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Primary care

Three monthly doses of 150,000 IU of oral cholecalciferol correct vitamin D deficiency in adolescents: A pragmatic study

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Abstract

Objectives: To assess the efficacy of an oral high-dose cholecalciferol regimen in correcting vitamin D deficiency (VDD) in adolescents and to explore potential predictive factors on the response to treatment.

Methods: This is a retrospective chart review conducted in the Adolescent Outpatient Clinic, Geneva University Hospitals, Switzerland. One hundred-three otherwise healthy vitamin D deficient [serum 25-hydroxyvitamin D, 25(OH)D, level <50 nmol/L] adolescents (mean age 16.6) attending the clinic between 1 January 2016 and 31 December 2018 received 150,000 IU of oral cholecalciferol every month for 3 months (cumulative dose of 450,000 IU). We measured the change in serum 25(OH)D levels pre- and post-treatment and the achievement of serum 25(OH)D level post-treatment ≥75 nmol/L.

Results: The mean serum 25(OH)D level increased by 320%, from 26 nmol/L at baseline to 83 nmol/L at the end of the study ($P < .001$). The rise was significantly higher for patients initially tested in the winter/spring (mean 65 nmol/L) compared with those initially tested in the summer/autumn (mean 48 nmol/L) ($P < .003$). No clear relationship was found between the response to treatment and the vitamin D status at baseline. The effect of age, gender, origin and body mass index was not statistically significant.

Conclusions: The present intermittent high-dose regimen is effective in treating VDD in healthy adolescents without significant variations in response between different subgroups.

1 | INTRODUCTION

Vitamin D deficiency (VDD) among adolescents is well documented worldwide[1-3] and is considered the most common nutritional deficiency.[4,5] However, recommendations about the treatment of VDD are not homogenous.[6] Heterogeneity concerns vitamin D formulation (cholecalciferol D3 or ergocalciferol D2), dosage (low or high), dosing interval (daily, weekly, monthly or single dosing) and administration route (oral or intramuscular).

Although daily oral dosing is recommended as the first line of management, especially in the United States,[7] it seems reasonable to provide more realistic therapeutic options in certain clinical situations. For example, adherence to treatment is a major problem in adolescents,[8,9] so considering loading doses is also an effective alternative for this age group. Besides, medical costs should be taken into account when prescribing medication. Vitamin supplements are not fully covered by health insurance in certain countries (the case of Switzerland), so deciding on the most affordable therapeutic measure, such as the "fewer-dose approach," seems preferable.

It appears that the current recommended daily dosage schemes are rather modest as they fail to achieve complete vitamin D replacement.[10] In addition, evidence shows that although low daily doses help to improve vitamin D status in the long run, they are not the optimal therapeutic modality in case of severe VDD because they require months before normal serum 25-hydroxyvitamin D [25(OH)D] levels can be restored.[11] This is particularly important when prescribing VDD treatment during adolescence and young adulthood, the life period where maximal bone accretion is observed, without also neglecting the potential non-musculoskeletal benefits of vitamin D.

Studies evaluating the efficacy of high vitamin D doses in VDD adolescent populations are limited. In general, it appears that a total dose of oral cholecalciferol in the range of 300,000 IU to 720,000 IU given in divided doses either weekly, monthly, quarterly or semi-annually was effective in raising serum 25(OH)D levels to above 50 nmol/L.[12-18] Yet, the majority of these regimens failed to rise the serum 25(OH)D concentration above the desired level of 75 nmol/L.[12-15]

It is well established that the serum 25(OH)D level is associated with several inter-individual factors, such as gender, age, body weight and skin pigmentation.[7] However, it is not sufficiently clear whether the response to a certain vitamin D dose varies significantly depending on these factors.[10]

Since data about the administration of high doses of vitamin D are still limited and inconsistent in adolescent populations, the present study was conducted with the objective to assess the efficacy of intermittent high-dosing with oral cholecalciferol in apparently healthy young people with VDD. A secondary aim was to explore the effect of potential predictors on the response to high-dose VDD treatment.

What's known

- Vitamin D deficiency is common in adolescence and has repercussions on adolescent growth and development.
- Adolescents' adherence to daily treatment regimens is low and other alternatives need to be sought.

