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Efficacy of high-dose vs. low-dose vitamin D_3 supplementation in children with chronic tic disorders: a randomized controlled trial

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Abstract

Background Vitamin D_3 has emerged as a potential therapeutic agent for alleviating tic symptoms in children with chronic tic disorders (CTDs). This study aims to evaluate the comparative efficacy of high-dose and low-dose vitamin D_3 supplementation on tic severity and serum 25-hydroxyvitamin D 25(OH)D levels in children with CTDs.

Methods A randomized controlled trial was conducted with 83 children aged 4 to 15 years diagnosed with CTDs. Participants were randomly assigned to receive either high-dose vitamin D_3 (5,000 IU/day) or low-dose vitamin D_3 (1,000 IU/day) for three months. The primary outcome was tic severity, assessed using the Yale Global Tic Severity Scale (YGTSS), while secondary outcomes included changes in serum 25(OH)D and calcium levels. Tic severity and biochemical markers were measured at baseline and after the intervention to assess the effects of vitamin D_3 supplementation.

Results Both the high-dose and low-dose groups showed significant improvements in tic severity and increases in serum 25(OH)D levels ($p < 0.05$). The high-dose group exhibited a significantly greater reduction in tic severity and a more substantial increase in serum 25(OH)D levels compared to the low-dose group ($p < 0.05$). No significant differences were observed in serum calcium levels between the group ($p > 0.05$). Furthermore, multivariate linear regression analysis revealed a significant negative association between increases in serum 25(OH)D levels and reductions in tic severity ($t = -2.816$, $p < 0.05$).

Conclusion High-dose vitamin D_3 supplementation is more effective than low-dose supplementation in reducing tic severity and increasing serum 25(OH)D levels in children with CTDs. These findings suggest that high-dose vitamin D_3 may serve as a valuable adjunctive therapy for managing CTDs.

Keywords Chronic tic disorder, Vitamin D supplementation, Tic severity, Serum 25(OH)D levels

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Introduction

Chronic tic disorders (CTDs) are neurodevelopmental conditions characterized by persistent motor or vocal tics, with Tourette's syndrome (TS) and chronic motor/vocal tic disorders being the most prevalent forms [1, 2]. These disorders typically emerge in childhood and affect approximately 1–3% of school-aged children, with a higher prevalence observed in boys [3–5]. CTDs are often comorbid with other neuropsychiatric conditions, such as obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD), further impairing social, academic, and emotional functioning [6, 7].

The pathophysiology of CTDs remains unclear, although genetic, environmental, and neurobiological factors have been identified as key contributors [8–10]. Dysfunction within the cortico-basal ganglia pathways, particularly involving dopaminergic regulation, is believed to play a central role in the development of CTDs [11]. Additionally, factors such as diet, environmental toxins, and physical activity may exacerbate tic symptoms [12].

Standard treatments for chronic tic disorders (CTDs) often involve pharmacological interventions [13], however, these medications often come with side effects and reduced long-term efficacy [14, 15]. Consequently, behavioral therapies like Habit Reversal Training (HRT), Comprehensive Behavioral Intervention for Tics (CBIT), Exposure and Response Prevention (ERP), and Differential Reinforcement of Other Behaviors (DRO) have emerged as effective, non-pharmacological alternatives. These approaches focus on increasing tic awareness, replacing tics with alternative behaviors, and reducing tic triggers, offering promising, sustainable treatment options [16, 17].

Despite the efficacy of these treatments, there remains a need for complementary therapies to further improve outcomes and address underlying biological mechanisms. Recent studies have highlighted vitamin D deficiency as a potential risk factor for CTDs, with children affected by these disorders showing significantly lower serum levels of 25-hydroxyvitamin D [25(OH)D] compared to healthy controls [18, 19]. A systematic review has further supported this association, suggesting that vitamin D deficiency may exacerbate tic severity [20].

