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ORIGINAL ARTICLE

Weekly regimen of vitamin D supplementation is more efficacious than stoss regimen for treatment of vitamin D deficiency in children with chronic liver diseases

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Abstract

There are no evidence-based recommendations on the ideal dose and regimen for supplementation of vitamin D in children with chronic liver disease (CLD). This study aimed to compare the safety and efficacy of weekly and stoss regimens for treatment of vitamin D deficiency in these children. Children between the ages of 1 to 18 years with CLD and hypovitaminosis D defined by 25-OH vitamin D (25(OH)D) < 30μg/l were included. They were randomized to receive either stoss regimen (600,000 IU on day 1) or weekly (60,000 IU weekly) regimen of vitamin D. The 25(OH)D levels at 3 and 6 months were compared in the two groups. A total of 210 suspected cases of CLD were assessed for eligibility. Of a total of 67 children satisfying the inclusion criteria, 33 and 34 were randomized to receive stoss and weekly regimen, respectively. Final analysis included 28 children in each group. Clinical rickets was seen in 25.4% of children with hypovitaminosis D. The rise in levels of 25(OH)D at 3 months was higher with weekly regimen (34.3 ± 30.7 μg/l) as compared to stoss regimen (17.2 ± 11.5 μg/l) ($p = 0.009$). Rise at 6 months as compared to baseline was significantly higher with weekly regimen (30.7 ± 24μg/l) as compared to stoss regimen (11 ± 8.4 μg/l) ($p < 0.001$). Normal levels of 25(OH)D at 6 months were achieved in 24/28 (85.7%) of those receiving weekly regimen and 9/28 (32.1%) of those receiving stoss regimen ($p < 0.001$). With stoss therapy, 25(OH)D increased at 3 months as compared to baseline but thereafter dropped significantly at 6 months ($p = 0.008$).

Conclusion: Weekly regimen of vitamin D supplementation is more effective than stoss regimen for treatment of hypovitaminosis D in children with CLD. Once normal levels are achieved, child should be shifted to 60,000 IU per month as maintenance dose.

What is Known:
- *Vitamin D deficiency is more common and severe in children with chronic liver diseases.*
- *Currently used doses fail to achieve normal vitamin D levels in these children.*

What is New?
- *Weekly regimen of 60,000 IU of vitamin D3 is the most effective regimen for treating vitamin D deficiency in children with CLD.*
- *Children with CLD should further receive maintenance dose of 60,000 IU every month.*

Keywords Chronic liver disease · Stoss regimen · Vitamin D deficiency

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Abbreviations

APRI	AST to platelet ratio index
BMP	Bone morphogenetic protein
CLD	Chronic liver disease
MMP	Matrix metalloproteinases
PELD	Pediatric end-stage liver disease
PTH	Parathormone
RDA	Recommended daily allowance
VDBP	Vitamin D binding protein
VDD	Vitamin D deficiency

Introduction

Vitamin D deficiency (VDD) is almost universal (92%) among patients with chronic liver disease (CLD) and at least one third of them suffer from severe VDD [4]. The severity of VDD is directly related to the severity of liver disease [9]. There are multiple factors which predispose patients with CLD to VDD [11, 13, 22]. The important mechanisms include impaired hepatic hydroxylation leading to decreased formation of 25-OH cholecalciferol, reduced production of vitamin D binding protein (VDBP), and decreased absorption due to portal hypertensive enteropathy. Other potential causes are poor diet in children with CLD, renal tubular dysfunction in certain metabolic liver diseases, increased catabolic removal by 24-hydroxylation, and decreased absorption due to effect of certain drugs like cholestyramine [11, 13, 22]. A recent study has shown that it is difficult to treat VDD in children with CLD with current therapeutic strategies [21]. In absence of studies on children with CLD, current treatment strategies in children with CLD are extrapolated from trials on normal children. Children without CLD are supplemented with either of daily, weekly or stoss regimen, each with equal efficacy [5, 10, 17]. There are no studies till date to compare the efficacy of these regimens in children with CLD. In addition, safety profile of high dose (stoss) therapy has been questioned by some studies [6, 14]. This study was planned to evaluate the safety and efficacy of two of the most commonly used regimens (stoss and weekly) for vitamin D supplementation in children with CLD.