What's new

- Three monthly doses of 150,000 IU of oral cholecalciferol could be a realistic alternative when treating vitamin D deficiency in apparently healthy adolescents in routine clinical practice.
- Efficacy of the present strategy remained the same regardless of variations in inter-individual factors.
- Current recommended doses of vitamin D need to be reconsidered in order to achieve sufficient vitamin D status.

2 | METHODS

2.1 | Study design and setting

We conducted a retrospective chart review at the Geneva Adolescent and Young Adult Outpatient Clinic, Switzerland. The centre provides health care to adolescents and young adults aged 12-25 across the canton of Geneva. It serves a large migrant population and has a specific refugee health program within which, among others, serum 25(OH)D level is determined in asylum-seeking youth resettling in Switzerland.

2.2 | Treatment protocol

As a result of the lack of a clearly defined VDD management protocol in our institution, we follow a pragmatic clinical approach in case of VDD: (a) administration of an empirical practical loading dose regimen, namely three monthly doses of 150,000 IU of oral cholecalciferol (D3 Streuli® Pharma), during nurse visits, which are otherwise scheduled for immunisation purposes, (b) assessment of adverse events at each nurse visit through a symptom checklist and (c) retesting of serum 25(OH)D level six weeks after the last dose.

This pragmatic regimen was designed based on a dose-escalation observation in combination with practical considerations in formulation administration: The high-dose vitamin D formulation, which is commercially available in Switzerland, contains 300,000 IU of D3 in single-use vials. We selected to administer half the vial (ie, 150,000 IU) per dose. In 2015, we administered two monthly doses of 150,000 IU of oral D3 [cumulative dose of 300,000 IU to achieve equivalence to the cumulative dose proposed by the Endocrine Society (ES) which is based on weekly dosing (50,000 IU once a week during 6 weeks)[7]] and we found poor response in more than half of patients and no cases of intoxication (unpublished data). We decided, therefore, to increase the total dose in the next years by adding a third dose, hence, reaching the cumulative dose of 450,000 IU.

2.3 | Sample

We searched all electronic records of patients attending our clinic between 1 January 2016 and 31 December 2018 in order to identify those with VDD who were treated with the above-stated regimen and had a serum 25(OH)D re-measurement after completing treatment. Exclusion criteria were: patients with clinical signs of rickets, patients with chronic diseases, such as cancer, hepatic failure or renal insufficiency, patients who used medicines known to affect vitamin D metabolism (ie, antifungals, AIDS medications, glucocorticoids amd anticonvulsants) and patients who already reported taking vitamin D supplements at baseline.

2.4 | Outcomes

Response to therapy was the primary outcome of the study. We used the change in circulating 25(OH)D level prior to and at the end of the treatment as the indicator of response. We also used the achievement of a serum 25(OH)D level post-treatment above the sufficient cut-off

as an indicator of complete response to treatment. A secondary outcome was the variation of the response to treatment according to certain predictive factors, namely the age, gender, origin, body mass index (BMI), season of testing and vitamin D status at baseline.

2.5 | Variables

2.5.1 | Origin

Documentation of patients' birth country was available. Countries were combined into four territories of origin: (1) Europe & America, (2) Sub-Saharan Africa, (3) Southern Asia, (4). Northern Africa & Western Asia.

2.5.2 | Body mass index

Calculation of BMI was based on measurements of height and weight realized during medical visits at baseline. Participants were classified into four BMI groups: underweight, normal weight, overweight, obesity, according to the International Obesity Task Force (IOTF) criteria[19] for patients below 18 years, and according to the World Health Organization (WHO) criteria (18.5, 25 and 30 cut-off levels)[20] for patients ≥18 years.

To ensure comparability, we combined BMI categories into two variables: Underweight/Normal Weight & Overweight/Obesity because of the small number of cases for some subgroups.

2.5.3 | Season of 25(OH)D testing

Seasons were regrouped in a dichotomous variable: summer/autumn and winter/spring.

2.5.4 | Vitamin D status

Deficiency was defined as serum 25(OH)D level <50 nmol/L, insufficiency as 50-74 nmol/L and sufficiency as ≥75 nmol/L. Severe deficiency was defined as <25 nmol/L. A dichotomous variable was also considered: sufficiency ≥75 nmol/L and non-sufficiency <75 nmol/L.

2.5.5 | Δ25(OH)D

Δ25(OH)D, measured in nmol/L, was defined as the change in circulating 25(OH)D prior to and after therapy.