Vitamin D supplementation has emerged as a promising adjuvant therapy for CTDs. Vitamin D is crucial in regulating neurotransmitters, particularly dopamine, which plays a key role in tic disorders [21]. The activation of vitamin D receptors in the central nervous system not only modulates dopamine but also contributes to neuroprotection and immune modulation [22]. Preclinical and clinical studies, including our own, have shown that vitamin D_3 supplementation can reduce tic severity, likely through its influence on neurotransmitter regulation and neuroprotection [23, 24].

Despite promising findings, the optimal dosage of vitamin D in this context remains unclear. This randomized clinical trial seeks to compare the effects of high-dose versus low-dose vitamin D_3 supplementation in children with CTDs, hypothesizing that higher doses will result in greater reductions in tic severity and increases in serum 25(OH)D levels. While the use of only two dosage levels may limit conclusions about the optimal dose, this study aims to provide valuable insights into effective dosing strategies for CTD management and to guide future research in this area.

Methods

Study design and participants

This randomized controlled clinical trial was approved by the Research Ethics Committee of the First Hospital of Jilin University (Approval Number: 22K106-001). Written informed consent was obtained from the parents or guardians of all participants in compliance with the Declaration of Helsinki. This study is part of a previously registered trial, registered with the Chinese Clinical Trial Registry under registration number ChiCTR2200056482.

A total of 141 participants, aged 4 to 15 years, diagnosed with CTDs, were initially assessed for eligibility and randomly assigned to one of two groups: a high-dose vitamin D_3 supplementation group and a low-dose group. After accounting for follow-up losses, 83 participants were included in the final analysis. Eligibility was determined based on DSM-5 diagnostic criteria. TS was diagnosed by the presence of both multiple motor tics and at least one vocal tic persisting for more than one year. In contrast, chronic motor or vocal tic disorder was diagnosed when only motor or vocal tics were present for over one year without both types occurring simultaneously [1]. Participants were excluded if they had used calcium or vitamin D supplements within the past three months, or if they had endocrine, liver, or kidney disorders. Additional exclusion criteria included neurodevelopmental conditions such as autism spectrum disorder, epilepsy, or tuberous sclerosis, autoimmune diseases like rheumatic fever, and comorbid attention-deficit hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD).

Demographic data, including age (in years), gender, body mass index (BMI), and daily outdoor activities, were collected for all participants. BMI-for-age percentiles were calculated using the following formula: BMI = weight (kg) / height^2 (m). Participants were classified into three groups based on their BMI percentile: normal weight (< 85th percentile), overweight (85–95th percentile), and obese (> 95th percentile) [25].

Sample size calculation

We first conducted a pilot study, which indicated that the mean change in YGTSS scores before and after treatment was 8.25 (SD = 4.85) for the high-dose group and 5.84 (SD = 2.98) for the low-dose group. These values were used to calculate the required sample size, with a 1.2:1 ratio between the high-dose and low-dose groups, aiming for a 95% confidence interval. Based on these calculations, we determined that 31 participants were needed in the high-dose group and 26 participants in the low-dose group. After accounting for a 20% attrition rate, the required sample sizes were adjusted to 38 participants for the high-dose group and 32 participants for the low-dose group.

Randomization and intervention

Participants were randomly assigned to either a high-dose or low-dose vitamin D_3 supplementation group using a computer-generated sequence with random block sizes of 4 or 8 to ensure balanced allocation. The intervention spanned 90 days, with the high-dose group receiving 5,000 IU daily and the low-dose group receiving 1,000 IU daily.

To maintain the integrity of the study, a single-blind design was implemented, ensuring that participants remained unaware of their group assignment throughout the duration of the study. Group allocations were concealed until the statistical analysis was completed. Adherence to the supplementation regimen was monitored through pill counts, and the vitamin D_3 tablets were supplied by NATURE'S BOUNTY, INC., Bohemia, NY 11,716, USA.

To maintain the integrity of the study, a single-blind design was implemented, ensuring that participants remained unaware of their group assignment throughout the duration of the study. Group allocations were concealed until statistical analysis was completed. The use of vitamin D_3 tablets, supplied by NATURE'S BOUNTY, INC. (Bohemia, NY 11716, USA), was essential for preserving the blinding protocol. Tablets (1000 IU and 5000 IU) were chosen over liquid forms to standardize the dosage across participants and prevent issues related to varying liquid volumes, which could compromise blinding. Adherence to the supplementation regimen was monitored through pill counts.