Materials and methods

The study was conducted at a tertiary care pediatric hepatology centre catering to referrals from all over the country. It was a prospective study from January 2015 to December 2016. The study was approved by the institutional ethics committee. Informed, written consent was taken from the parents of all children. Children between the ages of 1 to 18 years with CLD and hypovitaminosis D (25(OH)D < 30 μg/l) were included. US Endocrine Society has defined vitamin D deficiency as 25(OH)D < 20 μg/l (50 nmol/l) and vitamin D insufficiency as 25(OH)D between 21 and 30 μg/l (50–75 nmol/l) [12]. We have clubbed children with both vitamin D deficiency and insufficiency under the heading of hypovitaminosis D. One microgram per liter of 25(OH)D is equivalent to 2.5 nmol/l. CLD was defined on the basis of histological (presence of fibrosis) and/or radiological evidence (coarsened echotexture of liver, portal vein diameter greater than age specific upper limit, hepatofugal flow, presence of collaterals, and splenomegaly). Those with cholestatic liver diseases, tumors (benign or malignant), preexistent hypercalciuria, renal tubular defects, who had received vitamin D doses in last 6 months, and those on anticonvulsant therapy were excluded. For the purpose of exclusion, cholestatic liver diseases were diagnosed on the basis of clinical presentation (jaundice with/without pruritus), laboratory analysis (increased alkaline phosphatase, bile acids) and liver histopathology. Renal tubular defects were identified in presence of acidosis with glycosuria, proteinuria, aminoaciduria, and bicarbonaturia. However, none of our patients were excluded for renal tubular dysfunction. Hypercalciuria was defined on the basis of age specific urinary calcium to creatinine ratio [15]. All children satisfying the inclusion criteria were evaluated as per the protocol and the detailed clinical profile was entered in a prescribed proforma. The participants were randomized to receive therapy in one of the two regimens by block randomization with block size of 6 (allocation ratio of 1:1). Allocation concealment was done using sequentially numbered opaque sealed envelopes. The study design is depicted in Fig. 1. Children in stoss group received 600,000 IU of cholecalciferol orally (ten sachets of calcirol 60,000 IU, Cadila Pharma—mixed with milk) on day 1 followed by 600 IU/day (equivalent to RDA as maintenance) from day 2 onwards. A stoss dose (600,000 IU) was repeated at 3 months if child had persistent hypovitaminosis D. Children in weekly group received 60,000 IU/week of oral cholecalciferol granules (Calcirol sachet 60,000 IU/g, Cadila Pharma) administered on a fixed day each week. After 3 months, children with 25(OH)D levels less than 30 μg/l were continued on weekly and those with levels more than 30 μg/l were shifted to monthly dosing. To ensure compliance, weekly phone calls were made to the patients in weekly group and they were asked to show empty packets on follow-up. Non-compliance was defined as non-availability of empty sachets in the possession of the parents at follow-up visits. Oral calcium at a dose of 50 mg/kg/day was added to both regimens and continued till normalization of 25(OH)D levels. The total duration of follow-up was 6 months. The primary outcome measure was the difference in 25(OH)D levels at 3 and 6 months between the two regimens. The secondary outcome measures included safety of the regimens and normalization of parathormone (PTH) levels. Moreover at 6 months, we also studied the progression of CLD among those

