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ARTICLE

The optimal dosage regimen of vitamin D supplementation for correcting deficiency in adolescents: a pilot randomized controlled trial

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Abstract

Background/Objectives Vitamin D deficiency is common in adolescents but the optimal dosage regimen for correcting deficiency is unknown. To test the safety and efficacy of two different vitamin D dosage regimens to correct vitamin D deficiency in adolescents.

Subjects/Methods In this 12-month, double-blind, randomized placebo-controlled trial, 28 adolescents (serum 25 hydroxyvitamin D (25(OH)D) of 21 to 50 nmol/L) were randomly assigned to one of three groups: monthly ($n = 9$; vitamin D3 50,000 IU orally monthly plus three placebo tablets 3-monthly), 3-monthly ($n = 9$; 150,000 IU (3 × 50,000 IU tablets) 3-monthly and placebo orally monthly), or placebo ($n = 10$; placebo monthly and three placebo tablets 3-monthly). Serum 25(OH)D was measured at baseline, 3, 6 and 12 months.

Results Two participants withdrew after their baseline measurement from the 3-monthly group. At 12 months, one participant was deficient (≤50 nmol/L) in both the monthly and 3-monthly groups, whereas six out of ten in the placebo remained deficient ($P = 0.055$). At 12 months, the average serum 25(OH)D levels for the monthly, 3-monthly and placebo groups were 76.4, 64.7 and 49.7 nmol/L, respectively ($P < 0.001$ and $P = 0.04$ for differences between monthly and placebo groups and 3-monthly and placebo groups respectively, after adjustment for age, sex and seasonal variation). Adherence was 100% and adverse events were minor.

Conclusions Both 50,000 IU monthly and 150,000 IU 3-monthly of vitamin D3 safely and effectively corrects vitamin D deficiency in adolescents. These data provide treatment options which can be used by health practitioners to tailor vitamin D dosage regiments according to patient preference and context.

Background

Fractures are a major public health issue in older adults, which lead to increased mortality and reduced quality of life and create a substantial economic burden [1]. Of note, childhood fractures are also common, occurring at a rate comparable to fractures in older adults [2]. Low bone mineral density (BMD) is a major risk factor for fractures throughout life [3–6]. In particular, adult BMD depends on both peak bone mass (PBM, the maximum bone mass attained in a person's life) and the rate of bone loss after PBM is achieved [7]. It is estimated that a 10% increase in PBM could translate to a 50% reduction in the relative risk of hip fracture in later life [8, 9] and 80–90% of PBM is reached by late teenage years [10]. Therefore, optimising bone acquisition in childhood could potentially reduce the whole-life risk of fracture.

A modifiable risk factor affecting children's bone health is vitamin D deficiency (defined as serum 25-hydroxyvitamin D (25(OH)D) <50 nmol/L [11]), which is prevalent in children and adolescents [12]. This is readily correctable with oral vitamin D supplementation but the optimal dosage regimen of vitamin D supplementation to correct vitamin D deficiency in children and adolescents remains unknown. Poor adherence amongst this population

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may limit the effectiveness of correction [13]. In a small study of adolescents, intermittent oral high dose vitamin D supplementation (300,000 IU vitamin D3 given six-monthly) demonstrated high compliance and safely and effectively corrected vitamin D deficiency [14]. However, while no adverse effects were reported in this pilot study, recent data questions the safety of mega-dose therapy in the elderly [15], thus it is important to determine the efficacy and safety of lower vitamin D doses given more frequently.

Therefore, the aims of this study were to examine the safety and efficacy of lower doses of intermittent vitamin D supplementation (50,000 IU monthly and 150,000 IU 3-monthly) for correcting vitamin D deficiency in adolescents.

Methods

Participants

This was a registered 12-month, double blind, placebo-controlled parallel randomized controlled trial of intermittent vitamin D supplementation for improving vitamin D status in adolescents (ACTRN12613000700730). Participants were recruited from southern Tasmania through general practices, advertising (e.g., Facebook) and word of mouth. A total of 73 adolescents aged 15–17 years who agreed to participate were screened for vitamin D deficiency between 23 October 2013 and 12 March 2015, with most ($n = 67$) screening undertaken in late-spring to early summer of each year. Participants were included in the study if they had mild to moderate vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) between 12.5 and 50 nmol/L) [11], with no clinical signs of rickets and no known severe renal impairment, malabsorption, pregnancy or lactation. For ethical reasons, adolescents who were screened to have serum 25(OH)D < 12.5 nmol/L were referred to their general practitioners for assessment and consideration of treatment. The Tasmania Health & Medical Human Research Ethics Committee (EC00337) approved this study and both participants and their parents or guardian gave written informed consent.