Laboratory measurements

Serum 25(OH)D and calcium levels were measured at baseline and again at the study endpoint after 90 days of supplementation. Laboratory analyses were performed using high-performance liquid chromatography at Guangzhou King Medical Center. Serum vitamin D status was classified as optimal (30–90 ng/mL), insufficient (10–30 ng/mL), or deficient (< 10 ng/mL) [26]. Calcium levels were considered optimal at 2.2–2.7 mmol/L, insufficient at 2.0–2.2 mmol/L, and deficient if below 2.0 mmol/L.

Outcome measurements

The primary outcome was the change in tic severity, assessed using the Yale Global Tic Severity Scale (YGTSS), a semi-structured scale designed to evaluate both impairment and severity of tic symptoms. The YGTSS provides a total tic score that reflects the combined severity of vocal and motor tics by considering factors such as intensity, frequency, number, interference, and complexity, with a possible score range of 0–50. Additionally, the YGTSS includes an impairment rating scale to evaluate functional impairments associated with tics, particularly in psychosocial aspects, with scores ranging from 0 to 50 points [27].

This study employed the Chinese version of the YGTSS, which has demonstrated strong psychometric properties. According to the Diagnosis and Treatment of Childhood Tic Disorders Expert Consensus (2017), published by the Neurology Group of the Chinese Pediatric Society of the Chinese Medical Association, TD severity is categorized on the YGTSS as mild for a total score < 25, moderate for scores between 25 and 50, and severe for scores > 50 [28]. Secondary outcomes included changes in serum 25(OH) D and calcium levels from baseline to the study endpoint.

Data analysis

Data were analyzed using IBM SPSS Statistics, Version 27. The Kolmogorov-Smirnov test was applied to assess the normality of the data distribution. Normally distributed continuous variables were summarized as means with standard deviations (SDs), while non-normally distributed variables were presented as medians with interquartile ranges (IQRs). Categorical variables were expressed as frequencies and percentages.

Intra-group comparisons (before and after supplementation) were performed using paired-samples t-tests for normally distributed data and Wilcoxon signed-rank tests for non-normally distributed data. Differences between the high-dose and low-dose groups were assessed using independent t-tests for normally distributed data and Mann-Whitney U-tests for non-normally distributed data. Chi-square tests were used for categorical variables. Multivariate linear regression analysis was performed to examine the relationship between changes in serum 25(OH)D levels and tic severity, specifically focusing on the overall YGTSS score. A P-value ≤ 0.05 was considered statistically significant.

