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Original Article

Single high-dose oral vitamin D₃ (stoss) therapy — A solution to vitamin D deficiency in children with cystic fibrosis?

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Abstract

Objectives: To determine the safety and efficacy of stoss therapy on vitamin D levels over a 12 month period in children with cystic fibrosis and vitamin D deficiency (<75 nmol/L).

Study design: Retrospective chart review of 142 paediatric CF patients from 2007 till 2011.

Results: Thirty eight children received stoss therapy and 37 children with vitamin D deficiency were not treated and served as a control group. The stoss treated group had a significant and sustained increase in 25-hydroxyvitamin D levels measured at 1, 3, 6 and 12 months post treatment compared to controls (94.82±41.0 nmol/L, p=0.001; 81.54±24.6 nmol/L, p=0.001; 92.18±36.5 nmol/L, p=0.008 and 64.6±20.0 nmol/L, p=0.006 respectively). At 12 months post intervention, the mean difference in vitamin D levels from baseline between the stoss treated group and controls was significant at 15 nmol/L compared to 5 nmol/L (p=0.038).

Conclusion: Stoss therapy effectively achieves and maintains levels of 25-hydroxyvitamin D greater than 75 nmol/L over 12 months.

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Keywords: Cystic fibrosis; Bone health; Vitamin D; Stoss therapy

1. Introduction

Cystic fibrosis (CF), which is the most common genetic life-limiting condition of European descent, is characterised by progressive suppurative lung disease, pancreatic insufficiency and nutritional impairment. As median survival improves in individuals with CF, many are developing long-term complications such as CF related diabetes (CFRD) and bone disease. The aetiology of CF bone disease is multi-factorial and includes malabsorption of fat soluble vitamins D and K, poor nutrition, decreased physical activity, glucocorticoid therapy, hypogonadism, chronic pulmonary inflammation causing increased circulating cytokines and the direct effect of the abnormal cystic fibrosis transmembrane conductance regulator [1–6].

In bone, vitamin D has an important role in increasing the absorption of intestinal calcium, stimulating osteoblastic activity

and enhancing the production of osteoclasts [3]. Suboptimal vitamin D levels may lead to reduced peak bone mass [7].

In individuals with CF, low vitamin D levels are of concern because of the potential for chronic bone pain, chest deformity and vertebral fractures [5]. Additionally, recent studies have proposed possible immunomodulatory effects of vitamin D levels on lung inflammation and pulmonary function [8,9] and linked the degree of vitamin D deficiency with CF related diabetes [10]. Vitamin D has other potentially important roles such as effects on muscle function, cardiovascular disease and cancer risk [8,9]. These findings suggest that improving levels of vitamin D in individuals with CF is highly desirable. However, determining the optimum level of vitamin D supplementation and the best pharmacological strategy to achieve this in children is uncertain.

The US CF Foundation currently recommends a target 25-hydroxyvitamin D (25-OHD) level of 75–150 nmol/L (30–60 ng/ml) [3], those falling below this level being classified as vitamin D deficient. Recent European guidelines have defined a 25-OHD level of below 50 nmol/L (20 ng/ml)

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as vitamin D deficient in the paediatric CF population [11]. This recommendation is likely to be adopted by the Australian Standards of Care currently under revision (Scott Bell — personal communication).

The goal of vitamin D supplementation in the paediatric CF population is to modify the potential risk for the developing CF bone disease. There is an ongoing debate about the optimal dosing regime and the formula of vitamin D which is most efficacious. Many studies have demonstrated a lack of success in maintaining an increased 25-OHD level despite supplementation. Boyle et al. [2] and Green et al. [3] showed that in adult CF patients, treatment regimes based on US CF Foundation guidelines for bone health, such as 50 000 IU of ergocalciferol (vitamin D₂) weekly or twice weekly respectively, over 8 weeks, did not significantly increase 25-OHD levels. In contrast, single high-dose vitamin D₃ replacement therapy (100 000 IU–600 000 IU (2500–15 000 µg)), known as stoss therapy (from the German “to push”), is an effective method for treating vitamin D deficiency [12]. It involves a single oral or intramuscular dose of vitamin D based on the age and vitamin D level of the patient.

