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ORIGINAL ARTICLE

Safety and effectiveness of stoss therapy in children with vitamin D deficiency

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Aim: Paediatric vitamin D (25-hydroxyvitamin D (25OHD)) deficiency can lead to nutritional rickets and extra-skeletal complications. Compliance with daily therapy can be difficult, making high-dose, short-term vitamin D (stoss) therapy attractive to correct vitamin D deficiency. We compared the effectiveness and safety of standard versus stoss therapy in treating childhood 25OHD deficiency.

Methods: Children aged 2–16 years with 25OHD <50 nmol/L were randomised to either standard (5000 IU daily for 80 days) or stoss (100 000 IU weekly for 4 weeks) cholecalciferol. Participants underwent an evaluation of effectiveness and safety. The 25OHD level, random spot calcium: creatinine ratio (Ca:Cr) and compliance were measured at 12 weeks.

Results: A total of 151 children were enrolled in the study (68 standard and 83 stoss), median age 9 years (inter-quartile range (IQR): 6–12 years). Baseline 25OHD levels were 26 nmol/L (IQR: 19–35 nmol/L) and 32 nmol/L (IQR: 24–39 nmol/L) in the standard and stoss groups, respectively. At 12 weeks, the median 25OHD level was significantly greater in the standard versus stoss group (81 vs. 67 nmol/L; $P = 0.005$); however, >80% of participants in both groups achieved sufficiency (25OHD > 50 nmol/L) and had normal urinary Ca:Cr, with no significant difference seen between groups. Compliance was similar in the two groups.

Conclusions: Compared to stoss, standard therapy achieved higher 25OHD levels at 12 weeks; however, in both groups, there was a similar proportion of participants who achieved 25OHD sufficiency, with no evidence of toxicity. Unlike other studies, simplifying the treatment regimen did not improve compliance. These results support stoss therapy as an effective and safe alternative therapy for the treatment of paediatric vitamin D deficiency.

Key words: children; stoss; vitamin D deficiency.

What is already known on this topic

1 Vitamin D deficiency is a significant, but treatable, problem world-wide, resulting in disruption to bone homeostasis and clinical rickets.
2 There are a number of vitamin D formulations that have been studied; however, their safety and effectiveness are variable.

What this paper adds

1 This paper provides evidence for the use of this high-dose formulation (100 000 IU a week for 4 weeks) as a safe and effective alternative to standard daily therapy.
2 This study provides physicians with an alternative dosing regime, especially in situations where patients struggle with compliance with the standard daily regime.

Vitamin D is crucial for calcium homeostasis and skeletal health throughout the life-span. It is especially important to recognise and treat 25-hydroxyvitamin D (25OHD) deficiency in children to prevent osteomalacia and nutritional rickets, which can lead to pain; short stature; skeletal deformities; and extra-skeletal complications, including hypocalcaemic seizure, cardiomyopathy and rarely death.[1] A 25OHD deficiency results in decreased calcium and phosphorous absorption across the gastrointestinal tract, resulting in calcium deprivation and hypocalcaemia. In response, parathyroid hormone (PTH) is released to stimulate the reabsorption of calcium and excretion of phosphorous via the kidneys. While this may normalise serum calcium levels, it reduces bone mineralisation and results in osteomalacia and rickets.[2] In addition, the presence of the vitamin D receptor in lymphocytes, beta islet cells and major organs suggests that 25OHD and its metabolites may have important clinical effects outside

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Conflict of interest: FIT-Bioceuticals provided the high-dose stoss formulation, as well as funding to support a research co-ordinator.

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mineral homeostasis.[3] It has been suggested that 25OHD deficiency is associated with various disease processes such as exacerbation of asthma and bronchiolitis.[4,5]

In Australia, the majority of children have adequate exposure to ultraviolet B to maintain sufficient serum levels of vitamin D (25OHD > 50 nmol/L).[6] In 2006, the incidence of nutritional rickets in Australia was estimated to be 4.9/100 000/year, with the majority of cases found in immigrants and refugee populations.[7] With the recent 2015–2017 global refugee crisis, this is likely to increase (Hogler, Munns 2016). Multiple factors can contribute to 25OHD deficiency in children, including lack of sun exposure, dark skin colour/increased skin pigmentation and malabsorption. Breastfed infants born to 25OHD-deficient mothers are particularly at risk.[8]

A global consensus statement on the treatment of nutritional rickets recommended a daily vitamin D dose in children older than 2 years of age of 3000–6000 IU/day, with calcium supplementation to correct 25OHD deficiency and treat rickets.[9] The American Academy of Paediatrics suggests treating 25OHD deficiency in children >12 months of age with vitamin D therapy of 5000 IU per day for 2–3 months.[2,10] These recommended doses would be equivalent to a combined total vitamin D dose of between 300 000 and 450 000 IU. Adherence to a daily dosing regimen can be difficult in some patients, in which case stoss (from the German word stossen 'to push') therapy has been recommended.[11,12] Although stoss therapy is widely used in developing countries,[13] it is not routinely used in Australia. There are limited data on its efficacy, safety and effective dosing regimen.[11,12,14]

This study aimed to compare the safety and efficacy of stoss therapy (100 000 IU cholecalciferol every week for 4 weeks) versus standard therapy (5000 IU cholecalciferol daily for 80 days).