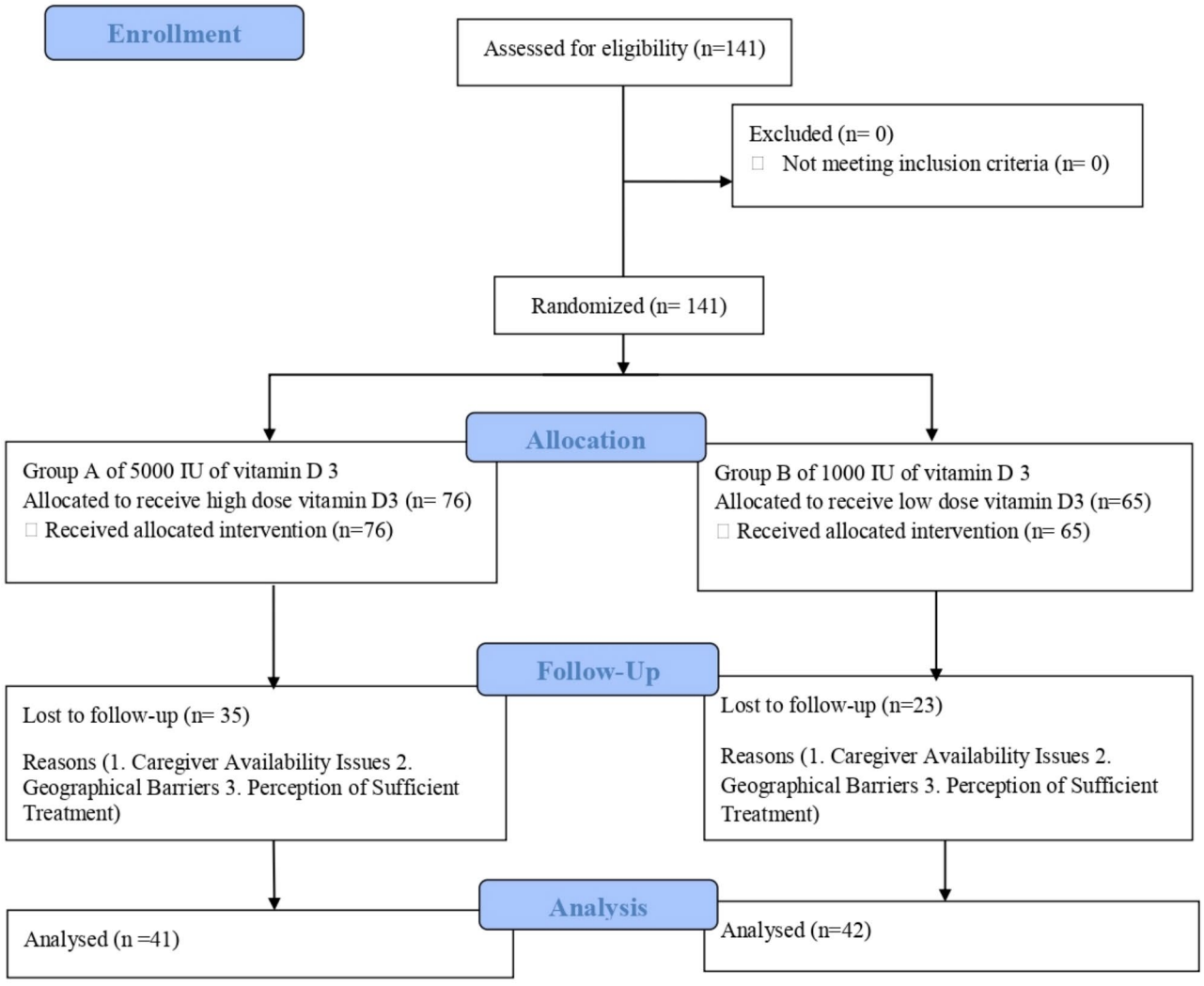

Fig. 1 Consort flow chart

Table 1 Major characteristics of the included participants

Variables	High dose ($n=41$)	Low dose ($n=42$)	p-value
Age (year)	8.0 (6.0, 10.0)	8.0 (6.0, 11.0)	0.379
Gender			
Male	33 (80.5%)	36 (85.7%)	0.366
Female	8 (19.5%)	6 (14.3%)	
Daily outdoor activity M (SD)	48.06 ± 34.72	44.93 ± 26.51	0.674
BMI			
BMI < 85th	31(75.6%)	27(64.3)	
BMI 85–95	9(22)	12(28.6)	0.42
BMI > 95	1(2.4)	3(7.1)	
Vitamin D status			
Optimal	4 (9.8%)	3 (7.1%)	0.842
Insufficient	35 (85.3%)	36 (85.8%)	
Deficient	2 (4.9%)	3 (5.8%)	

Notes: Data are presented as mean ± SD or medians (P25, P75). Abbreviations: BMI = Body Mass Index, SD = Standard Deviation

Results

Demographic and baseline characteristics of participants

A total of 83 participants were included in the final analysis, with 41 participants (median age: 8.0 years, range: 6–10) in the high-dose group and 42 participants (median age: 8.0 years, range: 6–11) in the low-dose group (Fig. 1). Baseline characteristics, including age, gender distribution, BMI, daily outdoor activity, and vitamin D status, showed no statistically significant differences between the two groups (all $p > 0.05$) (Table 1).