Randomization and intervention

Participants were randomly allocated 1:1 to one of three intervention groups using computer generated block randomization in blocks of six, with equal allocation ratios. These were: the monthly group (one 50,000 IU vitamin D3 tablet was given orally every month and three placebo tablets were given once every three months), the 3-monthly group (three 50,000 IU vitamin D3 tablets were given once every three months and one placebo tablet was given every month), and the placebo group (one placebo tablet was given every month and three placebo tablets were given once every three months). Hence all participants took the same number of tablets at monthly and 3-monthly intervals. Allocation concealment was ensured by use of identical inert placebo and a central automated allocation procedure. The monthly and 3-monthly doses were dispensed in separate containers with clear written instructions on each. Monthly reminders were given to participants by text or phone to encourage adherence.

Outcomes

The primary study outcome was proportion of adolescents with vitamin D deficiency at the end of 12 months. We measured serum 25(OH)D at baseline, three, six and twelve months using the DiaSorin radioimmunoassay kit (DiaSorin Corporation, Stillwater, MN) with a co-efficient of variation of 2.5–5.5%. Participants were classified as vitamin D deficient if their serum 25(OH)D levels were less than or equal to 50 nmol/L [11]. Safety monitoring of serum calcium (reference range 2.1–2.55 mmol/L) and phosphate (reference range 0.80–1.45 mmol/L) was performed at three months. Adherence was assessed by pill count at all follow up visits.

Other factors

Height was measured using a stadiometer (The Leicester height measure, Invicta Plastics Ltd, Oadby, England) and weight by a single set of calibrated scales (Heine, Dover, NH, USA) at baseline and 12 months. Body mass index was calculated [weight (kg)/height [2] (m^2)]. Sunlight exposure was measured by questionnaire recording the time of daily exposure during school days, weekends, and school holidays in both summer and winter. Categories are as follows: 1-less than two hours; 2-two to three hours; 3-three to four hours and 4-greater than four hours. Total sun exposure was calculated as the average of these categories, weighted by the number of school days, weekends and holidays in summer and winter. This measure correlates well with actual exposure with polysulphone badges in teenage children ($r = 0.62$) [16]. Tanner pubertal stage was measured by five stages of pubertal development using drawings made from Tanner's photographs. This correlates highly with actual examination ($r = 0.63$ for males and 0.81 for females) [17].

Sample size

A sample size of 33 adolescents was derived based on our previous pilot [14], as we expected near total correction of vitamin D deficiency in supplementation groups and that