Methods

Design/Participants

Children between the ages of 2 and 16 years with 25OHD status <50 nmol/L who were referred to the Endocrinology and/or the refugee clinic at the Children's Hospital at Westmead, Sydney, Australia from 2011 to 2016 were recruited to a randomised controlled trial of standard dose versus high dose of cholecalciferol (vitamin D3) supplementation. Children were excluded if they presented one or more of the following: (i) a pre-existing medical condition predisposing to 25OHD deficiency (e.g. malabsorption, liver failure); (ii) current use of any medications known to alter bone metabolism (e.g. bisphosphonates, cholecalciferol, calcitriol, anticonvulsants, barbiturates); or (iii) an underlying metabolic or genetic aetiology for rickets (e.g. X-linked hypophosphatemic rickets). All participants were under the care of a paediatric endocrinologist or paediatrician at Children's Hospital at Westmead. Parents or legal guardians of the participants provided informed consent, and the study was approved by the Sydney Children's Hospitals Network Human Research Ethics and Governance Committees (#12SCHN401).

Intervention

Using random number tables, participants were randomised by family to receive either standard therapy with cholecalciferol 5000 IU (5000 IU/mL) daily for 80 days or stoss therapy with cholecalciferol 100 000 IU (50 000 IU/mL) every week for 4 weeks. Both treatments were provided by BioCeuticals. Each batch was prepared in a Therapeutic Goods Administration-approved facility under 'Good Manufacturing Practice' and was reviewed before being released to ensure that concentration variation was within the minimal recommended limits.[15] Recognising the relationship between low dietary calcium intake and vitamin D status in the pathogenesis of osteomalacia and nutritional rickets,[16] both groups were also supplemented with 500 mg of elemental calcium for 4 weeks. Pharmacy study investigators reviewed the appropriate administration of the medications with participants or care givers prior to commencing therapy.

Data collection

A questionnaire previously used to collect data for nutritional rickets study[7] was used to collect baseline demographic and nutritional data and risk factors for the development of 25OHD deficiency (Appendix I). All participants underwent a medical visit at baseline, 4 weeks and 12 weeks. Height was measured using a Harpenden Stadiometer (Holtain Ltd., Crymych, UK), and weight was measured using the same electronic scale. Participants were questioned to assess for any adverse events such as polyuria, polydipsia, abdominal pain and constipation.

Primary end-points

Primary end-points were normalisation of 25OHD and serum alkaline phosphatase (ALP) status at 12 weeks.

Compliance monitoring

Compliance was assessed by counting the number of empty vials returned at week 12 in the first group (standard therapy) and week 4 in the second group (stoss therapy). A patient was noted to be compliant when he or she returned at least 75% of the vials empty.

Laboratory measurements and quality assurance

Serum and urine biochemistry data were collected at baseline, 4 weeks and 12 weeks. Serum biochemistry, including calcium, magnesium, phosphate and ALP, were measured using Vitros 5600 analyser (Ortho Clinical Diagnostics, Raritan, NJ, USA). PTH was measured using the Immulite Autoanalyser, Chemiluminescence (Siemens Healthcare, Surrey, UK). Serum 25OHD was measured using the Xevo TQS LCMSMS, LCMS (Waters Pty Ltd., Borehamwood, UK) as of July 2015 or the IDS iSYS Autoanalyser, Chemiluminescence (Immunodiagnostic Systems Holdings PLC, Tyne And Wear, UK) from 2010 to June 2015. The results between the two methods were comparable (Fig. 1). Biochemistry clinical ranges and cut-off values were consistent with paediatric norms.[17] Vitamin D status was defined in accordance with the Australian and New Zealand Consensus Statement[1]:

1 Sufficiency: ≥50 nmol/L
2 Deficiency: <50 nmol/L

There continues to be discussion surrounding the definition of vitamin D deficiency. The protocol for this study was written and