Oral cholecalciferol has been used safely and with success in children with vitamin D deficient rickets [7], children with kidney disease [8] and children with cystic fibrosis [16] with the advantage of avoiding an injection. Similarly, single high-dose (600 000 IU) intramuscular cholecalciferol followed by oral maintenance vitamin D has been shown to be safe in adult patients with osteoporosis [12]. Potential risks of this approach however may include hypervitaminosis D with resultant hypercalcaemia, hyperphosphataemia, nausea and renal calculi [12].

The risk of hypervitaminosis D is low, however, Schlingmann et al. [13] identified an autosomal recessive mutation in the CYP24A1 gene, which encodes 25-hydroxyvitamin D 24-hydroxylase (the key enzyme in 1,25-dihydroxyvitamin D₃ degradation) in six children with idiopathic infantile hypercalcaemia and in four children who developed hypercalcaemia post stoss therapy.

The aim of our study, therefore, was to investigate the safety and efficacy of a single oral high-dose vitamin D₃ (stoss therapy) followed by maintenance oral vitamin D supplementation, in children with CF who were vitamin D deficient (defined as <75 nmol/L).

2. Patients and methods

We performed a retrospective chart review of all children attending the CF clinic at Sydney Children’s Hospital, Randwick between 2007 and 2011. As part of standard clinical care, all children had annual fasting venous bloods for serum 25-OHD, calcium, magnesium, phosphate, albumin and alkaline phosphatase. Children also underwent detailed medical and dietary assessments and baseline anthropometry and pulmonary function were measured. 25-OHD levels were analysed on the automated Liason system utilising a chemoluminescent assay in the South Eastern Area Laboratory Service at Sydney Children’s Hospital.

Children with a serum 25-OHD level below 75 nmol/L were considered for a trial of stoss therapy. The individual dose of stoss

therapy was based on 25-OHD serum level and age as per Table 1. This dosing regimen was chosen following consultation with our Endocrinology department as it has previously been shown to be safe in children and adults with cystic fibrosis, rickets, kidney disease and vitamin D deficiency [7,8,12,14–17].

Stoss therapy was dispensed by the hospital pharmacy and given as a single oral dose, under direct observation following informed parental consent. Repeat serum levels were performed according to a standard clinical care protocol at 1, 3 and 12 months post dose. In some patients a 6 month result was obtained if the 3 month blood test had been omitted.

Children who were vitamin D deficient but did not receive stoss therapy due to consultant or parental wishes were assigned as the control group. Both the stoss therapy group and controls were given routine dietary advice according to current US and Australian guidelines for the prevention of childhood vitamin D deficiency. These recommend a vitamin D intake of 400 IU for those aged under one year and 800 IU for those aged older than one year age group [1,3,5]. The control group had serum 25-OHD, calcium, magnesium, phosphate, albumin and alkaline phosphatase measured at annual review and 12 months later as per standard clinical care.

3. Statistics

Data were analysed using the statistical software package SPSS V19 (SPSS Inc., Chicago IL). Continuous data were compared by paired t-tests and expressed as means±standard deviation. A general linear model was used to test the difference of means between those patients who received stoss and the control group. For all analyses a p value of <0.05 was considered statistically significant.

4. Ethics

The Human Research Ethics Committee (HREC) at the Sydney Children’s Network approved this as a low risk study (Approval number — LNR/11/SCHN/299).

Cholecalciferol is not commercially available in Australia so the medication of Cholecalciferol Strong (50 000 IU per tablet) was obtained on an individual patient basis through the Special Access Scheme via the Pharmacy Department of Sydney Children’s Hospital. All parents signed a consent form.

5. Results

Serum vitamin D and biochemical parameters were evaluated in 142 children attending the CF annual review clinic. There were an equal proportion of males and females with a

Table 1
Replacement doses of cholecalciferol — stoss therapy.