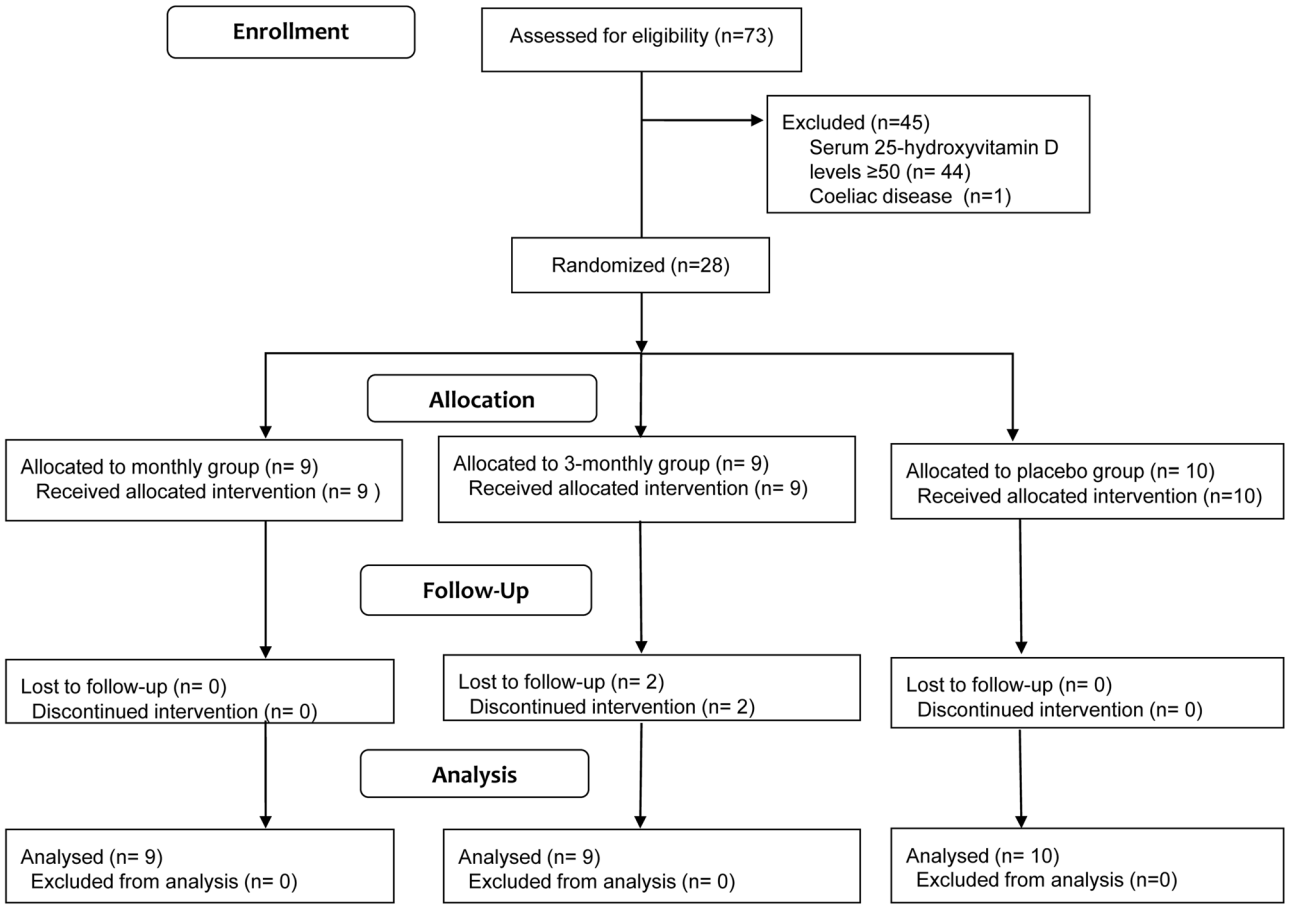

Fig. 1 CONSORT flow diagram of participant flow through the trial

Table 1 Baseline characteristics by study group

Characteristic	Placebo ($n = 10$)	3-monthly ($n = 9$)	Monthly ($n = 9$)	*P*-value
Age (years)	16.5 (0.9)	16.8 (1.0)	16.4 (0.8)	0.71
Male, *n* (%)	6 (60)	2 (29)	1 (11)	0.08
Pubertal stage, *n* (%)				
3	2 (20)	1 (12)	2 (22)	
4	5 (50)	4 (44)	2 (22)	0.75
5	3 (30)	4 (44)	5 (56)	
Serum 25(OH)D (nmol/L)	37.8 (9.4)	35.7 (7.5)	34.0 (10.6)	0.68
Body mass index (kg/m^2)	23.0 (3.8)	24.9 (5.8)	23.6 (5.4)	0.75
Sunlight exposure[a]	1.9 (0.7)	1.7 (0.3)	1.5 (0.4)	0.37

Values are mean (standard deviation) unless otherwise stated

[a]Weighted average of categories (less than 2, 2–3, 3–4 or more than 4 h) over summer and winter (see text)

only 16% of participants receiving placebo would correct the deficiency [14]. Assuming a dropout rate of 10% and with statistical significance set at $p < 0.05$ (two-tailed), we had power of 0.85 to detect a difference of 70% in prevalence of deficiency between each vitamin D supplemented group and placebo i.e., between 10% of children being deficient in the vitamin D groups and 80% of children being deficient in the placebo group.

Statistical methods

The statistical analysis was similar to our previously published study [14]. We tested the difference in proportions of children who were no longer deficient at 12 months between each vitamin D supplement group and placebo using Fisher's exact test. We used mixed-effects linear regressions to examine changes over time in serum 25(OH)D levels as a continuous variable (intention-to-treat analysis). This accounted for the within-subject correlation between multiple readings measured over time and examined the associations between treatment groups and 25(OH)D levels. To capture the seasonal variation, we fitted models in polynomial time up to the fourth power, as well as an interaction term (i.e., time by treatment arm). Participants were measured on a continuous timeline starting from the first vitamin D measurement (October 2013) and ending by the last

12-months measurement (April 2016.) Each analysis was adjusted for age and sex.