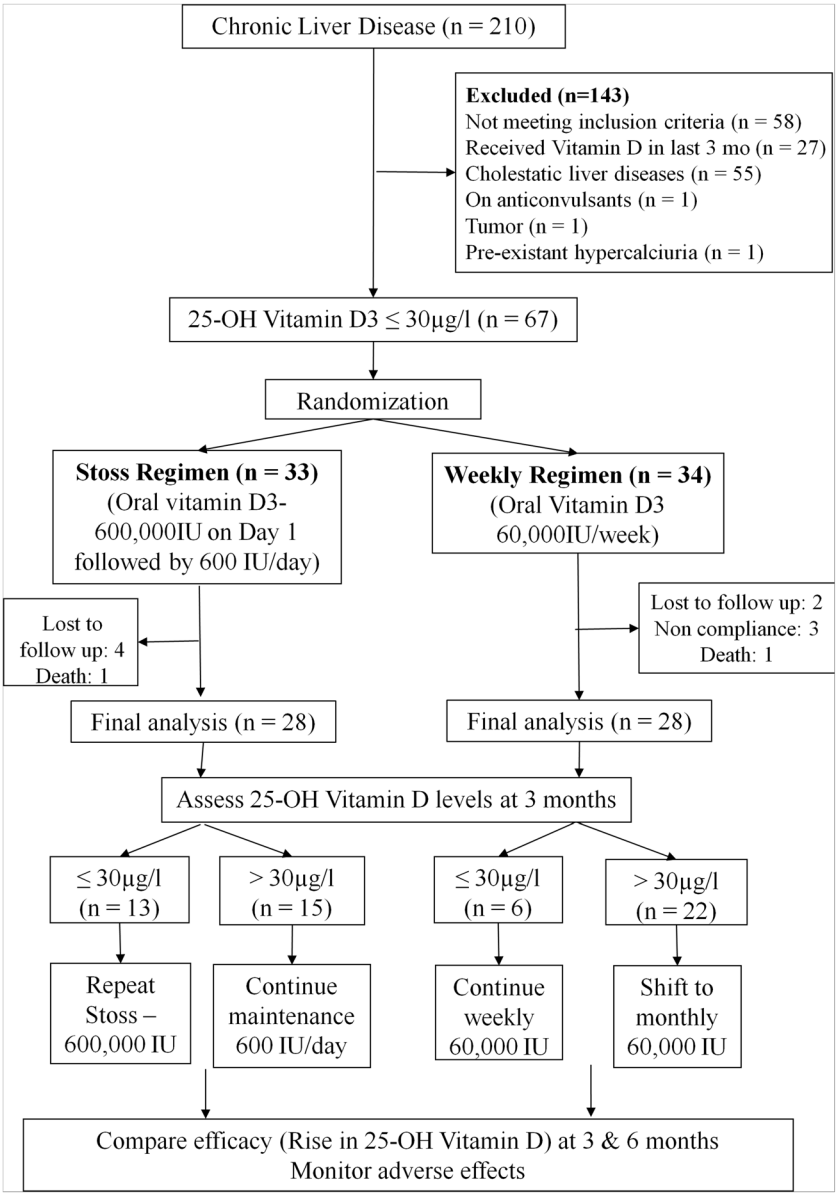

Fig. 1 Study design

achieving vitamin D sufficiency versus those with persistent hypovitaminosis D.

The quantitative estimation of 25(OH)D level was done using ARCHITECT 25-OH vitamin D assay, Biokit S.A, Product Code: MRG.JIT.JJX. The ARCHITECT 25(OH)D assay is a chemiluminescent microparticle immunoassay for the quantitative determination of 25(OH)D in human serum and plasma. The 25(OH)D levels were checked at least a week after the last dose of weekly therapy to eliminate false high levels in the weekly regimen. PTH assay was done using chemiluminescence immunoassay. PTH levels were done at baseline, 3 months, and 6 months. Age-specific PTH cutoffs as described by Cioffi et al. were used to define hyperparathyroidism [7]. The parents were educated about the symptoms and signs of hypervitaminosis D. Monitoring for vitamin D toxicity was done at 3 and 6 months based on history, serum calcium, urinary calcium to creatinine ratio, and evidence of nephrocalcinosis on USG. To assess the effect of vitamin D supplementation on progression of CLD, parameters of those who achieved normal levels of 25(OH)D by 6 months were compared to those who were still deficient/insufficient at 6 months. The parameters compared were changed in fibroscan, pediatric end-stage liver disease (PELD), and AST to platelet ratio index (APRI) between baseline and 6 months.