25-Hydroxyvitamin D level (nmol/L)	<3 years	3–12 years	>12 years
≤25	200 000 IU	400 000 IU	600 000 IU
25–50	150 000 IU	350 000 IU	500 000 IU
50–75	100 000 IU	200 000 IU	300 000 IU

median age of 8 years (range 2–18 years). Seventy nine (56%) children had vitamin D levels less than 75 nmol/L. Of these, 42 received stoss therapy. Follow up blood investigations, as per protocol, were available in 38. Two patients transitioned to adult care and two patients had no or refused follow-up blood tests. Of the 38 children with complete blood results at baseline, 17 (45%) had levels at the 1 month time point, 24 (63%) at 3 or 6 months and 30 (79%) at 12 months.

The control group consisted of thirty seven children and 12 month follow up results were available in 34 (92%).

The stoss and control groups had no significant differences in the sex ratio, BMI percentage, genotype, pancreatic status, calcium level and lung function. They did however differ in age and initial 25-OHD levels (Table 2).

6. Efficacy

Stoss therapy followed by maintenance 25-OHD resulted in a significant rise in the mean 25-OHD level at all time points (Fig. 1, Table 3). Although there was a decrease in the 25-OHD level at 12 months compared to the first month's result ($p=0.006$), levels at 12 months remained significantly increased compared to the pre-treatment level. Similarly, values at 1 month ($p=0.049$) and combined 3–6 month data ($p=0.027$) were significantly elevated above the target level of 75 nmol/L.

Individual changes in 25-OHD levels are shown in Fig. 2. Despite individual variation in 25-OHD levels following stoss therapy, the majority of patients had 25-OHD levels higher than baseline when measured 12 months later.

The control group, had a mean 25-OHD level of 59.18 ± 11.9 nmol/L and 64.30 ± 15.17 nmol/L at baseline and twelve months respectively ($p=0.132$). Importantly, 82.4% of the control group remained vitamin D deficient.

In children who had received stoss therapy, the mean increase in 25-OHD level over the 12 month period was 15 nmol/L. This was significantly greater than the mean change

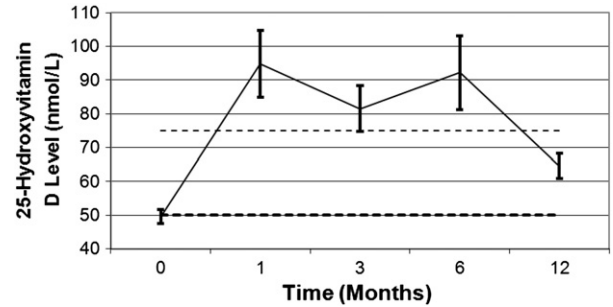


Fig. 1. Mean 25-hydroxyvitamin D levels of stoss treated patients over time.

in the control group, who on average had a 5 nmol/L increase in 25-OHD levels ($p=0.038$).

7. Safety

There was no evidence of vitamin D toxicity, such as hypercalcaemia, hyperphosphataemia, nausea or renal calculi in the stoss treated children (Table 4).

8. Discussion

This study has demonstrated that a single, high-dose cholecalciferol (vitamin D₃) treatment in conjunction with maintenance 25-OHD therapy can elevate and maintain an elevated 25-OHD level over a 12 month period in children with CF. Stoss therapy effectively and safely achieves and maintains 25-OHD levels above 75 nmol/L in the majority of children with CF. These results are likely to inform future decisions on choosing target levels for vitamin D in CF.

We have also demonstrated a high prevalence of vitamin deficiency (56%) in children with CF attending an Australian CF Clinic (Sydney, 34°S latitude) where sunlight availability is not a limiting factor. Furthermore, the average age of the children with CF and vitamin D deficiency was 9.6 years which overlaps with the critical period of peak bone mass accrual [24].