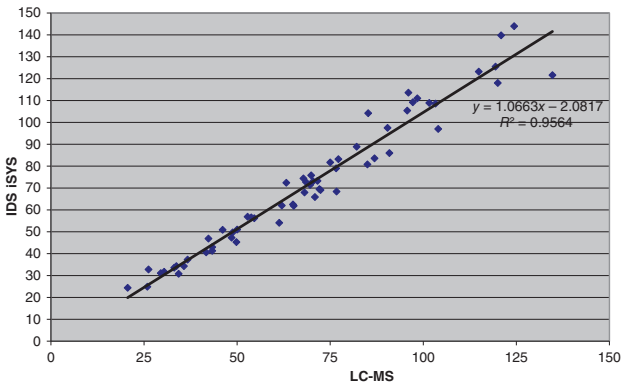

Fig. 1 Comparison of the two assays (iSYS and liquid chromatography (LC) with massspectrometry (MS)) used in this study for 25OHD measurement using 59 DEQAS (Vitamin D External Quality Assessment Scheme) samples.

implemented prior to the global consensus guidelines.[16] This study uses a higher threshold for vitamin D deficiency, which is consistent with other published guidelines.[1,5,9,16,18]

Statistical methods

Power calculations estimated a total of 111 participants needed to detect a 10% difference in treatment success between the two groups, with 80% power and 5% level of significance. Group differences in primary and secondary end-points were determined using the student *t*-test for continuous variables and χ^2 test for categorical data. Statistical calculations for group differences with small outcomes were determined using the Fisher exact test. All statistical analyses were based on the intention-to-treat principle and were performed using SAS version 9.3 (SAS, Cary, NC, USA) and R version 3.2.4 (GNU, Boston, MA, USA).

Results

A total of 170 participants were randomly assigned to the stoss (n = 93) or standard therapy group (n = 78; Fig. 2). Sixteen children were excluded from the study due to 25OHD levels ≥ 50 nmol/L at baseline. A further two participants were excluded because they did not have any recorded 25OHD levels at baseline, and one child was excluded because he or she was over the age of 16 years. The final number of participants who received treatment was 151, with 68 and 83 in the standard and stoss groups, respectively. There were 16 lost to follow-up, with absent 25OHD levels at 12 weeks. The final analysis was made up of a total of 135 participants, with 62 and 73 participants in the standard and stoss groups, respectively.

Patient characteristics were similar in both groups. The age of the participants ranged from 2 to 16 years, with a median age of 9 years (Table 1). The majority of the participants were of Middle Eastern and African descent, with the Middle Eastern ethnicity over-represented in the stoss group (Table 1). Height, weight and body mass index data were similar across both groups (Table 1).

The median 25OHD level at baseline was significantly lower in the standard group, compared to the stoss group (26 vs. 32 nmol/L; P = 0.01). The median 25OHD status for both groups increased to sufficient status (≥50 nmol/L) at 4 and 12 weeks (Fig. 3; Table 2). However, the median 25OHD level at 12 weeks was significantly greater in the standard group (81 vs. 67 nmol/L; P = 0.005) (Fig. 3; Table 2). Change in 25OHD levels between baseline and 12 weeks was greater in the standard (50 nmol/L