2.6 | Laboratory measurements – analytic method

Blood samples were collected all year around. Serum 25(OH)D concentration was measured using electrochemiluminescence immunoassay (ECLIA) [Roche® $25(OH)D_2 + 25(OH)D_3$ assay; detection limit 8 nmol/L, intra-assay CV 2.6%-4.6%]. To enable calculation procedures, serum 25(OH)D levels below the assay's detection limit were given the value of 8 nmol/L (required in one case).

2.7 | Statistical analysis

Descriptive statistics were performed for baseline sample characteristics. Values are shown as means and standard deviations (SD) for continuous variables [age, serum 25(OH)D concentration] and as frequencies and percentages for categorical variables (gender, origin, BMI group, testing season, vitamin D status). T-test, one-way ANOVA and linear regression were used to compare the difference in mean baseline serum 25(OH)D concentration between different patients' groups. Logistic regression was performed to explore factors contributing to severe VDD at baseline. Predictive factors included age, gender, origin, BMI group and season of testing.

Δ25(OH)D was examined with the paired t-test. Linear regression analysis was used to examine the correlation between Δ25(OH)D and potential predictors: age, gender, origin, BMI group, season of testing, serum 25(OH)D concentration at baseline and severity of VDD at baseline. Logistic regression analysis was used to explore the influence of these same factors on reaching the sufficient preset 25(OH)D cut-off level at the end of the treatment. Multivariate models in both linear and logistic analyses used all variables that were found significant in univariate analyses and entered them into the final models by forced entry.

All p-values were two-tailed with a significance level of 0.05. Statistical analyses were conducted with the statistical package SPSS version 26.0 (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

The study sample included 103 participants (Table 1). The majority were males (61%) originating from the Sub-Saharan Africa (48.5%). The mean age was 16.6 years (SD ± 2.1). More than three quarters (81.6%) had normal weight. Baseline blood samples were obtained during winter/spring in about the 60% of the sample.

Mean serum 25(OH)D concentration at baseline was 26 nmol/L (SD ± 10) and fifty patients (48.5%) had severe VDD. Baseline serum 25(OH)D level was significantly lower in overweight/obese (mean 19 nmol/L) compared with underweight/normal weight (mean 27 nmol/L) adolescents ($P = .012$). In addition, there was a significant difference between adolescents who were screened in winter/spring (mean 24 nmol/L) compared with those screened in summer/autumn (mean 28 nmol/L) ($P = .047$). No significant effect for age, gender or origin on baseline serum 25(OH)D level was found in this study population. Severe VDD at baseline was significantly associated with BMI group (4.7 times greater risk in overweight/obese compared with underweight/normal weight) and season of testing (2.6 times more if testing in winter/spring compared with summer/autumn) and was not associated with age, gender or origin (data not shown).

TABLE 1 Characteristics of the sample and comparisons of means of serum 25(OH)D concentration at baseline

Characteristics	Descriptive statistics N (%)	Comparing group means[a] Serum 25(OH)D (±SD) (nmol/L)	*P*-value
Age	16.6 (±2.1)[b]	r = −0.096	.337
Gender			
Male	63 (61.2)	26 (±9)	.305
Female	40 (38.8)	24 (±11)	
Territory of Origin[c]			
Sub-Saharan Africa	50 (48.5)	25 (±10)	.314
Southern Asia	24 (23.3)	29 (±11)	
Northern Africa & Western Asia	15 (14.6)	23 (±10)	
Europe/America	14 (13.6)	25 (±10)	
BMI group			
Underweight/normal weight	91 (88.3)[d]	27 (±10)	**.012**
Overweight/obesity	12 (11.7)[d]	19 (±7)	
Screening season			
Summer/Autumn	43 (41.7)	28 (±11)	**.047**
Winter/Spring	60 (58.3)	24 (±9)	
Severity of VDD[e]			
Severe VDD	50 (48.5)	17 (±5)	**<.001**
Non-severe VDD	53 (51.5)	33 (±7)	
All	103 (100.0)	26 (±10)	

Bold values designate *P*-values that are considered statistically significant (i.e. < 0.05).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; SD, standard deviation; VDD, vitamin D deficiency.

[a] Differences in mean baseline serum 25(OH)D concentrations examined through T-test (gender, BMI, season), one-way ANOVA (origin) and linear regression (age).