Vitamin D deficiency is commonly thought of as a spectrum, from optimal vitamin D status, to inadequacy, through vitamin D deficiency [19]. In this study we used a level of greater than 75 nmol/L to indicate optimum 25-OHD levels as recommended by the US CF Foundation. We acknowledge that there are no adult or paediatric randomised control studies assessing the effect of 25-OHD levels on long term bone health, immune function, cancer or cardiovascular risk in individuals with CF and that this cut-off is arbitrary [11]. Indeed, recent European CF guidelines have defined deficiency as a vitamin D level of <50 nmol/L, which may reflect this paucity of CF specific evidence [11].

Table 2
Clinical characteristics of study population.

	Control group	Stoss treated group	P value
Males, n (%)	18 (53%)	17 (45%)	0.249
Females, n (%)	16 (47%)	21 (55%)	
Age (median)	6.5	12	0.009
0–9 years	24 (71%)	13 (34%)	
>10 years	10 (29%)	25 (66%)	
BMI percentage	55.4 ± 27.7	43.84 ± 28.1	0.084
Genotype			0.408
Delta F508/DF508	20 (59%)	22 (58%)	
Delta F508/other	13 (38%)	9 (24%)	
Other	1 (3%)	7 (18%)	
Pancreatic insufficiency	30 (88%)	35 (92%)	0.870
25-Hydroxyvitamin D level (nmol/L)	59.2 ± 11.9	49.6 ± 12.9	0.002
Season vitamin D measured			
Summer/spring (%)	20 (59%)	18 (47%)	0.338
Autumn/winter (%)	14 (41%)	20 (53%)	0.238
Calcium (mmol/L)	2.35 ± 0.09	2.34 ± 0.07	0.63
Lung function (% FEV1)	98.7 ± 16.5	93.5 ± 12.5	0.22

Table 3
25-Hydroxyvitamin D levels over time with stoss therapy.

Time (months)	0 (n=38)	1 (n=17)	3 (n=13)	6 (n=11)	12 (n=30)
Mean (nmol/L)	49.6 ± 12.9 *	94.82 ± 41	81.54 ± 24.6	92.18 ± 36.5	64.6 ± 20
P value		0.001	0.001	0.008	0.006

* Values are mean ± standard deviation.

