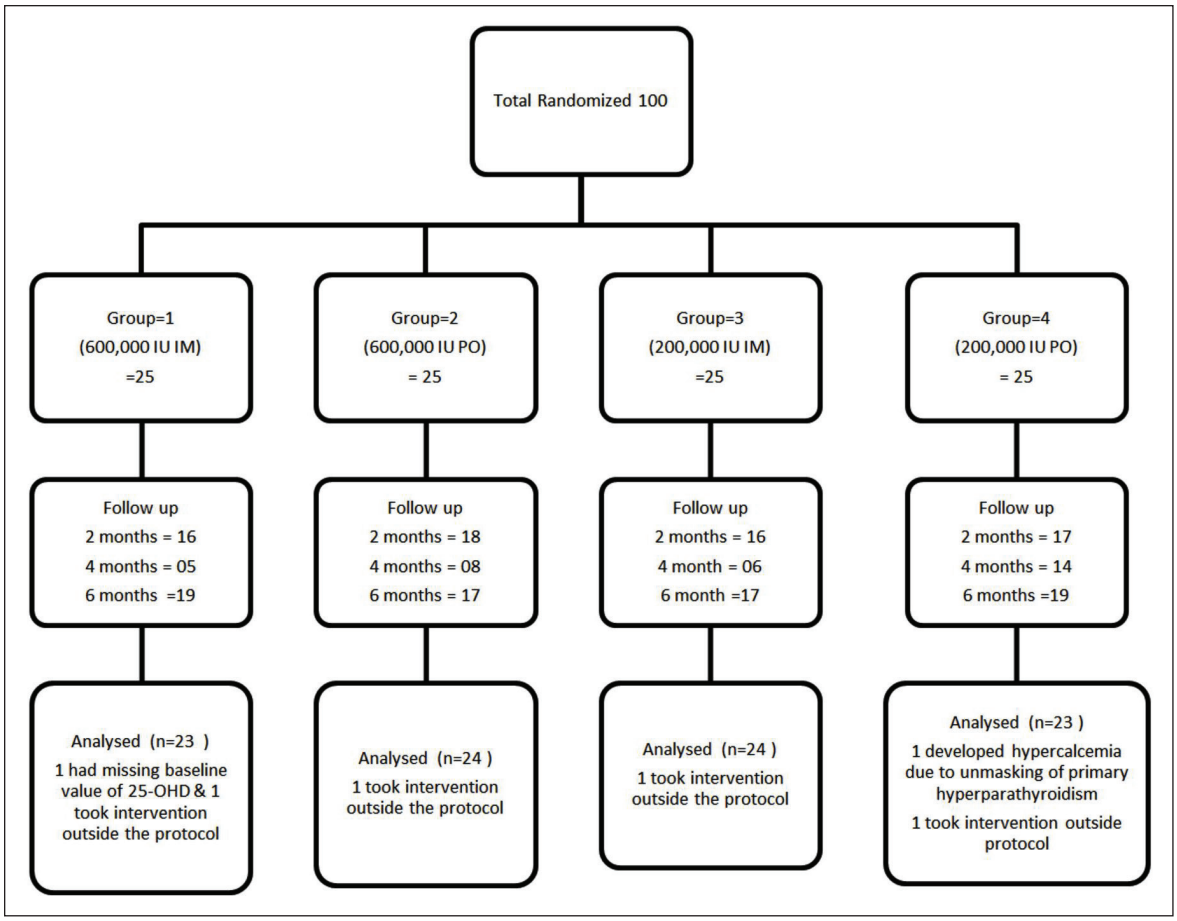

Fig. 1. Study flow chart.