Intra-group analysis

Low-dose vitamin D_3 supplementation

Participants in the low-dose group experienced a significant reduction in tic severity over three months. The mean YGTSS score decreased from 27.19 ± 8.54 at baseline to 24.00 ± 4.52 after three months ($t = 2.14$, $p < 0.05$), indicating an improvement associated with low-dose

Table 2 Comparison of tic severity between high and low dose groups at baseline

Variables	High dose ($n=41$)	Low dose ($n=42$)	p-value
YGTSS Score	28.85 ± 7.19	27.19 ± 8.54	0.341
Motor Score	12.73 ± 4.50	10.88 ± 5.44	0.096
Vocal Score	4.90 ± 4.23	5.60 ± 5.49	0.522
Total Tic Score	17.88 ± 5.87	16.50 ± 7.27	0.346
Impairment	10.00 (10, 10)	10.00 (10, 20)	0.438
Tic Severity Levels			
Mild(YGTSS < 25)	14 (34.1%)	21 (50.0%)	0.107
Moderate (YGTSS 25–50)	27 (65.9%)	21 (50.0%)	

Notes: Data are presented as mean ± SD or medians (P25, P75). Abbreviations: YGTSS: Yale Global Tic Severity Scale

Table 3 Comparison of tic severity between high and low dose groups after 3 months

Variables	High dose ($n=41$)	Low dose ($n=42$)	p-value
YGTSS Score	18.13 ± 4.30	24.00 ± 4.52	0.004
Motor Score	5.87 ± 4.15	10.33 ± 4.97	0.027
Vocal Score	2.00 (0, 4)	5.00 (0, 6)	0.238
Total Tic Score	8.13 ± 4.30	14.00 ± 4.52	0.004
Impairment	10.00 ± 0.00	10.00 ± 0.00	N/A
Tic Severity Levels			
Mild(YGTSS < 25)	35 (85.4%)	23 (54.8%)	0.005
Moderate(YGTSS 25–50)	6 (14.6%)	19 (45.2%)	

Notes: data are presented as mean ± sd or medians (P25, P75). Abbreviations: YGTSS: Yale global tic severity scale; N/A: not applicable

supplementation. Additionally, serum 25(OH)D levels increased significantly, rising from 20.22 ± 6.13 ng/mL at baseline to 26.81 ± 6.00 ng/mL after three months (t = – 4.98, $p < 0.05$), demonstrating the effectiveness of low-dose supplementation in improving vitamin D levels (Supplementary material 1).

High-dose vitamin D_3 supplementation

The high-dose group exhibited a more substantial reduction in tic severity over the same period. YGTSS scores dropped from 28.85 ± 7.19 at baseline to 18.13 ± 4.30 after three months (t = 8.19, $p < 0.05$), suggesting a greater therapeutic benefit with high-dose supplementation. In addition, serum 25(OH)D levels in this group increased substantially, rising from 20.25 ± 7.02 ng/mL at baseline to 48.65 ± 10.07 ng/mL after three months (t = – 14.11, $p < 0.05$). This marked increase highlights the superior efficacy of high-dose supplementation in raising vitamin D levels and reducing tic severity, potentially enhancing therapeutic outcomes (Supplementary material 2).

Inter-group analysis

Effects of high-dose and low-dose vitamin D_3 on tic severity

At baseline, there were no significant differences in YGTSS scores between the high-dose and low-dose groups ($p > 0.05$). However, after three months, the high-dose group exhibited a significantly greater reduction in tic severity than the low-dose group ($p < 0.05$). Specifically, the mean YGTSS score in the high-dose group decreased from 28.85 ± 7.19 to 18.13 ± 4.30, whereas the low-dose group's score declined only from 27.19 ± 8.54 to 24.00 ± 4.52, suggesting enhanced efficacy of the high-dose intervention in alleviating tic symptoms.

Regarding tic severity levels, the high-dose group demonstrated a marked shift. Initially, 65.9% of participants in this group were classified with moderate tic severity and 34.1% with mild severity, with no cases of severe tics. Post-treatment, 85.4% had mild tic severity, with only 14.6% remaining in the moderate category. In the low-dose group, baseline severity distribution was similar.