Results

The flow of the study participants is shown in Fig. 1. From 25 October 2013 to 17 December 2014, 73 adolescents aged 15–17 years agreed to participate in this study, of whom, 28 (38.4%) had mild to moderate vitamin D deficiency (defined as serum 25(OH)D of 12.5 to 50 nmol/L) and were included in the study. Nine were randomly allocated each to the monthly and 3-monthly groups and ten to the placebo group. Baseline age, BMI and serum 25(OH)D levels were similar across the three intervention groups, but there was a larger proportion of males in the placebo group (Table 1).

After baseline assessment, two participants withdrew from the 3-monthly group. At 12 months, one participant each was mildly deficient in both monthly (25(OH)D = 46 nmol/l) and 3-monthly (50 nmol/L) groups, whereas six in the placebo remained deficient (Figure 2) ($P = 0.055$). At 12 months, the mean serum 25(OH)D levels for the monthly, 3-monthly and placebo groups were 76, 65 and 50 nmol/L, respectively ($P < 0.001$ and $P = 0.04$ for differences between monthly and placebo groups and 3-monthly and placebo groups respectively, after adjustment for age, sex and seasonal variation) (Fig. 3). The difference between

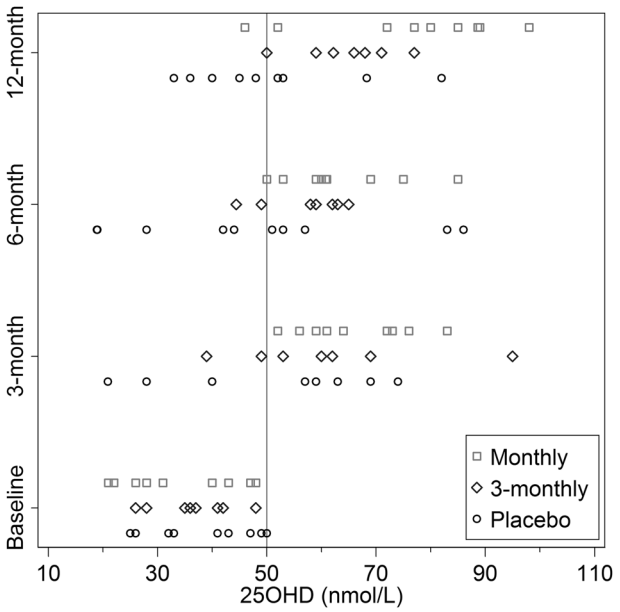

Fig. 2 Individual participant serum 25(OH)D levels by intervention group at each time point. Two or three participants had the same serum 25(OH)D levels at baseline ($n = 2$, 25(OH)D = 32 nmol/L), 3 ($n = 3$, 74 nmol/L), 6 ($n = 2$, 19 nmol/L) and 12 months ($n = 2$, 40 nmol/L) in the placebo group; two had the same at baseline in the 3-monthly group (35 nmol/L). Observations to the left of the vertical line are for deficient individuals, defined as serum level less than 50 nmol/l

one-monthly and three-monthly groups reached statistical significance at 12 months (difference = 13.3 nmol/L, 95% confidence interval: 0.02–26.6; $P = 0.05$).

One participant reported a face rash in the placebo group that lasted for 12 days and one reported a mild headache in the monthly group for one day. At three months, one participant in the monthly group had a mild elevation of serum calcium (serum calcium levels = 2.6 mmol/L compared to upper limit of reference level of 2.55 mmol/L), and one participant each had hyperphosphatemia in both monthly and placebo groups (serum phosphorus levels = 1.47 and 1.53 mmol/L). No other adverse outcomes were detected.

Discussion

Both 50,000 IU vitamin D3 monthly (one 50,000 IU tablet every month) and 150,000 IU 3-monthly (three 50,000 IU tablets once every three months) of vitamin D3 effectively and safely corrected mild to moderate vitamin D deficiency in adolescents. The 50,000 IU monthly dose may be marginally more effective, doubling serum 25(OH)D levels while 150,000 IU 3-monthly dose increased serum 25(OH)D level by more than 80% over 12 months. Minor adverse events were reported during the study. These data provide treatment options that can be used by health practitioners to tailor vitamin D dosage regiments according to patient preference and context. Seen in conjunction with existing evidence, our study's results also support that recommendations for correcting vitamin D deficiency in children should include recommending a duration of supplementation of 12 months at a dosage level equivalent to a total of 600,000 IU per year.