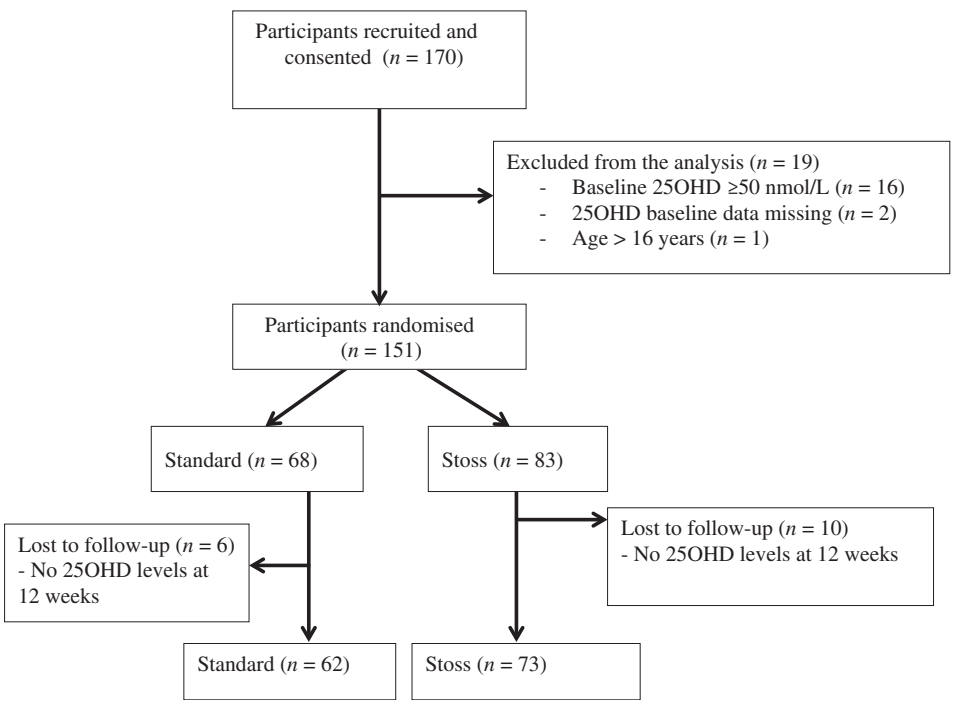

Fig. 2 Consolidated standards of reporting trials flow diagram of participants throughout this study.

Table 1 Baseline characteristics of all participants in the final analysis

Characteristic	Standard (*n* = 68)	Stoss (*n* = 83)	All (*n* = 151)
Female, *n* (%)	32 (47)	39 (47)	71 (47)
Age, years, median (IQR)	9 (6–12)	8 (5–11)	9 (5–12)
Ethnicity			
African, *n* (%)	16 (24)	15 (18)	31 (21)
Asian, *n* (%)	9 (13)	8 (10)	17 (11)
Caucasian, *n* (%)	5 (7)	6 (7)	11 (7)
Indian subcontinent, *n* (%)	16 (24)	12 (14)	28 (19)
Middle Eastern, *n* (%)	16 (24)	35 (42)	51 (34)
Other, *n* (%)	6 (9)	7 (8)	13 (9)
Weight, kg, median (IQR)†	34 (19–51)	30 (20–39)	30 (19–44)
Weight *z*-score, median (IQR)‡	0.4 (−0.6, 1.0)	0.1 (−0.8, 0.6)	0.2 (−0.8, 0.8)
Height, cm, median (IQR)†	136 (115–157)	134 (110–146)	134 (114–151)
Height *z*-score, median (IQR)‡	0.0 (−0.7, 1.0)	−0.3 (−1.2, 0.8)	−0.2 (−1.1, 0.9)
BMI *z*-score, median (IQR)‡	0.1 (−0.9, 0.9)	0.2 (−0.6, 0.9)	0.1 (−0.8, 0.9)

†Data available for 61 participants in standard group and 72 participants in stoss group, with a total of 133 participants. ‡Centre for disease control 2000 growth charts. BMI, body mass index; IQR, inter-quartile range.

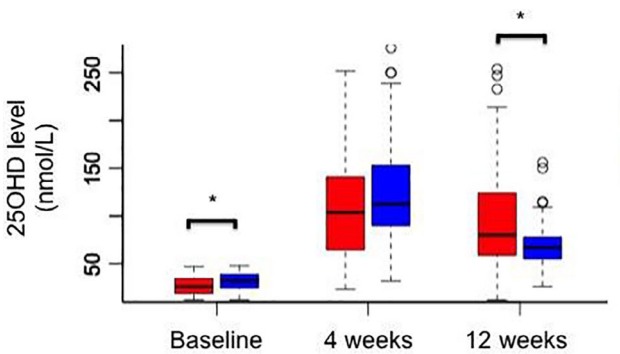

Fig. 3 Comparison of 25OHD levels throughout the study. One extreme outlier in the standard therapy group with a 25OHD level of 440 nmol/L at 4 weeks was not included in this box plot (*P < 0.05). (■) Standard; (■), stoss.

change; inter-quartile range: 35–98 nmol/L) versus stoss group (35 nmol/L change; inter-quartile range 25–36 nmol/L; P = 0.0005). At both 4 and 12 weeks, the proportion of participants who were vitamin D sufficient did not differ between the groups (Table 3). At 4 weeks, there were two children in the standard and one in the stoss group with 25OD levels within the elevated range (>250 nmol/L). At 12 weeks, there were two participants in the standard group, and no participants in the stoss group, with elevated levels of 25OHD. None of those with elevated 25OHD status had raised urinary Ca:Cr ratio or elevated serum calcium levels. As both elevated 25OHD levels and hypercalciuria are required for a diagnosis of vitamin D toxicity,[1] none of the participants met these criteria. Therefore, the treatment regimen was continued, and further 25OHD measurements were found to be below 250 nmol/L.