[b] For age: Description as mean (± SD) in years.

[c] Top 3 countries of origin (N, %): Eritrea (29, 28.0), Afghanistan (19, 18.0), Somalia (8, 8.0) and Syria (8, 8.0)

[d] Frequencies distribution within the 4 BMI groups (N, %): underweight (7, 6.8), normal weight (84, 81.6), overweight (11, 10.7), obesity (1, 1.0).

[e] Severe VDD defined as serum 25(OH)D level <25 nmol/L.

After completing three months of treatment, the average serum 25(OH)D level increased by 320% and reached 83 nmol/L (SD ± 21). All except one patient (1%) increased their serum 25(OH)D level above 50 nmol/L, 65% of them reaching a level above 75 nmol/L. No case of severe VDD was found in the post-treatment testing. There were no reported adverse symptoms. The maximum serum 25(OH)D level detected post-treatment was 159 nmol/L.

The Δ25(OH)D was 58 nmol/L [95% Confidence Intervals (CI): 54, 62, $P < .001$] for the cumulative dose of 450,000 IU of D3, equivalent to 1.16 nmol/L per 100 IU D3 intake given for 3 months. This increment was significantly greater for patients initially tested in the winter/spring (mean 65 nmol/L) compared with those initially tested in the summer/autumn (mean 48 nmol/L) ($P < .003$). The season of testing alone accounted for 16% of the variance in the Δ25(OH)D. In addition, the Δ25(OH)D was inversely related to the baseline serum 25(OH)D concentration ($\beta = -0.217$, 95% CI: −0.87, −0.80, $P = .019$) after controlling for age, gender, origin and BMI group. Baseline serum 25(OH)D level alone explained 8% of the variance in the Δ25(OH)D. The association of age, gender, origin, BMI group and severity of VDD at baseline was not statistically significant with the Δ25(OH)D in this study population (Table 2, Figure 1).

Non-sufficient vitamin D status post-treatment was marginally significantly related to the season of testing (Table 3). In particular, after controlling for the possible effect of all potential predictors, it was found that the likelihood of not reaching the 75 nmol/L cut-off level post-treatment was 2.4 times higher in those initially tested in the summer/autumn compared with those initially tested in the winter/spring period ($P = .056$). There was a trend towards not reaching sufficiency at the end of the study for patients presenting severe VDD at baseline [odds ratio (OR) = 2.2, $P = .064$]. Non-sufficiency after treatment was found more pronounced in females

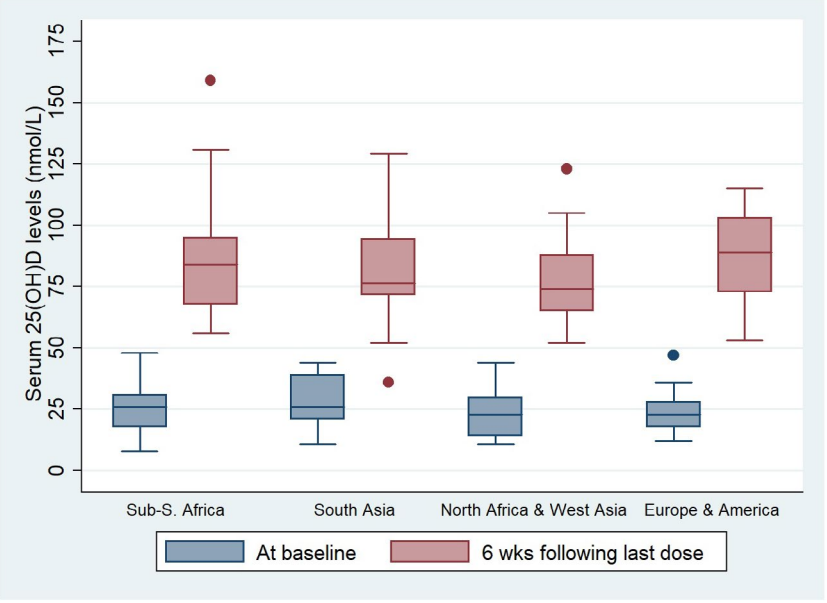
TABLE 2 Factors associated with the mean change in circulating 25(OH)D pre- and post-treatment [Δ25(OH)D)]: results from linear regression analysis