Table 1
Baseline Parameters of the 4 Groups

Parameter	600,000 IU		200,000 IU	
Group (route)	**Group 1 (IM)**	**Group 2 (PO)**	**Group 3 (IM)**	**Group 4 (PO)**
Age[a] (year)	41.2 ± 13	44.3 ± 14.3	41 ± 16.4	44.3 ± 13.3
Sex M:F[b]	4:19	3:21	5:19	4:20
BMI[a] (kg/m^2)	28.5 ± 8.2	28.1 ± 5.3	28 ± 7.7	28.9 ± 5.8
25-OHD[c] (ng/mL)	7.5 (5.5-10.4)	9.3 (4.7-14.4)	10 (6.5-13.8)	9.4 (6.9-12)
PTH[c] (pg/mL)	68.9 (41.1-103.5)	55.1 (43.5-77)	74.4 (56.8-87.9)	50.8 (35.4-66.9)
Serum calcium[a] (mg/dL)	9.3 ± 0.41	9.2 ± 0.53	9.3 ± 0.58	9.1 ± 0.58
Phosphorus[c] (mg/dL)	3.3 (3-3.5)	3.6 (2.9-4)	2.3 (3-3.47)	3.2 (3.1-3.7)
Albumin[a] (g/dL)	4.3 ± 0.38	4.2 ± 0.32	4.3 ± 0.31	4.3 ± 0.3
Creatinine[c] (mg/dL)	0.70 (0.60-0.90)	0.71 (0.60-0.87)	0.8 (0.70-0.90)	0.7 (0.60-0.80)
Alkaline phosphorus[c] (IU/L)	84 (70-107)	72 (67-91)	84.5 (70.5-111)	82.5 (67.2-110.7)
Urinary Ca-Cr ratio[c] (mg/mg)	0.08 (0.03-0.14)	0.08 (0.07-0.16)	0.07 (0.03-0.14)	0.11 (0.05-0.18)

Abbreviations: BMI = body mass index; IM = intramuscular; 25-OHD = 25-hydroxy vitamin D; PO = oral; PTH = parathyroid hormone.
[a] Mean ± SD.
[b] Numbers of participants
[c] Median (range)

Table 2
Number of Participants Who Received Vitamin D at Different Time Points

	600,000 IU			200,000 IU			
	Single	Dose 2		Single	Dose 2	Dose 3	
Intramuscular dose(s)	600,000 IU	1,200,000 IU	Total	200,000 IU	400,000 IU	600,000 IU	Total
Baseline	16	7	23	15	6	3	24
2 months	---	6	6	---	5	3	8
4 months	---	1	1	---	1	3	4
Oral dose(s)	600,000 IU	1,200,000 IU		200,000 IU	400,000 IU	600,000 IU	
Baseline	14	10	24	12	8	3	23
2 months	---	8	8	---	7	3	10
4 months	---	2	2	---	1	3	4

ments. Inverse relationships between 25-OHD levels at 6 months and PTH at 6 months were only observed in Group 1 (Table 5). No correlation was observed between 25-OHD levels and the urinary calcium to creatinine ratio at any time point in any group. Similarly, we did not find any correlation between PTH levels and the urinary calcium to creatinine ratio.

Safety and Adverse Events

None of the participants in Groups 1 or 3 developed hypercalcemia, but transient hypercalcemia was noticed in 1 participant in Group 2. One subject in Group 4 had hypercalcemia at the 2-month visit due to unmasking of primary hyperparathyroidism and was therefore excluded from the final analysis. One participant had 10 IM injections of 600,000 IU; their serum 25-OHD level rose to 130 ng/mL at 6 months and decreased to 42 ng/mL at 1 year. Another participant took 6 IM injections of 600,000 IU resulting in a serum 25-OHD level that increased to 125 ng/mL at 6 months. None of these subjects developed hypercalcemia.

Hypercalciuria was observed in 2 participants in Group 1; both had baseline hypercalciuria and remained hypercalciuric at the 2-month visit. None of the participants in Groups 2 or 3 developed hypercalciuria. Three participants developed hypercalciuria in Group 4 at 2 months, and 2 of them had baseline hypercalciuria.

Table 3
25-OHD Levels at Different Time Points

600,000 IM	Baseline	2 months	4 months	6 months
Overall	8.67 ± 4.77	37.28 ± 14.44	36.06 ± 16.81	30.38 ± 11.3
Single dose	8.53 ± 4.63	41.43 ± 14.14	29.35 ± 2.19	28.4 ± 10.98
Multiple dose	8.99 ± 5.44	24.80 ± 5.68	40.53 ± 22.1	33.77 ± 11.85
600,000 PO				
Overall	9.64 ± 5.02	29.04 ± 11.93	29.27 ± 10.37	19.83 ± 7.45
Single dose	9.69 ± 5.43	33.01 ± 15.52	29.15 ± 16.62	20.03 ± 6.86
Multiple dose	9.6 ± 4.7	25.86 ± 7.52	29.32 ± 9.60	19.69 ± 8.20
200,000 IM				
Overall	10.18 ± 4.35	27.99 ± 9.18	28.57 ± 8.75	18.46 ± 6.4
Single dose	9.93 ± 3.81	32.41 ± 12.12	32.15 ± 10.39	16.09 ± 4.28
Multiple dose	10.6 ± 5.36	24.54 ± 4.19	26.77 ± 8.87	20.57 ± 7.44
200,000 PO				
Overall	9.74 ± 3.43	23.72 ± 7.44	24.14 ± 5.34	19.22 ± 9.43
Single dose	8.56 ± 2.65	29.18 ± 9.68	24.5 ± 9.33	17.81 ± 9.84
Multiple dose	11.03 ± 3.83	20.73 ± 3.75	24.07 ± 5.05	20.62 ± 9.35

Abbreviations: IM = intramuscular; 25-OHD = 25-hydroxy vitamin D; PO = oral.