In our previous study [14] intermittent high dose vitamin D3 (300,000 IU 6-monthly) was effective in treating vitamin D deficiency. This is important, as long-term adherence to daily vitamin D supplementation is typically poor in clinical practice. However, subsequent to the initiation of that trial, data emerged questioning the potential safety of high intermittent doses. For example, a randomised controlled trial showed that annual high-dose oral vitamin D3 (500,000 IU) increased risk of falls and fractures in older women [15]. This detrimental effect was mostly found three months after the supplementation when serum 25(OH)D levels experienced a huge fluctuation [15]. One explanation is that the activity of enzymes regulating synthesis and degradation of the active vitamin D metabolite (1,25-dihydroxyvitamin D) might be dysregulated by the wide fluctuations in circulating 25-hydroxyvitamin D levels after bolus dosing may, resulting in declined levels of this metabolite in extra-renal tissues [18]. Thus, to better enable clinicians to balance potential safety concerns with improved adherence, it was desirable to test other regimens

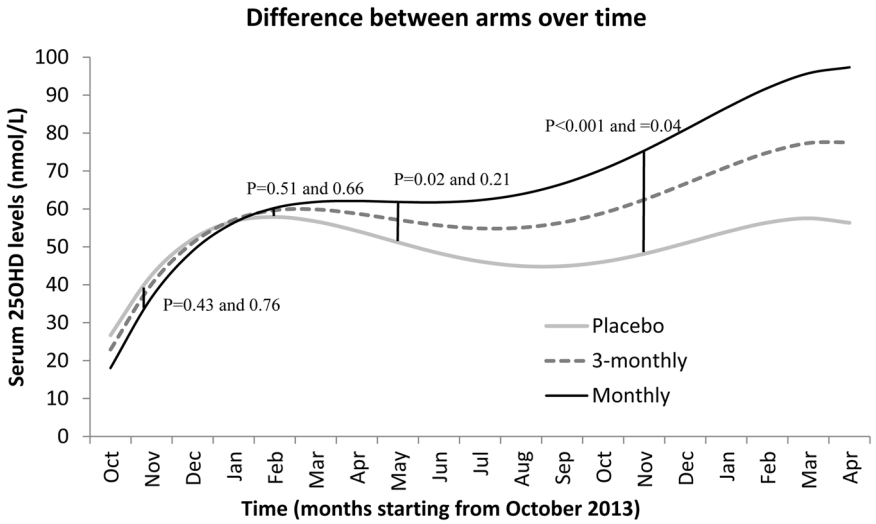

Fig. 3 Average vitamin D levels by group over time, adjusting for seasonal variation. To adjust for seasonal variation, participants were measured on a continuous timeline starting from when the first baseline vitamin D measurement was taken and ending when the last 12-months measurement was taken. The study was carried out in the southern hemisphere, hence, spring is from September to November, summer is from December to February, autumn is from March to May and winter is from June to August. The vertical lines intersecting the curves in the figure indicate the average dates at which vitamin D levels were measured at baseline, 3 months, 6 months and 12 months. *P*-values were for the comparison between monthly and placebo groups (listed first) and 3-monthly and placebo groups (listed second) at these time points

using less high doses but that still allowed for intermittent dosage to enhance adherence.

The fact that both 50,000 IU monthly and 150,000 IU 3-monthly were highly effective for correcting deficiency provides practitioners with useful treatment options to manage vitamin D deficient adolescents. In particular, they can tailor therapy to both patient preferences and the clinical context, expecially where they percieve that adherence is at risk of being poor. Adherence in adolescents completing the study was 100% (except for the two dropouts at baseline) as each dose was taken with monthly reminders via text or phone. A high adherence rate is still likely to be achievable with this dose interval, because a simple reminder can be sent via the practice reminder system or using an APP reminder [19]. Comparing with our previous pilot study [14], this trial further supports that vitamin D3 dosage's equivalent to 300,000 IU over a six month period are a safe and effective dosage for repletion without clinically important hypercalcemia or any other adverse events.

The slightly greater effectiveness of the 50,000 IU monthly dose compared to the 150,000 3-monthly dose even though the cummulative dose of vitam D3 is the same is probably mostly due to the shorter doage interval. Published data documenting the response of serum 25(OH)D levels after a single dose of 100,000 IU vitamin D shows that serum 25(OH)D levels increase sharply until about two weeks, then decline steadily to reach near baseline level by about 100 days [20]. We postulate that participants in the 3-monthly group are likely have a similar pattern and when measured 3-months after their last dose their levels would be approaching a nadir. However, in the monthly group, the interval between last dose and testing was only one month, so serum 25(OH)D levels most likely would have only begun to decline back to baseline. Measurements at closer time points are needed in further research to confirm this.