Table 2 Median levels of 25-hydroxyvitamin D (25OHD), parathyroid hormone (PTH) and alkaline phosphatase (ALP) at baseline, 4 weeks and 12 weeks

	Standard (*n* = 68)	Stoss (*n* = 83)	*P* value†
25OHD, nmol/L, median‡ (IQR); *n*			
Baseline	26 (19–35); 68	32 (24–39); 83	0.01
Week 4	104 (65–142); 53	113 (90–153); 78	0.10
Week 12	81 (59–124); 62	67 (55–78); 73	0.005
PTH, nmol/L, median (IQR); *n*			
Baseline	4.3 (2.7–6.2); 66	4.2 (3.0–6.8); 76	0.69
Week 4	2.5 (1.6–4.0); 53	2.8 (1.7–3.7); 77	0.81
Week 12	2.6 (1.7–4.6); 62	3.8 (2.3–5.4); 74	0.01
ALP, nmol/L, median (IQR); *n*			
Baseline	218 (184–307); 67	221 (155–281); 77	0.39
Week 4	220 (176–282); 53	224 (170–273); 76	0.98
Week 12	224 (176–284); 63	224 (184–288); 72	0.68

†Calculated using Mann–Whitney-Wilcoxon test. ‡Median levels used because the data had a non-normal distribution. IQR, inter-quartile range.

Median PTH and ALP levels were within normal limits throughout the study (Figs 4 and 5; Table 2). Both markers had similar median levels between the two groups at baseline and 4 weeks; however, the median PTH level at 12 weeks was significantly higher in the stoss group (3.8 vs. 2.6 pmol/L; P = 0.0115) (Figs 4 and 5; Table 2). The majority of participants had PTH levels measured within normal range, at 4 and 12 weeks, with no significant difference between the two groups (Table 3).

There were no cases of hypo- or hypercalcaemia in the cohort. In both groups, urinary Ca:Cr ratios were similar throughout the length of follow-up (0.11–0.25; P > 0.3). Over 80% of participants had normal urinary Ca:Cr ratio. Those with an elevated ratio had normal serum 25OHD levels.

Compliance data were unavailable for half of the cohort. From the data available, there was no significant difference in compliance between the stoss and standard groups (Table 4).

Discussion

We aimed to compare the safety and efficacy profiles of standard and stoss vitamin D therapies in a cohort of children with suboptimal 25OHD levels (25OHD < 50 nmol/L).[16] Both treatment regimens were found to be similar in the safety and effectiveness of normalising 25OHD levels in children, despite a small percentage of children who had 25OHD levels above the normal range. However, the overall 25OHD level was higher in the standard

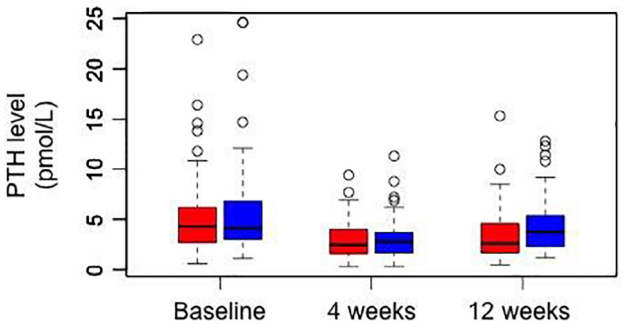

Fig. 4 Comparison of parathyroid hormone (PTH) levels throughout the study. One extreme outlier in the standard group with a PTH level of 102 pmol/L at baseline was not included in this box plot. (■) Standard; (■), Stoss.

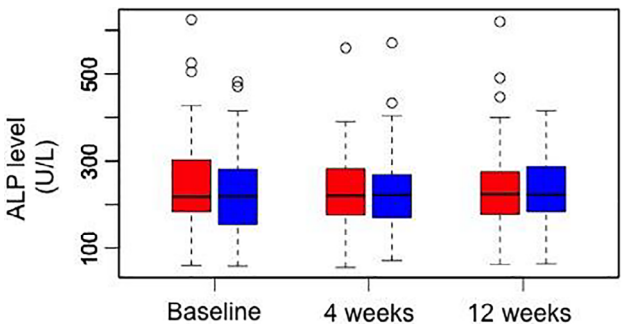

Fig. 5 Comparison of alkaline phosphatase (ALP) levels throughout the study. One extreme outlier in the stoss group with an ALP level of 1190 U/L at baseline was not included in this box plot. (■) Standard; (■), stoss.

group at 12 weeks, and the toxicity beyond a 12-week course has not been investigated in this study.