Table 4 Comparison of vitamin D and calcium levels between high dose and low dose groups

Variables	High dose ($n=41$)	Low dose ($n=42$)	p-value
Vitamin D levels (ng/mL)			
Baseline	20.25 ± 7.02	20.22 ± 6.13	0.981
After 3 months	48.65 ± 10.07	26.81 ± 6.00	< 0.001
Calcium Levels (mmol/L)			
Baseline	2.46 ± 0.11	2.44 ± 0.11	0.315
After 3 months	2.53 ± 0.07	2.51 ± 0.10	0.473

After treatment, 54.8% of participants had mild tic severity, while 45.2% remained moderate ($p < 0.05$). These findings show that high-dose supplementation is more effective in reducing symptoms than low-dose treatment (Tables 2 and 3).

Impact of vitamin D_3 supplementation on serum 25(OH)D and calcium levels

At baseline, both groups had comparable serum 25(OH)D levels, with the high-dose group at 20.25 ± 7.02 ng/mL and the low-dose group at 20.22 ± 6.13 ($p > 0.05$). After supplementation, the high-dose group exhibited a significantly greater increase, reaching 48.65 ± 10.07 ng/mL, compared to 26.81 ± 6.00 ng/mL in the low-dose group ($p < 0.05$). Regarding serum calcium levels, both groups exhibited similar trends, with no statistically significant differences between them at baseline or after three months ($p > 0.05$) (Table 4).

Multivariate regression analysis of serum 25(OH)D and tic severity reduction

A multivariate linear regression analysis revealed a significant negative association between the increase in serum 25(OH)D levels and tic severity reduction (t = -2.816, $p < 0.05$). This finding suggests that greater increases in serum 25(OH)D levels are associated with more substantial reductions in tic severity, highlighting the importance of achieving sufficient vitamin D levels to optimize therapeutic outcomes (Table 5). Additionally,

Table 5 Regression analysis of YGTSS scores based on vitamin D levels after three months of supplementation

Coefficients[a]						
	B (SE)	**β**	**t**	**P**	**R^2**	**95% CI**
Vitamin D levels (ng/mL)	-0.184 (0.065)	-0.515	-2.816	0.010	0.265	((-0.319)-(-0.048))

a. Dependent Variable: YGTSS score. **Notes**: Abbreviations: YGTSS = Yale Global Tic Severity Scale, B = unstandardized regression coefficient, SE = standard error, β = standardized regression coefficient, t = t-statistic, p = *p*-value, R^2 = coefficient of determination, CI = confidence interval

a negative association was observed in the subscales of the YGTTS score, including the Vocal and Motor subscales (t = -2.030 and – 1.274, respectively). However, neither of these associations reached statistical significance ($P > 0.05$) (Supplementary Materials 3 and 4).

Discussion

This study provides important insights into the impact of low-dose and high-dose vitamin D_3 supplementation on tic severity and serum 25(OH)D levels in children with CTDs. The results demonstrate that vitamin D_3 supplementation, particularly at higher doses, significantly reduces tic severity, underscoring its potential as a therapeutic intervention.

Efficacy of vitamin D_3 supplementation in reducing tic severity

Both the high-dose and low-dose supplementation groups experienced significant reductions in tic severity over the three-month intervention. However, the high-dose group demonstrated more pronounced improvements, indicating a dose-dependent effect. These findings align with previous research on the association between vitamin D and neurological function, suggesting that higher dosages may provide greater therapeutic benefits in alleviating tic severity [29].

The marked improvement in tic severity observed in the high-dose group may be attributed to vitamin D_3's capacity to regulate neurotransmitters, particularly dopamine, which is essential for motor control. Dysregulation of dopamine pathways is believed to contribute to tic disorders, and vitamin D_3 supplementation may help restore this balance, thereby reducing tic severity [30]. Moreover, vitamin D's neuroprotective and anti-inflammatory properties likely enhance its effectiveness [31]. By modulating cytokine production and promoting an anti-inflammatory environment in the brain, vitamin D can counteract neuroinflammation, a known factor in tic exacerbation, Therefore, the combined impact of neurotransmitter regulation and inflammation reduction suggests that vitamin D_3 offers a comprehensive therapeutic strategy for managing tic disorders [32].