Sample size and statistical analysis

Sample size calculation was done based on a previous study in children comparing stoss therapy with weekly regimen, where

the difference between the two groups was 1.6 μg/l. Assuming α error 5%, power 90%, equivalence margin 5 μg/l, and effect size 0.75, the calculated sample size was 28 in each arm. Assuming a 10% dropout rate, we decided to take 30 children in each arm. OpenEpi version 3.01 was used for sample size calculation. Continuous data was represented as mean ± SD and categorical variables as percentages. Continuous data were compared using independent samples t test and categorical using chi-square test. To see the change in vitamin D level at different time points, repeated measures ANOVA followed by post hoc comparison by Bonferroni method was done. *P* value less than 0.05 was considered significant. All analysis was done using SPSS v 21.

Results

Of the 210 cases (68.5% males) of CLD evaluated, 67 (79.1% males) fulfilled the inclusion criteria: 33 received stoss therapy and 34 weekly therapy. Among the children with low 25(OH)D levels, 47 (70.1%) were deficient (levels less than 20 μg/l), whereas 20 (29.9%) were insufficient (levels between 21 and 30 μg/l). Figure 1 depicts the flowchart for enrolment, allocation, follow-up, and analysis of the subjects. Final analysis included 28 children each in the two regimens. The etiology of underlying CLD included Wilson's disease ($n = 16$), chronic hepatitis B ($n = 16$), autoimmune hepatitis ($n = 13$), glycogen storage disease ($n = 5$), non-alcoholic fatty liver disease ($n = 5$), hepatic venous outflow tract obstruction ($n = 3$), and others ($n = 9$). The mean age of children included in the study was 11.1 ± 4.5 years (range 1.5–18 years). The mean 25(OH)D levels in children included in the study was 16.86 ± 5.8 μg/l (range 4.9–29.2 μg/l). Clinical evidence of rickets was seen in 17/67 (25.4%) of children with hypovitaminosis D.

Efficacy of vitamin D supplementation regimens

Baseline characteristics including the 25(OH)D levels of the children in the two groups were comparable (Table 1). Both

Table 1 Baseline characteristics of children included in the two therapeutic regimens