Dosing regimens from guidelines vary for children aged 1–18 year with different vitamin D status around the world [21] and the optimal regimen is unclear. For example, for children who are vitamin D deficient, the Endocrine Society recommends an intake of 2000 IU/day of vitamin D2 or vitamin D3 (though vitamin D3 is more preferable [22]) for at least 6 weeks or 50,000 IU of vitamin D2 once a week for at least 6 weeks to achieve a blood level of 25(OH)D above 75 nmol/L, followed by maintenance therapy of 600–1000 IU/d [23]. This gives a total yearly dose of between 277,000 and 622,000 IU, the upper limit of which is similar to that provided in our two dosage regimens (600,000 IU over a year) and would seem likely to raise vitamin D levels to above 50 nmol/L by the end of 12 months. However, the effectiveness seen in correcting vitamin D deficiency with 2000 oral IU daily vitamin D over 6 weeks in infant and toddlers (on which this recommendation was in part based) may not be as effective in older children given our results. Moreover, in older children, the lower end of this recommended dose may not be sufficient, as seen in our previous study where correction of deficiency by 150,000 IU vitaminn D given 6-monthly was suboptimal [14]. As another example, in Australia the recommended dose to correct

deficiency in children who are mildly deficient (30–49 nmol/L serum 25(OH)D) is 1000–2000 IU/day for 3 months or a single dose of 150,000 IU given immediately, followed by 1000–2000 IU/day for 6 months. For children who are moderately to severely deficient (<30 nmol/L) recommended doses are 1000–2000 IU for 6 months or 3000–4000 IU/day for 3 months, or 150 000 IU stat, then repeated 6 weeks later [24]. In both situations ongoing supplementation of 400 IU daily or 150,000 IU at the start of autumn for children with ongoing risk factors for deficiency is recommended. However, it seems uncertain that the initial doses delivered over 3 or 6 months would be optimal for correcting deficiency given the substantial further increases in serum 25(OH)D observed from 6 to 12 months in our study, and the incomplete correction of deficiency observed in a study of 210 schoolchildren aged 14–20 years. In that study supplementation of 50,000 IU monthly or bi-monthly for five months increased serum vitamin D levels but corrected deficiency in only 36 and 26% of girls respectively [25]. Another study [25, 26] giving 12 months of supplementation with 60,000 IU monthly of vitamin D reduced deficiency from 92.2% at baseline to 2.6% after 12 months. Thus, on balance, we propose that in children (but not infants and toddlers) with mild to moderate vitamin D deficiency, supplementation using a dosage regimen delivering a total of 600,000 IU annually should be used and supplementation should be given for at least one year at this level.

The optimal dosage interval is less certain. The half-life of 25(OH)D3 has been determined by radio-isotope labelling only in small samples, but appears to be from 15 [27] up to 27.5 days [28]. However, in healthy adults after a single dose of 100,000 IU vitamin D3, it took over 50 days for the serum25(OH)D level to drop by 50% from its peak [20], suggesting that extended dosage intervals are feasible. Nonetheless, we suggest from our data that extending dosage intervals beyond one month may be less effective, and given safety concerns in adults from high dose intermittentt adminstration, that the risks and benefits of extending dosage intervals beyond 3 months by using very high doses would have to carefully assessed by the treating practitioner before using such a regimen. This would have to include consideration of the potential benefits of vitamin D supplementation in children, which are demonstrable in the case of rickets in severely deficient children [12], but less clear for bone health [13] and other non-skeletal health outcomes [24].

This study has some limitations. We fell slightly short of our recruitment goal of 33 participants, but only two participants were lost to follow-up and we were nonetheless able to demonstrate large between-group differences that are both clinically important and statistically significant. In addition, while there was no evidence of any safety issues rarer adverse outcomes may not be detectable in this small sample.

Conclusion

Both 50,000 IU monthly and 150,000 IU 3-monthly doses of vitamin D are safe and effective regimens to correct mild to moderate vitamin D deficiency in adolescents likely resulting with high adherence. These data provide treatment options which can used by health practitioners to tailor vitamin D dosage regiments according to patient preference and context. Seen in conjunction with existing evidence, the data also suggest that recommendations for correcting vitamin D deficiency in children should include recommending a duration of supplementation of 12 months, a dosage interval of 3 months or less, and a dosage level equivalent to a total of 600,000 IU per year.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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