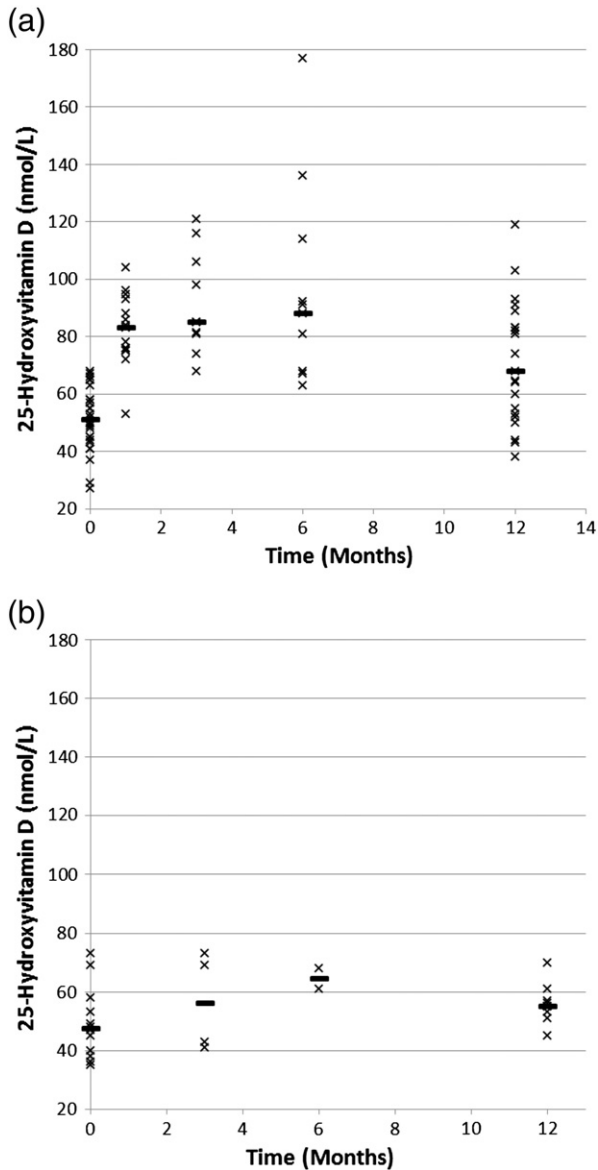


Fig. 2. a. Mean 25-OHD levels of responders. b. Mean 25-OHD levels of partial and non responders.

Table 4
Biochemical parameters in CF children who received stoss therapy.

Time (months)	0	1	3–6	12
Calcium (mmol/L)	2.341±0.07* n=37	2.346±0.07 n=16	2.373±0.08 n=20	2.342±0.088 n=26
Magnesium (mmol/L)	0.877±0.05 n=35	0.860±0.06 n=16	0.883±0.056 n=19	0.882±0.07 n=24
Phosphate (mmol/L)	1.54±0.21 n=37	1.580±0.20 n=16	1.539±0.19 n=20	1.5±0.23 n=26
Albumin (g/L)	38.9±2.87 n=35	37.3±3.47 n=16	37.9±3.15 n=17	39±4.2 n=25
ALP (U/L)	228±69 n=34	252±81 n=16	239±89 n=17	225±93 n=25

* Values are mean±standard deviation.

Similarly in Australia, Munns et al. [14] used a cut-off of 50 nmol/L to identify deficiency.

One practical argument for choosing the lower level of 50 nmol/L as the cut-off is that several research groups have found it difficult to achieve 25-OHD levels above 75 nmol/L, despite large doses and multiple vitamin D replacement regimens [2,3,18]. Recent evidence based on optimal levels of PTH in patients with CF indicates that higher levels (>87.5 nmol/L) are required to maintain a PTH level below 50 pg/ml, as levels above this are associated with increased bone resorption [20]. However in studies in children with CF, the association of vitamin D and PTH levels remains unclear [21–23]. Furthermore, the normal mean 25-OHD level measured in large healthy paediatric control groups is approximately 65 nmol/L [23].

Our study has demonstrated that higher levels of 25-OHD are achievable through stoss therapy and that this approach is practical, efficient and safe. Almost three-quarters (70%) of the stoss treated group achieved a 25-OHD level above 75 nmol/L during the 12-month follow up period. Therefore, we suggest retaining the vitamin D target level at 75 nmol/L which is supported by a recent update by the US CF Foundation [25].

Our findings are unique in that this study is the first to show that optimum 25-OHD levels can be maintained for 12 months. Previously, short-term improvements in 25-OHD levels have been achieved in CF. Green et al. [15] showed that daily treatment with 50 000 IU of ergocalciferol for 28 days in a paediatric CF population was effective in raising the 25-OHD level above 75 nmol/L in 54% of patients. However, in most, vitamin D levels were only measured 6 months post-treatment and therefore long-term vitamin D sufficiency was not determined. Interestingly, our study demonstrated that with the intervention of a single high-dose cholecalciferol, 25-OHD levels remained significantly elevated over all time points compared to the pre-treatment level (Table 2) despite the half-life of 25-OHD in serum being 22–28 days [26]. Cipriani et al. [27] showed that in healthy adults aged 35–56 years old, a single high dose (600 000 IU) of vitamin D₃ resulted in significant increase in 25-OHD levels at 1 month and up to 3 months post dosing. Heanley et al. [28] showed that the response of serum 25-OHD levels to oral vitamin D₃ dose is biphasic; initially a rapid increase occurs at low vitamin D₃ levels and then a slower response at higher concentrations. They hypothesised that the vitamin D₃ is stored in body tissues including fat and possibly muscle and is then released over many months. A single oral dose of vitamin D₃ (100 000 IU) in healthy adults had a half life of greater than 50 days, compared to 20–30 days at lower physiological doses. Our study has investigated not only the effect of a single high dose of vitamin D₃, but also in conjunction with ongoing routine maintenance doses of vitamin D₃. We hypothesise that this approach is likely to have resulted in the prolongation of the elevation of serum 25-OHD levels seen in this study.