There are various studies identifying baseline characteristics, such as 25OHD level, ethnicity, age, BMI and gender as predictors of treatment response.[19–22] In our study, baseline characteristics (i.e. ethnicity, gender and anthropometry) were similar between the two groups, indicating that appropriate randomisation was achieved and, in so doing, accounted for these characteristics as confounding factors. In the overall cohort, the disproportionate representation of 25OHD levels <50 nmol/L amongst immigrant and ethnic populations is consistent with findings in other studies.[1,23–25] Despite randomisation, the baseline median 25OHD level was statistically lower in the standard group compared to the stoss group (Table 2). This does not explain the 14 nmol/L greater 25OHD value in the standard therapy group at 12 weeks (81 vs. 67 nmol/L). With both groups having similar levels of sufficiency, it is not possible to report that this difference in 25OHD level would have clinical sequelae. We did not have children with nutritional rickets in the study and are unable to comment on the efficacy of either therapy in its treatment. The median 25OHD level in the standard group was statistically higher than the stoss group at 12 weeks. While it was

Table 3 Proportion of participants with biochemical levels within normal range

	Standard, *n* (%)	Stoss, *n* (%)	OR (stoss vs. standard) (95% CI)	*P* value
25OHD below normal limits (<50 nmol/L)				
Week 4	5/53 (9)	3/78 (4)	0.39 (0.05–2.09)	0.27†
Week 12	12/62 (19)	11/73 (15)	0.74 (0.27–2.00)	0.67†
25OHD within normal limits (50–250 nmol/L)				
Week 4	46/53 (87)	74/78 (95)	2.60 (0.59–11.40)	0.19
Week 12	49/62 (79)	62/73 (85)	1.35 (0.55–3.32)	0.51
25OHD greater than normal limits (>250 nmol/L)				
Week 4	2/53 (4)	1/78 (1)	0.33 (0.01–0.57)	0.56†
Week 12	1/62 (2)	0/73 (0)	0 (0.00–33.12)	0.46†
PTH within normal limits (1–7 pmol/L)				
Week 4	47/53 (89)	68/77 (88)	0.96 (0.32–2.89)	0.95
Week 12	55/62 (89)	63/74 (85)	0.73 (0.26–2.01)	0.54
ALP within normal limits (50–320 U/L)				
Week 4	48/53 (91)	70/76 (92)	1.22 (0.35–4.21)	0.76
Week 12	56/63 (89)	67/72 (93)	1.68 (0.50–5.57)	0.40

†Calculated using the Fisher exact test (instead of the χ^2 test used in the remainder of the analysis) as it is more precise when assessing small samples. OR and *P* values calculated using χ^2 test unless otherwise indicated. 25OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone.

Table 4 Compliance with vitamin D therapy

Characteristic	Standard	Stoss	OR (95% CI)	*P* value
Compliance with vitamin D therapy†	23/30 (77)	38/47 (81)	1.29 (0.42–3.92)	0.66

†A participant was compliant when ≥75% of vials were returned empty. CI, confidence interval; OR, odds ratio.

not associated with significant differences in ALP, serum calcium or urinary Ca:Cr, it was associated with a relative reduction in PTH levels, indicating that it did have an effect on calcium homeostasis.

Multiple studies, with varying treatment regimens, support stoss therapy as an effective way to normalise 25OHD status.[1,26,27] A study of 42 children with vitamin D deficiency (25OHD < 50 nmol/L) found that a total single dose of 150 000 IU significantly increased 25OHD levels compared to 84 000 IU given as 2000 IU/day for 6 weeks (125 and 60 nmol/L, respectively) (electrochemiluminescense enzyme immunoassay method).[27] Compared to Emel *et al.*, where the stoss dose was almost twice that of the daily total dose, our study gave the same total vitamin D dose in the stoss and standard treatment arms and did not see such large difference between treatment groups. A small prospective cohort study of 18 children with cystic fibrosis showed replenishment of 25OHD levels in 17 participants, using a total ergocalciferol dose of 700 000 IU (50 000 IU daily for 2 weeks).[22] However, it is important to note that

25OHD ≥ 75 nmol/L was used as the cut-off for sufficiency, and the participants included those with pancreatic insufficiency and suboptimal vitamin D absorption. Shepherd *et al.* found a significant increase in mean 25OHD levels amongst children with inflammatory bowel disease 1 month post-treatment with stoss therapy, ranging from 200 000 to 800 000 IU given as a single dose (the 25OHD assayed using automated Liason system (DiaSorin Corp, Saluggia, Italy).[26] A *single* high stoss dose of 600 000 IU of cholecalciferol, via both oral and intramuscular administration, has been shown to be both safe and effective in treating children (5 months to 9 years) with vitamin D deficient rickets.[11,28]