	Univariate analysis			Multivariate analysis		
Factors	**β**	**95% CI**	***p*-value**	**β**	**95% CI**	***P*-value**
Age						
For each increase of age by 1 year	0.049	−1.52, 2.54	.620			
Gender						
Male (ref) Female	- 0.158	−15.64, 1.62	.110			
Territory of origin						
Europe/America (ref)						
Sub-Saharan Africa	−0.091	−12.42, 4.56	.360			
Southern Asia	0.128	−3.43, 16.55	.196			
Northern Africa & Western Asia	0.059	−8.46, 15.65	.555			
BMI						
Underweight/Normal (ref) Overweight/Obesity	−0.019	−14.58, 11.97	.846			
Screening season at baseline						
Summer/Autumn (ref) Winter/Spring	0.399	9.56, 25.39	**<.001**	0.357	7.72, 23.51	**<.001**
Serum 25(OH)D at baseline						
For each increase of 25(OH)D by 1 nmol/L	−0.287	−1.05, −0.22	**.003**	−0.217	−0.87, −0.80	**.019**
Severe VDD at baseline						
No (ref) Yes	0.124	−3.09, 13.82	.211			

Bold values designate *P*-values that are considered statistically significant (i.e. < 0.05).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence intervals; VDD, vitamin D deficiency.

FIGURE 1 Mean serum 25(OH)D levels pre- and post-treatment in different origin subgroups



compared with males (OR = 2.5, *P* = .035) in univariate analysis, but this failed to retain significance in the multivariate model (*P* = .164). The association of age, origin and BMI group with non-sufficiency post-treatment was not statistically significant.

TABLE 3 Predictors of not achieving serum 25(OH)D ≥ 75 nmol/L post-treatment: results from logistic regression analysis

	Univariate analysis			Multivariate analysis		
Predictors	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age						
For each increase of age by 1 year	0.9	0.78-1.15	.559			
Gender						
Male (ref)	1.0					
Female	2.5	1.06-5.63	**.035**	1.9	0.77-4.55	.164
Territory of origin						
Sub-Saharan Africa (ref)	1.0					
Southern Asia	1.4	0.50-3.90	.520			
Northern Africa & Western Asia	2.7	0.82-8.69	.104			
Europe/America	0.9	0.25-3.45	.918			
BMI						
Underweight/Normal (ref)	1.0					
Overweight/Obesity	2.0	0.60-6.84	.252			
Screening season at baseline						
Winter/Spring (ref)	1.0					
Summer/Autumn	2.9	1.24-6.61	**.014**	2.4	0.98-5.70	**.056**
Serum 25(OH)D at baseline						
for each increase of 25(OH)D by 1 nmol/L	1.0	0.93-1.01	.182			
Severe VDD at baseline						
No (ref)	1.0					
Yes	2.2	0.96-5.01	.064			

Bold values designate *P*-values that are considered statistically significant (i.e. < 0.05).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI =body mass index; CI, confidence intervals; OR, odds ratio; VDD, vitamin D deficiency.

4 | DISCUSSION

4.1 | Main findings

The present study demonstrated that administration of oral cholecalciferol to apparently healthy adolescents with VDD at a dosage of 150,000 IU every month during three months led to a tripling of the mean serum 25(OH)D concentration, from 26 nmol/L at baseline to 83 nmol/L at the end of the study, even though it was not enough to ensure the desired level of 75 nmol/L for all young patients. Season was found to have a significant effect on the response to treatment. No significant association was observed between the correction of hypovitaminosis and common demographic factors (age, gender and origin) as well as BMI. No clear relationship was found between the response to treatment and the vitamin D status at baseline. In addition, the present regimen seemed to be well-tolerated and safe for this study population.

4.2 | Strengths and limitations

To our knowledge, this is the first study to estimate the efficacy of three monthly doses of 150,000 IU of oral cholecalciferol in apparently healthy deficient adolescents. Our findings add to the limited existing evidence about the administration of high doses of vitamin D in this specific age group. Another benefit is the high adherence of the participants. In fact, we ensured excellent adherence by administering vitamin D during monthly nurse visits (witnessed ingestion), thus counteracting the increased risk of poor compliance usually observed when supplementing adolescents, a fact that mainly contributes to the discrepancy of efficacy observed in the literature within different D3 regimens already tested. Besides, blood samples and administration of D3 were distributed at different times throughout the year (summer included), hence even at maximal sun exposure, which further supports the notion of safety of the used regimen.