Characteristics		Stoss group ($n = 33$)	Weekly group ($n = 34$)	Effect size (95% CI)	*p* value
Age		10.9 ± 4.8	11.35 ± 4.1	− 0.5 (− 2.7 to 1.7)	0.674
Sex (M/F)		25/8	28/6	1.5 (0.5 to 4.9)[a]	0.56
Clinical rickets (%)		30.3%	20.6%	1.7 (0.5 to 5.1)[a]	0.41
Weight for age *z* score		− 1.3 ± 1.7	− 0.86 ± 1.3	− 0.4 (− 1.2 to 0.3)	0.253
Height for age *z* score		− 1.21 ± 1.4	− 0.6 ± 1.12	− 0.6 (− 1.2 to 1.2)	0.058
BMI for age *z* score		− 0.69 ± 1.45	− 0.81 ± 1.3	0.12 (− 0.6 to 0.8)	0.719
Sun exposure (h)		2.7 ± 1.2	2.7 ± 1.3	0 (− 0.8 to 0.6)	0.945
Baseline 25(OH)D		15.6 ± 5.6	18 ± 5.9	− 2.4 (− 5.2 to 0.4)	0.095
Vitamin D status	Deficient Insufficient	25 8	22 12		
Baseline calcium (mg/dl)		8.7 ± 0.6	8.9 ± 0.5	− 0.2 (− 0.5 to 0.02)	0.069
Baseline PTH (pg/ml)		56.6 ± 33.8	43.3 ± 20.1	13.3 (− 3.1 to 30)	0.11
PELD		4.5 ± 10.3	7.3 ± 20.1	− 2.8 (− 10.5 to 5)	0.48
CTP score		6.5 ± 2.2	6.4 ± 1.9	0.1 (− 0.9 to 1.1)	0.886
Fibroscan		19.1 ± 19.8	23.8 ± 20.9	− 4.7 (− 14.7 to 5.2)	0.34
Urine Ca/creatinine ratio		0.07 ± 0.05	0.09 ± 0.09	0 (− 0.1 to 0.02)	0.265
Vitamin A deficiency		21.2%	29.4%	0.65 (0.2 to 2)[a]	0.576
Hemoglobin (g/dl)		11.99 ± 2.5	11.99 ± 1.9	0 (− 1.1 to 1.1)	0.886
Bilirubin (mg/dl)		1.75 ± 4	2.1 ± 3.3	− 0.4 (− 2.2 to 1.4)	0.695
Albumin (g/dl)		3.7 ± 0.9	3.6 ± 0.9	0.07 (− 0.4 to 0.5)	0.746
INR		1.4 ± 0.5	1.3 ± 0.3	0.1 (− 0.1 to 0.3)	0.574
Fibrosis Grade (Ishak's)	0–3 4–6	14 5	14 7		
AST to platelet ratio index		1.9 ± 3.2	1.9 ± 2.2	0 (− 1.4 to 1.3)	0.979
Alkaline phosphatase (IU/L)		280 ± 162	280 ± 118	− 0.2 (− 69 to 69)	0.996

25(OH)D 25-hydroxy vitamin D, *AST* aspartate aminotransferase, *CTP* Child Turcotte Pugh score, *INR* international normalized ratio, *PELD* pediatric end stage liver disease score, *PTH* parathormone

[a] Odds ratio

the groups showed significant increase in 25(OH)D levels after 3 and 6 months of therapy as compared to the baseline. The rise in 25(OH)D levels from baseline to 3 months (weekly 34.3 ± 30.7 μg/l vs stoss 17.2 ± 11.5 μg/l, mean difference 17.1, 95% CI 4.5 to 29.6, $p = 0.009$) and 6 months (weekly 30.7 ± 24 μg/l vs stoss 11 ± 8.4 μg/l, mean difference 19.6, 95% CI 9.8 to 29.4, $p < 0.0001$) of therapy was significantly higher in weekly regimen as compared to stoss regimen (Table 2). The 25(OH)D levels at baseline, 3 months, and 6 months with the two regimens are depicted in Table 1. Using repeated measures ANOVA and post hoc analysis, it was seen that among children receiving stoss therapy, 25(OH)D concentrations at 3 and 6 months of therapy were significantly higher than baseline but concentration at 6 months was significantly lower than the level at 3 months ($p = 0.008$). In weekly regimen, 25(OH)D concentration at 3 and 6 months of therapy was significantly higher than baseline and there was no significant decline in concentration of 25(OH)D from 3 months to 6 months ($p = 1.000$) (Fig. 2). Normalization of vitamin D levels (25(OH)D level > 30 μg/l) at 3 months was achieved more often with weekly regimen as compared to that with stoss regimen, although the difference was not statistically significant (weekly 78.6% vs stoss 53.6%, OR 3.2, 95% CI 0.99 to 10.2, $p = 0.089$) (Fig. 3). However, by 6 months, there were 12 times higher odds of achieving normal levels of 25(OH)D with weekly regimen (weekly group 85.7% vs stoss group 32.1%, OR 12.67, 95% CI 3.38 to 47.54, $p < 0.0005$). Among those who had normal 25(OH)D levels at 3 months, 7/15 (46.7%) assigned to stoss regimen (thereafter on RDA-600 IU/day) versus 2/22 (9.1%) of those initially assigned to weekly regimen (shifted on monthly 60,000 IU after 3 months) went on to again become deficient/insufficient at 6 months (Fig. 3). As shown in Fig. 3, 13/28 (46.4%) children in stoss regimen remained hypovitaminotic at 3 months. All of them received another stoss dose at 3 months, yet 12/13 (92.3%) of those remained hypovitaminotic at 6 months. Despite, the extra 600,000 IU dose in 13 children in stoss group, stoss therapy achieved vitamin D sufficiency in only 32.1% in contrast to weekly regimen where vitamin D sufficiency was achieved in 85.1% ($p < 0.0005$). All children who continued to have hypovitaminosis D at 6 months were given single intramuscular dose of 600,000 IU. Noncompliance with weekly group was seen in 3/31 (9.7%) children.