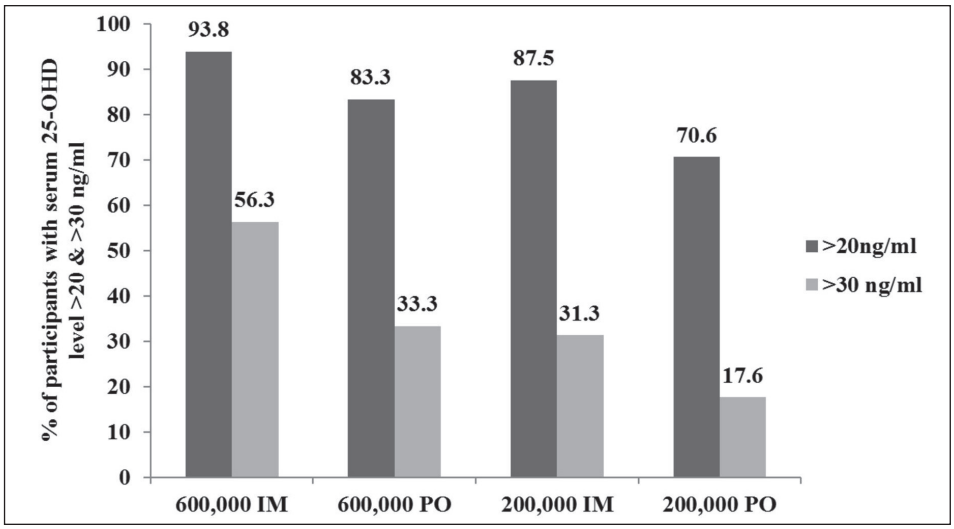

Fig. 2. Percentage of participants with 25-OHD >20 and 30 ng/mL at 2 months.

DISCUSSION

Controversies exist regarding vitamin D replacement in VDD subjects; intermittent bolus doses, the so-called Stoss therapy (a single high dose of vitamin D) is a valid option, particularly as it precludes treatment nonadherence (19). However, the safe upper limit of the bolus dose and dose frequency are poorly defined. There are also considerable differences among countries with regard to the availability of vitamin D supplements, resulting in variable practices (20). We attempted to answer these questions with the 2 commonly available preparations in our country. Our study demonstrated important implications of dose differences and administration routes.

In our study, Group 1 stands out as treatment of choice to correct VDD. The 600,000 IU dose given IM corrected VDD and VDI in a greater number of patients at 2 months compared to the same dose given PO (Group 2) or when lower doses were used as in Groups 3 and 4. The effect of a single dose in Group 1 was maintained at least up to 6 months, as 83% of participants had 25-OHD levels >20 ng/mL at this time point. Groups 2 and 3 exhibited comparable results in terms of correction of VDD and VDI at 2 months despite the dose difference (600,000 vs. 200,000 IU). These differences are likely due to the different pharmacokinetics of vitamin D given via different administration routes.

Earlier work by Whyte et al (22) and Haddad et al (23) showed that parenterally administered depot VD, similar to endogenously synthesized VD, travels in plasma while almost exclusively bound to vitamin D-binding protein, providing for slower hepatic delivery of the vitamin D and a more sustained increase in plasma 25-OHD. In contrast, PO-administered vitamin D absorbs with chylomicrons