Nevertheless, our study has also some drawbacks, the main being the lack of a matched placebo control group. Yet, our findings are based on a pragmatic study focusing on routine outpatient clinical practice. Dietary intake of vitamin D and calcium was not assessed. However, it has been shown that adolescents present a very low intake of calcium and vitamin D from food.[3,21,22] Skin pigmentation was not systematically tested by the physicians because of limited resources and time. We estimate, however, that the correspondence between skin colour and origin is likely to be high in this population, mainly migrant-based. Moreover, adverse

events were assessed by means of a symptom checklist. We did not test for hypocalcaemia. However, we emphasize that our regimen was generally well tolerated and did not lead to undesirable rise in serum 25(OH)D concentrations. The maximum post-treatment concentration was 159 nmol/L, significantly lower than 250 nmol/L, which constitutes a reliable biomarker of potential intoxication.[23]

4.3 | Comparison with other studies

In our study, a dosage of 150,000 IU of D3 every month during three months (cumulative dose of 450,000 IU) to healthy young people with VDD resulted in significant increases in serum 25(OH)D concentrations. Our findings are in accordance with those reported by Garg et al who showed that weekly doses of 60,000 IU of oral cholecalciferol for 4-8 weeks (cumulative dose of 240,000-480,000 IU) was an effective strategy to achieve vitamin D sufficiency (>75 nmol/L) in apparently healthy Indian deficient adolescents.[16] Similarly, Maalouf et al showed that weekly doses of 14,000 IU of oral D3 for 12 months (cumulative dose of 720,000 IU) increased serum 25(OH)D above 75 nmol/L in Lebanese adolescents with VDD.[17]

Normalisation of serum 25(OH)D level was observed in 65% of our study population (99% if sufficient cut-off set at 50 nmol/L). This finding is in total agreement with that reported in the above-mentioned study performed in Lebanon which found that 64% of adolescents with hypovitaminosis D achieved a rise in serum 25(OH)D level post-treatment above 75 nmol/L.[18] The respective percentage reported by Garg et al was above 90%.[16] This difference may be related to the time relapse between the last dose administered and the time of 25(OH)D retesting (6 weeks in our study, at the end of the treatment in Garg et al's study). In addition, in a meta-analysis published by Brett et al, the increment in circulating 25(OH)D post-treatment was found higher in trials using fortified foods than in those using daily supplements or bolus injections.[24] This could also explain the higher proportion of complete response observed in the study by Garg et al where D3-fortified milk was used.

Our study found that adolescents with lower serum 25(OH)D at baseline presented significantly higher increase in serum 25(OH)D after treatment. Garg et al found no significant correlation between the change in serum 25(OH)D level post-treatment and the serum 25(OH)D level at baseline.[16] It is important to highlight that serum 25(OH)D concentration at baseline alone explained 8% of the total variance of the Δ25(OH)D in our study. The extent to which this finding is of clinical interest remains unclear. When looking at the findings of the multilogistic regression analysis, Al-Shaar et al found that serum 25(OH)D levels at baseline ≥50 nmol/L had significantly greater likelihood to lead to serum 25(OH)D levels post-treatment ≥75 nmol/L in comparison to baseline serum 25(OH)D levels <50 nmol/L.[18] Similarly, our study demonstrated a trend towards a greater risk of not reaching serum 25(O)D levels ≥75 nmol/L post-treatment for those patients presenting baseline 25(OH)D levels <25 nmol/L.

Season of testing at baseline was found to be associated with the efficacy of the present regimen. Adolescents who were initially tested in the winter/spring, and consequently treated during spring/summer, achieved, better response in comparison to those initially tested in the summer/autumn (thus, treated during autumn/winter). This finding highlights the simultaneous positive effect of the endogenous synthesis of vitamin D because of the higher sun exposure in addition to the proposed treatment regimen. Adolescents who were initially tested in winter/spring started with lower 25(OH)D levels and were therefore expected to respond better to the treatment strategy, that is present a higher Δ25(OH)D at follow-up. This has already been documented in previous studies.[7]