The biochemical effectiveness of treatment of vitamin D deficiency may be assessed by normalisation in PTH and ALP levels, markers of total body calcium sufficiency. Reductions in both PTH and ALP have been associated with high-dose vitamin D therapy.[29] The study by Emel *et al.* found that PTH and ALP levels were similar in both low-dose vitamin D (2000 IU/day for 6 weeks) and stoss therapies (150 000 IU once).[27] In our study, ALP levels were similar in both treatment groups, but PTH levels were lower in the standard group. This is likely a reflection of the higher 25OHD level seen in the standard treatment group and resultant effect on mineral homeostasis. It should be noted, however, that PTH levels were normal at 12 weeks in both treatment groups and that the difference in PTH levels was not associated with any clinical difference between groups. Whether this potential biochemical sign of increased effectiveness of standard versus stoss therapy could be extrapolated to suggest greater effectiveness in the treatment of nutritional rickets is uncertain.

Vitamin D toxicity can be defined by 25OHD levels >250 nmol/L with or without hypercalciuria and/or hypercalcaemia.[16,30] We, however, support a definition that is not based solely on 25OHD levels but also on serum calcium and urinary Ca:Cr elevation.[16] In this current study, two children in the standard therapy group and one child in the stoss group had 25OHD levels >250 nmol/L. None of these children had elevated serum calcium or urinary Ca:Cr. Our results are consistent with others in the literature. Hypercalciuria complications have not been reported in studies using lower single doses (≤150 000 IU).[27,31] In contrast, hypercalciuria has been described in children receiving single doses of stoss therapy ≥300 000 IU.[32,33]

Daily vitamin D replacement and subsequent maintenance therapy may be associated with poor compliance, and intermittent high-dose vitamin D supplementation may improve this.[1,34] In this randomised control trial, it was hypothesised that stoss therapy would result in improved compliance; however, the compliance rate between the two groups were similar. The external validity of our compliance data is limited by the controlled setting of the study. Participants were aware that they were required to return the packaging and remaining tablets at the end of their treatment. This may have encouraged compliance rates greater than would be seen in the regular clinical setting. However, similar compliance allowed a more accurate comparison of effectiveness and safety. It must be noted that there were missing data for returned vitamin D medications, which may have led to an inaccurate expression of compliance. However, the proportion of missing data was similar for both groups, with no statistical significance ($P = 0.23$).

Potential errors with 25OHD measurement may have been introduced because the 25OHD assay was changed during the study period. However, we believe the impact of this change to be minimal as results from the two assays were almost co-linear ($R^2 = 0.96$) (Fig. 1).

There a number of strengths of this study. It is a relatively large randomised and prospective study with a small loss to follow-up. Both groups met the required number for the power calculation, therefore reducing type 2 errors. The children were followed to 12 weeks, providing time to investigate the study objectives. Specifically, we measured the normalisation of 25OHD levels and both serum and urine calcium levels to assess for toxicity. The number of returned empty vials, instead of directly observing the children taking the medication, assessed compliance. This increased external validity as it simulated a normal clinical environment.

The majority of children in our study were from non-Caucasian ethnic backgrounds. This represents the Australian experience of vitamin D deficiency being greater in children who are immigrants or born to immigrant parents compared to the overall Australian paediatric population.[7]

Conclusions

A regimen of cholecalciferol 100 000 IU every week for 4 weeks is a safe and effective alternative treatment for achieving sufficient 25OHD levels in children over 2 years of age. Standard therapy was associated with a lower PTH level at 12 weeks. This study is the largest randomised control trial to date, comparing stoss vitamin D therapy to standard therapy, of the management of vitamin D insufficiency and deficiency in children.

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APPENDIX I

SIMPLE VITAMIN D DEFICIENCY RICKETS Questionnaire
Australian Paediatric Surveillance Unit
Please keep a record of the child's unit number in your APSU folder.
Please contact Dr Craig Munns on (02) 9845-3200 or craigm2@chw.edu.au if you have any questions about this form

REPORTING CLINICIANS DETAILS

1. APSU Dr Code ☐☐☐☐

PATIENT DETAILS

2. First 2 letters of first name: ☐☐
3. First 2 letters of surname: ☐☐
3. Date of Birth: ☐☐ / ☐☐ / ☐☐
4. Sex: ☐ M ☐ F
5. Date of diagnosis: ☐☐ / ☐☐ / ☐☐
6. Post code of family: ☐☐☐☐
7. Country of birth of child:_____
8. Has the child's mother immigrated to Australia? Yes ☐ No ☐ Unknown ☐
If yes, from what country? _____ **If yes,** when (month/year)? ☐☐ / ☐☐

If this patient is primarily cared for by another physician who you believe will report the case and could provide additional deta please write the other physician's name in the space below then complete questionnaire details above this line and return to APSU. If no other report is received for this child we will contact you for further information.