Serum 25(OH)D levels and therapeutic implication

This study revealed that both low-dose and high-dose supplementation significantly increased serum 25(OH)D levels, with the high-dose group achieving a more substantial increase. This finding aligns with previous research demonstrating a dose-dependent relationship between vitamin D_3 intake and circulating 25(OH)D level [33]. The substantial increase observed in the high-dose group underscores the effectiveness of vitamin D_3 supplementation in correcting vitamin D deficiency in children with CTDs [24].

Adequate vitamin D_3 levels are crucial not only for bone health [34], but also for immune regulation [35], and neurodevelopment [36]. Previous studies have shown improvements in conditions such as depression [37], multiple sclerosis [38], and autism spectrum disorders (ASD) with vitamin D_3 supplementation [39]. Optimizing vitamin D levels through higher-dose supplementation may, therefore, contribute to broader neurodevelopmental improvements and symptom management in children with TDs.

The observed increase in serum 25(OH)D levels underscores the clinical importance of appropriate dosing strategies in pediatric populations. Given the dose-dependent improvements in both serum vitamin D levels and tic severity, clinicians might consider adjusting supplementation based on baseline vitamin D status and individual patient needs. While higher doses of vitamin D_3 may be more effective in quickly correcting deficiencies and improving outcomes, further research is required to determine the optimal long-term dosing regimens.

Safety considerations: serum calcium levels

Although the primary focus was on tic severity and vitamin D levels, monitoring serum calcium levels helps ensure the safety of high-dose supplementation. In this study, both groups exhibited modest, non-significant increases in calcium levels, indicating that the supplementation regimen did not disrupt calcium homeostasis. This finding is particularly important, as excessive vitamin D intake can lead to hypercalcemia and associated risks [40, 41]. While these results support the safety of the dosing strategy, further studies are needed to confirm long-term safety.

Clinical implications

The dose-dependent reduction in tic severity and increase in serum 25(OH)D levels suggest that high-dose vitamin D_3 supplementation could serve as a practical, non-invasive adjunctive treatment for children with

CTDs. This approach not only addresses the common issue of vitamin D deficiency but also offers potential benefits for managing neuropsychiatric symptoms. Clinicians may consider tailoring vitamin D_3 dosing based on individual patient needs, baseline serum levels, and clinical responses to optimize outcomes.

Study limitations

Several limitations must be acknowledged. First, the relatively small sample size may limit the generalizability of these findings. Additionally, the high follow-up loss rate (approximately 42%) introduces potential attrition bias, and this should be considered when interpreting the results. Second, the study did not include assessments using the Clinical Global Impression Severity of Illness (CGI-SI), which could have provided further insights into the overall clinical impact of the intervention. Finally, potential confounders such as seasonal variations and diet recall for vitamin D intake were not systematically examined in this study, which could have influenced vitamin D status. Future research should focus on improving participant retention, controlling for these potential confounders, and strengthening the validity and robustness of the findings.

Conclusion

In summary, high-dose vitamin D_3 supplementation is more effective than low-dose supplementation in reducing tic severity and improving serum 25(OH)D levels in children with CTDs. These findings indicate that high-dose vitamin D_3 may serve as a valuable adjunct in managing CTDs. However, further research is needed to confirm the long-term safety and efficacy of this therapeutic approach.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01112-w.

Supplementary Material 1

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Author contributions

Z.A.M. conceptualized and drafted the manuscript. M.B and H.D. conducted data collection and analysis. Y.X. revised the manuscript. F.J. and J.F conceived and supervised the entire process. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki guidelines and received approval from the Ethics Committee of the First Hospital of Jilin University, Changchun, China (Approval Number: 22K106-001). It was registered with the Chinese Clinical Trial Registry (Registration Number: ChiCTR2200056482, Registration Date: 2022-02-06). Written informed consent was obtained from the parents or guardians of all participants.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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