Effect of vitamin D supplementation on parathormone levels

PTH values were available at baseline for 21 children in stoss regimen and 24 children in weekly regimen. PTH values were increased above the age specific cutoff in 19/21 (90.5%) among stoss group and 21/24 (87.5%) among weekly group. There was no significant difference in the frequency of PTH normalization at 3 months (weekly group 52.4% vs stoss group 38.9%, $p = 0.523$) and 6 months (weekly group 76.2% vs stoss group 50%, $p = 0.108$) of therapy.

Safety of vitamin D treatment regimens

Vitamin D toxicosis (25(OH)D > 150 μg/l) was not seen in patients of either group. Asymptomatic hypervitaminosis (25(OH)D > 100 μg/l) was seen in five patients receiving weekly regimen and none in stoss group. Treatment was temporarily stopped in all of them with normalization of levels after 1 month. Asymptomatic hypercalcemia developed in one patient receiving stoss regimen. None developed hypercalciuria or nephrocalcinosis.

Effect of vitamin D supplementation on CLD parameters

A total of 33/56 children achieved normal levels of 25(OH)D by 6 months. The baseline parameters (fibroscan, PELD and APRI) were comparable between those who achieved normal levels at 6 months and those who remained deficient. There was a greater decrease in fibroscan in those achieving normal vitamin D levels at 6 months (Median decrease 1.8 vs 0.6 kPa, $p = 0.024$) (Supplementary Digital Content 1). However, the change in PELD and APRI was not different in the two groups.

Discussion

linical rickets was seen in only 25.4% of the children with biochemical hypovitaminosis. This may emphasize the need for testing 25(OH)D status in all children with CLD in order to detect and treat hypovitaminosis at a subclinical stage [16].

Table 2 Comparison of 25-OH vitamin D levels at different time points in the two regimens

	25-OH vitamin D levels (μg/l)		Mean difference (95% CI)	*p* value
	Stoss regimen	Weekly regimen		
At baseline	15.8 ± 5.9	18.5 ± 6.3	− 2.9 (− 6.2 to + 0.4)	0.082
After 3 months	*33.1 ± 11.6*	*52.8 ± 32.3*	*− 19.9 (− 33 to − 6.8)*	*0.004*
After 6 months	*26.9 ± 7.6*	*49.2 ± 24.8*	*− 22.3 (− 32.3 to − 12.3)*	*< 0.0001*

Italics indicate significant difference in the two regimens

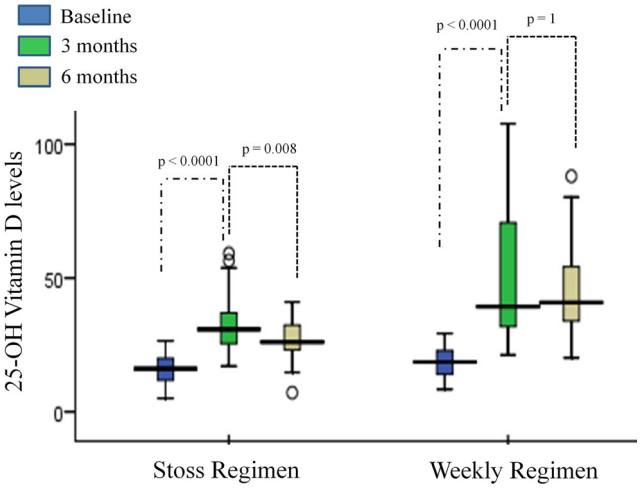

Fig. 2 Trend of 25-OH vitamin D levels in the two regimens: With stoss therapy, there was a decline in levels between 3 and 6 months after an initial rise at 3 months. This dip in level between 3 and 6 months was not seen with weekly therapy