Based on the treatment protocol which we administered (cumulative dose of 450,000 IU of oral D3 over 3 months), we found that for each 100 IU of additional daily oral intake of cholecalciferol, an increase of serum 25(OH)D concentration of 1.2 nmol/L was observed. This finding is in agreement with the previously published "rule of thumb" according to which each additional 100 IU D3 input is related to an ~1.7 nmol/L elevation in the serum 25(OH) level.[25]

The Δ25(OH)D in our study was not associated with common predictive factors usually taken into consideration in studies exploring the efficacy of various vitamin D regimens. Response to treatment was achieved independent of adolescents' age, gender, origin and BMI. Similarly, Garg et al found no correlation between age and gender. Al-Shaar et al found no relationship with age, yet a significant association with gender (males more likely to respond to treatment). Regarding the role of BMI, findings are also inconsistent. Al-Shaar et al found a positive correlation between correction of 25(OH)D levels and normal weight whereas Garg et al found that only 1% of the variance in the Δ25(OH)D could be attributed to the effect of BMI.

4.4 | Implications for clinicians and for research

Our findings show that intermittent high-dose vitamin D treatment may be an effective and safe alternative to more frequent lower dosing in adolescents. Concerns about administrating large bolus doses have been raised by certain scientists who consider a potential risk of vitamin D toxicity in case of rare genetic defects.[26] However, vitamin D excess is infrequent. Adverse event analysis has identified increased hypercalcemia risk with cumulative doses above 400,000 IU in infants,[11] but it remains unanswered whether the potentially toxic doses for adolescents have to be considered equal or rather higher, taking into consideration the specific needs of their growing skeleton. In the present study, no reports of toxic levels of 25(OH)D were detected. This would suggest that clinicians in parts of the world where it is difficult and costly to obtain blood tests and vitamin supplements may consider treating VDD with intermittent high-doses of D3.

One interesting element of the present study is the fact that the proposed high-dose regimen seems effective for different adolescent subgroups. Physicians can prescribe the present regimen

without the need to adapt the dose depending on their patients' characteristics. Yet, certain patients will fail to reach sufficient vitamin D status. We hypothesize that the non-responders may present genetically defined altered vitamin D metabolic pathways. In fact, a growing body of evidence supports a genetic basis for low circulating 25(OH)D as well as low response to a defined D3 dose, based on polymorphisms in enzymes or proteins involved in the vitamin D synthesis, hydroxylation and transport, such as the vitamin D receptor, the 25-hydroxylase (CYP2R1) and the vitamin D binding protein genes.[27,28] The efficacy of either higher doses or longer periods of treatment or even shorter intervals between doses remains to be examined for these non-responders.

The rarity of loading dose arms originating from North America may explain why vitamin D position statements from American scientific societies make no mention of loading therapy. In light of the observed rise in serum 25(OH)D concentration in response to the present regimen (equivalent to 5,000 IU/d), it is logical to reinforce re-considering the recommended daily doses published by the Endocrine Society (2,000 IU/d)[7] and other scientific organisations[6] for VDD children and adolescents. Clearly what is required is prospective, properly designed trials exploring dose–response models and investigating the effect of supplementation/treatment not only on serum 25(OH)D levels but, also, on relevant clinical outcomes; besides certain study groups do not recommend treating asymptomatic patients.[29] Moreover, it has been shown that oral calcium administration with vitamin D is more effective than therapy with vitamin D alone in healing nutritional rickets in children.[30,31] Perhaps the same consideration also applies to simple VDD in adolescents. This remains to be determined.

4.5 | Conclusion

Our study indicates that intermittent therapy with three monthly doses of 150,000 IU of oral cholecalciferol could be an appropriate alternative when treating VDD in healthy adolescents regardless of variations in several inter-individual factors. Our findings support the notion that non-compliance alone probably does not explain the generally reported poor response to treatment; the relatively small increase which is usually observed in serum 25(OH)D concentration after the administration of a treatment regimen is largely because of prescribing inadequate amounts of vitamin D. Recommended doses need to be increased to raise the serum 25(OH)D level above 75 nmol/L. The efficacy of the regimen we present in this study along with more precise monitoring of potential adverse events should be evaluated in prospective randomized controlled trials before considering widespread use.

DISCLOSURES

The authors declare no conflicts of interest and did not receive any funding.

ETHICS APPROVAL

The study protocol was approved by the institutional ethics research committee (No. PB_2016-00970, 13-223R) and it was part of a retrospective clinical audit.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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