Not all patients who received stoss had an increase in serum 25-OHD levels in our study (Fig. 2b). This phenomenon has been reported previously. In a study by Green et al. [15], the non responder rate (defined as a decline or no change in 25-OHD) was 36%; in our study this was 13%. We had a

response rate (defined as reaching the cutoff of ≥ 75 nmol/L) of 70% compared to 54% in the Green et al. [15] study. Seventeen percent of the stoss group had an elevation in serum 25-OHD, but did not reach the 75 nmol/L cutoff and were labelled partial responders. The five non responders had no difference in genotype, pancreatic status or BMI percentage compared to the responders. We hypothesise that these non responders probably did not absorb the vitamin D₃ dose. We have since changed our protocol to administering the dose together with food and pancreatic enzyme supplementation.

To our knowledge this is the first study to demonstrate a significant long-term elevation of 25-OHD with vitamin D supplementation over a 12 month period in children with CF. The potential advantage of our replacement regimen is that it is a single, directly observed dose, which achieves maximum compliance. However, our study has several limitations, the main being a lack of a matched placebo control group. Children who formed the control group were vitamin D deficient (<75 nmol/L) at baseline and although they did not receive stoss therapy, they did receive CF specific dietary advice and vitamin replacement therapy from our CF dietitian. Paired serum 25-OHD in the control and stoss groups during the subsequent twelve months would have helped address the potential impact of seasonal variation, but would have involved increased venipuncture for the control group. Several studies have shown that vitamin D varies according to season, with the highest readings being recorded during the summer months [15,18]. In our study, the baseline and 12 month tests occurred throughout the year. Green et al. [15] demonstrated that vitamin D levels are highest when taken in summer and spring. The difference in seasonal distribution between the stoss group (48% in spring and summer) and control group (59% in spring and summer) was not significant ($p=0.338$), indicating potential seasonal bias is unlikely to account for the differences in baseline and 12 month 25-OHD levels in the two groups.

Additionally, we did not quantitatively control for the actual vitamin D maintenance therapy regimen or dietary advice given to each group. All CF patients attending the clinic are provided with dietary advice and vitamin replacement. However, it is also possible that extra vitamin D was being administered from other dietary sources such as fish oil supplements. Maintenance vitamin D doses varied from 0 to 2440 IU/day in the stoss group and 0 to 2000 IU/day in the control group. There was a difference in the age of the two groups, with the stoss group having a median age of 12 years and the control group with a median age of 6.5 years (Table 2).

The strength of this study was that it was a pragmatic study reflecting routine clinical practice. As such, it underscores the feasibility of effectively and non-invasively raising vitamin D levels in young children and adolescents with CF, during usual outpatient care, to recommended optimal levels with long-term benefit.

9. Conclusion

This study has shown that it is possible to obtain and sustain vitamin D levels higher than 75 nmol/L with stoss therapy over

a 12 month period and that stoss therapy is well tolerated in children with CF. Importantly we did not detect any biochemical abnormalities following administration. While we did not undertake ultrasound examinations specifically for renal calculi, no patient complained of renal pain.

We recognise that while we have shown it is possible to achieve high serum levels of vitamin D with stoss, we have not demonstrated an improved clinical outcome for CF bone disease, the most important research question. Clearly what is required is a prospective, properly designed study looking at the effect of supplementation of vitamin D on serum levels and, most importantly, on relevant clinical outcomes. Until then, the debate on the appropriate cutoff level for vitamin D will continue. This study has shown that it is possible to obtain and sustain vitamin D levels higher than 75 nmol/L with stoss therapy over a 12 month period and challenges the dogma that these levels are difficult to achieve in children with CF.

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