FAMILY DETAILS

9. Mother's Ethnicity: ☐Aboriginal/Torres Strait Islander ☐Caucasian ☐Islander ☐ Asian ☐Middle Eastern ☐Africa ☐Latin American ☐Indian subcontinent ☐Other ☐Please Specify:_____
10. Country of birth of mother:_____
11. Father's Ethnicity**:** ☐Aboriginal/ Torres Strait Islander ☐Caucasian ☐Islander ☐Asian ☐Middle Eastern ☐Africa ☐Latin American ☐Indian subcontinent ☐Other ☐Please Specify:_____
12. Country of birth of father:_____
13. Number of children in the family: ☐1 ☐2 ☐3 ☐4 ☐5 ☐>5
14. Number of other children in family diagnosed with simple vitamin D deficiency rickets: ☐1 ☐2 ☐3 ☐4 ☐5 ☐>5

MEDICAL HISTORY

15. Does the child have other medical conditions (including allergies to food and medications)? Yes ☐ No ☐ DK ☐
If yes, please specify: _____
16. Was the child on medications at diagnosis (other than Vitamin D)? Yes ☐ No ☐ DK ☐
If yes, please specify: _____
17. Gestational age:_____ weeks DK ☐
18. Birth-weight: _____ grams DK ☐

NUTRITIONAL HISTORY CHILD

19. For children < 3 years old, how many weeks/months was the child exclusively breast fed?_____ weeks/months DK ☐
20. For children < 3 years old, at what age did the child receive commercially available formula?_____ weeks/months DK ☐
21. Did the child receive multi-vitamin or vitamin D supplementation prior to the diagnosis of rickets? Yes ☐ No ☐ DK ☐
If yes, which vitamin preparation was used? _____ DK ☐
If yes, at what age was was the vitamin supplementation started?_____ weeks/months DK ☐
If yes, for how long did the child take the vitamin supplement? _____ weeks/months DK ☐

NUTRITIONAL HISTORY MOTHER

22. Did the mother receive multi-vitamin or vitamin D supplementation during her pregnancy? Yes ☐ No ☐ DK ☐
If yes, which vitamin preparation was used? _____ DK ☐
If yes, what was the daily vitamin D dose?_____ IU DK ☐
If yes, for how long did the mother take the multivitamin/vitamin D supplementation? _____ weeks/months DK ☐

OTHER RISK FACTORS FOR VITAMIN D DEFICIENCY

23. What is the child's skin colour? Dark ☐ Intermediate ☐ Fair ☐

24. What is the mother's skin colour? Dark ☐ Intermediate ☐ Fair ☐

25. Was the mother veiled during the pregnancy? Yes ☐ No ☐ DK ☐

If yes, please tick the appropriate category below (tick one only):

☐ Consistently covered – was always covered up, including arms, hair and neck, when outdoors

☐ Inconsistently covered – did not usually cover fully in her own backyard/garden

☐ Uncovered – did not generally cover up arms, hair and neck when outdoors

26. Is the child veiled? Yes ☐ No ☐ DK ☐

If yes, please tick the appropriate category below (tick one only):

☐ Consistently covered –always covered up, including arms, hair and neck, when outdoors

☐ Inconsistently covered – did not usually cover fully in her own backyard/garden

☐ Uncovered – did not generally cover up arms, hair and neck when outdoors

If yes, from what age (years) has the child been veiled? _____ years

CLINICAL PRESENTATION AND DIAGNOSTIC STUDIES

27. What were the child's presenting signs and symptoms? *(tick as many as apply):* Limb deformity ☐ Fracture ☐ Seizur ☐ Motor delay ☐ Poor growth ☐ Respiratory illness ☐ Hypotonia ☐ Bone pain ☐ Other:_____

28. (a) Was the child diagnosed during screening because of affected siblings? Yes ☐ No ☐

29. Were there radiological signs of rickets? Yes ☐ No ☐ Not Done ☐ DK ☐

Biochemical Data at Diagnosis, If known

Parameter	Results at Diagnosis	Units	Normal range	DK
25-Hydroxyvitamin D				
Alkaline phosphatase				
Ionized calcium				
Total calcium				
Albumin				
Phosphate				
Parathyroid hormone				
Haemoglobin				
Mean corpuscular volume (MCV)				
Ferritin				

TREATMENT OF RICKETS

30. Was the child commenced on treatment? Yes ☐ No ☐ DK ☐ **If yes,** what was prescribed?

Medication	Dose (units)	Frequency	Duration of therapy (weeks/days/months)

Thank you for your help with this research project.
Please return this questionnaire to the APSU in the reply-paid envelope.

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