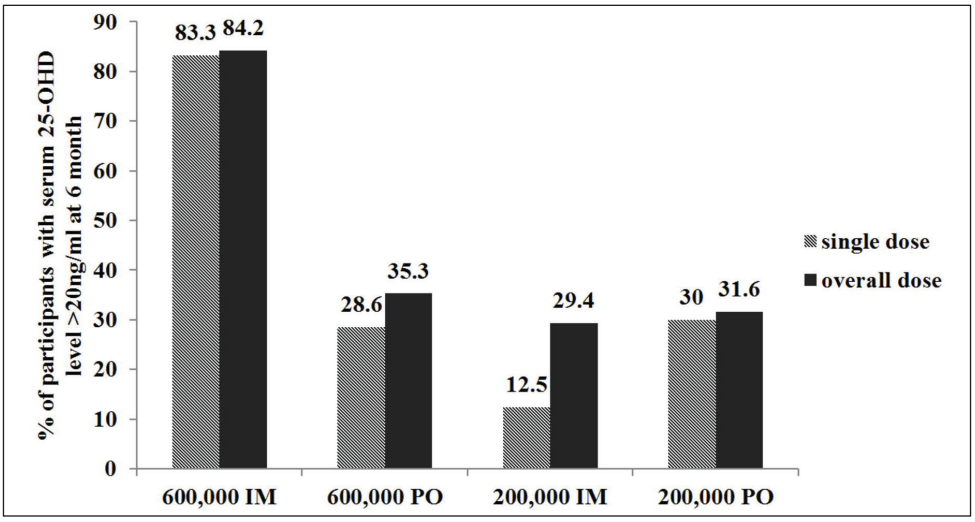

Fig. 3. Percentage of participants with 25-OHD >20 ng/mL at 6 months.

Table 4
Cumulative Dose and Mean 25-OHD Levels at 6 Months

		Intramuscular Dose(s)		Oral Dose(s)		
	Dose quantity	**n**	**Mean ± SD**	**n**	**Mean ± SD**	***P* value**
Participants received 600,000 IU dose(s)	**600,000 IU**	12	28.4 ± 10.9	7	20.0 ± 6.8	.042
	1,200,000 IU	7	33.7 ± 11.8	10	19.6 ± 8.2	.005
	***P* value**		.332		.930	
Participants received 200,000 IU dose(s)	**200,000 IU**	8	16.0 ± 4.2	9	17.8 ± 9.8	.681
	400,000 IU	6	19.2 ± 5.3	6	17.4 ± 4.3	.266
	600,000 IU	3	23.1 ± 11.6	3	26.9 ± 14.5	.629
	***P* value**		.262		.313	

and lipoproteins, allowing for receptor-mediated, rapid hepatic delivery of vitamin D, and the reportedly rapid but less sustained increase in plasma 25-OHD.

The lower level of 25-OHD in Group 2 compared to Group 1 and the similar levels in Groups 2 and 3 at 2 months suggests that we might have missed the peak serum level of 25-OHD in Group 2. We propose that at 2 months, 25-OHD levels in Group 2 were declining, while there were still increasing in Group 3, resulting in similar levels even with the dose difference.

Tellioglu et al (24) compared the kinetics of single oral and IM doses of VD_3 (600,000 IU) and found that the improvement in the 25-OHD level was greater at the 6th week in the oral group, whereas it was at the 12th week in the IM group. Romagnoli et al (16) studied 32 elderly females who received 300,000 IU of VD_2 and VD_3 by PO and IM routes. With the oral dose of VD_3, the levels of 25-OHD rose as early as on day 3 and were maintained up to day 30, after which it started to decline. With IM dosing, the levels rose gradually, achieving sufficiency for VD_3 only at day 60. The same researchers (18) followed 24 young subjects for 120 days after administering 600,000 IU of VD_2 and VD_3 via PO and IM. With oral VD_3, the peak levels were achieved at day 30 and decreased slowly thereafter. The IM administration of VD_3 resulted in a slow increase in total serum 25-OHD levels, peaking on day 120.

Kearns et al (21) systematically reviewed 30 studies and found that with oral bolus dosing, peak levels are achieved at 7 to 30 days. In our study, we preferred monitoring 25-OHD at 2 and 4 months to capture the peak for IM dosing, which is a more common local practice.

In our study, Group 1 had the potential advantages of higher dose and better pharmacokinetics that resulted in greater achievement of VDD correction at 2 months and maintenance of at 6 months. A dose of 600,000 IU or above was also suggested by Pepper et al (25), who compared the most effective doses for achieving vitamin D sufficiency in the context of different repletion regimens.

Table 5
Correlations Between 25-OHD and PTH at Baseline and 6 months

		Mean 25-OHD	
		Baseline	***6 months***
	All Participants		
PTH	*Baseline*	0.043 (0.692)	–0.085 (0.494)
	6 months	–0.041 (0.756)	–0.219(0.090)
	600,000 IM		
	Baseline	–0.020 (0.930)	–0.238 (0.341)
	6 months	–0.223 (0.391)	–0.507 (0.038)*
	600,000 PO		
	Baseline	0.215 (0.336)	–0.097 (0.721)
	6 months	0.306 (0.249)	–0.257 (0.337)
	200,000 IM		
	Baseline	–0.092 (0.678)	0.206 (0.443)
	6 months	0.038 (0.897)	–0.491 (0.075)
	200,000 PO		
	Baseline	0.029 (0.902)	–0.207 (0.425)
	6 months	–0.186 (0.524)	0.097 (0.742)

Abbreviations: IM = intramuscular; 25-OHD = 25-hydroxy vitamin D; PO = oral; PTH = parathyroid hormone.