Similar differences have been seen in normal pediatric population: clinical rickets in 8.5% and biochemical VDD in 65.7% [2].

Efficacy of vitamin D supplementation regimens

The cumulative dose of vitamin D administered in the two regimens over 3 months were similar (stoss 654,000 IU vs weekly 720,000 IU). There was a greater increase in 25(OH)D levels at 3 months in children receiving weekly regimen of vitamin D as compared to those receiving stoss therapy. The difference was even more accentuated at 6 months. The higher rise with weekly therapy could be attributed to the fact that the half life of orally administered vitamin D in humans is 28 days and the plateau concentration is usually achieved by 1–2 months [24]. Thus, further increase in 25(OH)D levels would only happen with additional doses of vitamin D or may drop if no further supplementation is given. However, previous studies in children, albeit in those without liver diseases, have shown comparable efficacy of weekly and stoss therapy [8, 17]. To explain the difference, we hypothesize that three steps in vitamin D metabolism—(i) absorption across the intestine affected by portal hypertensive enteropathy, (ii) limited absorption of fat and fat soluble vitamins in non-cholestatic CLD, and (iii) 25-hydroxylation which is limited due to decreased hepatic reserve—now become the rate limiting steps in children with CLD. Limited amount of vitamin D can be absorbed due to malabsorption on account of portal hypertensive enteropathy and only a proportion of the absorbed drug can get activated in the liver. These limiting steps affect patients with stoss therapy more prominently than weekly therapy. Administration of same cumulative dose in smaller fractions and at well spaced intervals will overcome these limitations and maintain sustained bioavailability with less wastage and might be the reason for better response to weekly therapy in this study.

Among those who achieved normal 25(OH)D at 3 months, 46.7% in stoss therapy as against 9% in weekly therapy went on to become deficient/insufficient at 6 months. This can be explained by difference in the maintenance doses given to the two groups as per protocol. The stoss therapy group received maintenance vitamin D equivalent to RDA—600 IU/day, whereas the weekly group received 60,000 IU/month. This suggests that high-dose maintenance therapy of 60,000 IU per month is required to maintain long term vitamin D sufficiency in children with CLD. This study is the first to analyze the effect of