The mean levels achieved in all 4 groups remained significantly increased from baseline even at 6 months. This is in contrast with other studies where levels returned to baseline at 90 days after 250,000 IU (26) and 120 days after 600,000 IU (18), both of which were given PO. The mean change from baseline in the 600,000 IU IM group achieved at 2 months (29.6 ng/mL) was two- to threefold higher than those reported by Khan et al (27, 28) (9 and 12.6 ng/mL). Similarly, Cipriani et al (18) reported a peak difference of 11.2 ng/mL at 4 months with VD3 given IM,

which is much lower than what we measured. Additionally, Cipriani et al (18) reported peak differences of 12.4 and 10.9 ng/mL from baseline at 30 and 60 days, respectively, after PO VD3. In contrast, the 600,000 PO group achieved a peak difference of 19.8 ng/mL from baseline at 2 months. These differences are most likely due to their higher baseline 25-OHD levels (18,27-28). Zhao et al (10) used a stepwise linear regression model to identify predictors for vitamin D response variation among 1,063 subjects and found an inverse relationship between baseline serum 25-OHD and the 12-month increase in serum 25-OHD levels. Others (29,30) reported comparable results. A similar phenomenon was also observed in vitamin D supplement trials with UV irradiation (31,32).

The most interesting finding in our study is the lack of significant difference in serum 25-OHD levels in participants who received a single or multiple doses of VD_3. The major reason may be the higher 25-OHD level after the initial dose, resulted in smaller increases after repeat dosing as mentioned above. Another reason for this may be what was reported by Alshayeb and colleagues (33), who showed activation of compensatory degradation pathways of 25-OHD when serum levels are >20 ng/mL, as measured by increased serum fibroblast growth factor (FGF)-23 and 24,25(OH)2D levels. Additionally, the differences in 25-OHD after supplementation may vary according to common differences in the genes encoding vitamin D 25-hydroxylase, 24-hydroxylase, and the vitamin D receptor (34).

The Stoss therapy has been successfully employed in patients with cystic fibrosis, in children with rickets and VDD, and in institutionalized elderly population (35-38). The biggest advantage of the "Stoss" therapy is that it avoids treatment nonadherence (19). Large oral dosing would be ideal where rapid correction is needed as in patients with rickets (36) or osteomalacia, and IM dosing is preferred when malabsorption is suspected (37).

Concerns have been raised regarding the safety of high PO doses. Sanders et al (39) demonstrated increased risks of fall and fractures with a 500,000 IU PO dose, particularly in the first 3 months of the annual dose. Kearns et al (21) in their systematic review concluded that bolus doses of >500,000 IU must be used with caution due to a potential of increased fracture risk and altered biochemical markers. This increased fracture risk and higher bone turnover markers with high PO doses may be due to a rapid fluctuation in vitamin D status. The pharmacokinetic profile of the IM dose could potentially overcome this issue (19).

We did not find safety issues with these large doses. Even patients who used multiple doses outside the study protocol did not develop hypercalcemia. In our study, PTH was measured at baseline and 6 months, and a negative correlation between 25-OHD and PTH at 6 months was observed in Group 1 (Table 5).

Some important limitations of our study include the complex design and difficult analysis due to multiple dosing, limited follow-up at 4 months, a lack of incorporation of maintenance dose, and recruitment of participants from November to July. In general, season is an important confounder; however, it may not have been as important in our study as Karachi in Pakistan is relatively close to the equator, and dermal vitamin D synthesis occurs throughout the year (40).

CONCLUSION

The findings of this study will have important implications in the way VDD and VDI are treated with mega-dose preparations. First, a dose of VD3 ranging from 200,000 to 600,000 IU given PO or IM will correct the deficiency in more than 70% of individual at 2 months. Second, a dose of vitamin D 600,000 IU given IM will correct the deficiency in more than 90% of individuals at 2 months and maintain levels >20 ng/mL in 83% of individuals at 6 months. Third, as frequent mega doses are not required, the risk of toxicity is minimized. Daily maintenance doses may be necessary to maintain levels, particularly after the oral loading dose; however, this will require further studies.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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