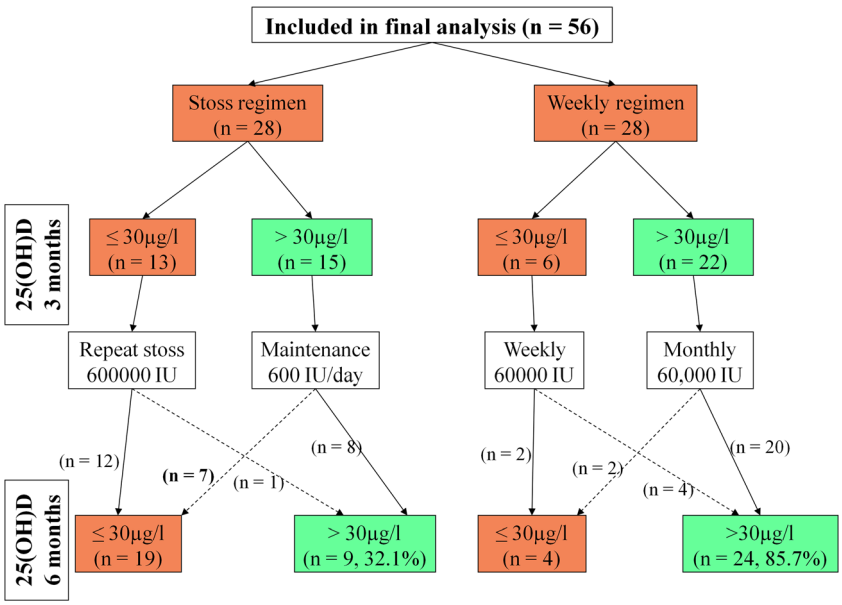

Fig. 3 Comparison of outcome (normalization of 25-OH vitamin D) at 3 and 6 months with the two supplementation regimens

different vitamin D treatment regimens in children with CLD. Compliance was acceptable with weekly group (91.2%).

Safety of vitamin D supplementation regimens

At 3 months, asymptomatic hypervitaminosis D was seen in five children receiving weekly regimen and asymptomatic hypercalcemia in one child receiving stoss therapy. Although most pediatric studies report no hypercalcemia with vitamin D supplementation [17, 18, 20], a few have reported hypercalcemia in 10–32% with stoss therapy [6, 14] as well as with daily supplementation [23]. Presence of hypervitaminosis albeit asymptomatic implies that children on vitamin D supplementation might benefit from regular monitoring of the levels. However, we did not do 25(OH)D and calcium levels before completion of 3 months, where more number of children could possibly have had hypercalcemia and hypervitaminosis D.

Effect of vitamin D supplementation on progression of liver disease

There was a greater decrease in fibroscan between baseline and 6 months in children who achieved normal 25(OH)D level at 6 months as compared to children who continued to remain deficient. Vitamin D supplementation did not lead to a change in other parameters (APRI, PELD) over 6 months. Both the groups of children (those achieving normal 25(OH)D at 6 months or not) also received specific treatment for their primary disease. The decrease in fibroscan could be attributable to the antifibrotic properties of vitamin D. Vitamin D inhibits or delays fibrosis in the liver by various mechanisms: inhibition of TGF-β1 induced stimulation of α-smooth muscle actin expression [19]; decreased expression of collagen I, III, and other collagen isoforms; increased expression of several antifibrotic factors such as BMP7, MMP8, and follistatin [3]; and inhibition of lipopolysaccharide mediated activation of hepatic stellate cell [1]. Although there was a greater drop in APRI in those achieving normal 25(OH)D versus those remaining deficient/insufficient, the difference was not statistically significant. It is possible that the difference in the two groups would become significant at longer follow-up. Studies with longer duration of follow-up are required to analyze the effect of vitamin D supplementation on progression of liver diseases.

An important limitation of our study was the heterogeneous etiologies of the CLD included. We need larger studies in specific etiology based cohorts to determine the effect of vitamin D supplementation on halting the progression of CLD. We also did not evaluate daily regimen which could be another potential regimen for treating these children based on our hypothesis. However, children with CLD are already on multiple drugs and adding another drug daily to their prescription will increase the complexity and may affect compliance. We did not do radiology to confirm active rickets in our children. Another interesting area to look at would be the pharmacokinetics of orally administered vitamin D in children with CLD. To conclude, weekly regimen is more effective than stoss regimen for treatment of hypovitaminosis D in children with CLD. We suggest that all children with CLD should have a baseline measurement of 25(OH)D level; 60,000 IU of vitamin D3 should be supplemented weekly in all children with hypovitaminosis D. The treatment should be continued till vitamin D levels are more than 30 μg/l. Once adequate levels are achieved, child should be shifted to maintenance 60,000 IU per month.

Authors' Contributions BBL and SA conceptualized and designed the work. BBL collected the data. SA and BBL analysed the data and prepared the first draft. SA, BBL, DR and RK critically reviewed, revised and approved the final version.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval Number: IEC/IRB-F.25/5/75/ILBS/AC/2014/387.

Informed consent Informed consent was obtained from the parents of all the children included in the study.

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