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Serum 25 (OH) Cholecalciferol, hematological and thyroid functions in children with Down syndrome and effect of supplementation of 400 I.U. of vitamin D: an interventional study

Abstract

Background: Children with Down syndrome (DS) are at risk of 25 (OH) Cholecalciferol deficiencies because of multiple environmental and hormonal factors. Vitamin D supplementation plays a vital role in growth and development of children.

Objectives: The primary objective is to assess serum 25 (OH) Cholecalciferol level and observe effect of 400 IU daily vitamin D supplementation for 6 months in children with DS. Secondary objectives were to observe associated hematological, cardiac anomaly abnormalities and thyroid functions.

Methods: This study enrolled 72 DS children, aged one year and above confirmed by karyotyping (Group I) and age and sex match normal healthy children taken as a control (Group II). Detailed histories, thyroid profile, 2D Echocardiography, hematological and renal profile were assessed. All children with DS were given 400 I.U. of vitamin D for 6 months. Blood samples were collected and concentrations of 25-hydroxy cholecalciferol were done at the end of study.

Results: The mean serum vitamin D level was 22.3±11.4 in (Group I) as compared to 34.6±20.1 in control (Group II) and was significantly low (p- value< 0.001). In DS children, 8.3% had deficient (< 10 ng/ml), 45.8% had insufficient and only 45.8% children had adequate vitamin D levels. After 6 months, 25(OH) Cholecalciferol was done in only 57 children only. No DS (Group I) children had vitamin deficiency but 26.3% had insufficient levels. Mean hemoglobin concentration of DS children was 10.97±2.56 gm/dL. Common cardiac anomalies are VSD (18.05%), AVSD (13.8%) and ASD (4.16%). Nineteen children had sub-clinical hypothyroidism and 2 had congenital hypothyroidism.

Conclusion: vitamin D deficiency and insufficiency were more prevalent in children with DS as compared to normal children and 400 IU vitamin D is not sufficient to correct deficiency and insufficiency.

Keywords: down syndrome, 25-oh cholecalciferol, cardiac anomaly, hypothyroidism

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Introduction

Down syndrome (DS) is the most common Chromosomal disorder, occurring 1 in 700-1000 live births[1] and a leading cause of intellectual disability. They may have various associated health problems such as learning and memory, congenital heart diseases (CHD), hematological malignancy, endocrinal and gastrointestinal abnormalities. Vitamin D is one of the fat soluble vitamins that enhance the intestinal absorption of calcium, phosphate, and zinc.[2] It is essential for bone health,[3] calcium homeostasis, and skeletal mineralization[4] and also has immune-modulatory effects.[5]

In Down syndrome, several environmental and hormonal factor such as muscle hypotonia, low physical activity, poor calcium and vitamin D intake, hypogonadism, growth retardation, and thyroid dysfunction may contribute to low bone density and prone to osteoporosis and fracture.[6,7] Vitamin D plays a significant role in the health of patient with Down syndrome.[8] The present study was conducted to assess serum vitamin D level and to observe effect of 400 IU daily vitamin D supplementation for 6 months in DS and also to observe associated cardiac, hematological, and thyroid co-morbidities.

Methods

This prospective interventional study was conducted in Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi from October 2019 to July 2023.The Ethics Committee of Institute approved the study protocol. Informed consent was obtained from parents or legal guardians of patients prior to enrollment in the study.

Sample size: The sample size was calculated based on pilot study, assuming increase of vitamin D level by 10 ng/dL in 50 % children with 90% power and 95% confidence limit and 25% dropout (including mortality), over a period of 6 months, the sample size calculated was 54.

Inclusion criteria: children aged one year and above, who had visited outdoor or admitted with typical phenotypic characteristics of Down syndrome and later confirmed by karyotyping were enrolled in study. Age and sex matched healthy children attending outdoor were taken as control.

Exclusion criteria: Children on prior calcium, vitamin D, and any drug affecting calcium and vitamin D metabolism in past six month,

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history of hyperthyroidism, skeletal diseases, malabsorption, renal diseases and hepatic disease were excluded from study.

Intervention: All children of Group-I was given 400 I.U. of vitamin D supplementation as per recommended daily dietary requirement apart from complementary feeding for 6 months.

History was taken including mother age, antenatal, perinatal, natal, developmental history, and other important factors that may affect Vitamin D synthesis, such as exposure to light, physical activity. The detailed physical examination including anthropometric measurements (Weight, height, head circumference, BMI, general examination including characteristics of Down phenotype were noted. In all enrolled children, complete systemic examinations were done.

Laboratory investigations included complete blood count (CBC), renal and liver function tests, Karyotyping, echocardiography, serum calcium, phosphate and alkaline phosphate level, serum Iron, TIBC, ferritin, T3, T4, TSH and iPTH at enrollment.

Serum 25 (OH) cholecalciferol levels of all enrolled children was done at the end of study. After 6 months of Vitamin D supplementation, plasma 25(OH) D levels, serum calcium, phosphate and alkaline phosphate were done in children with of DS(Group-I) only.

Assessment of Serum level of vitamin D**:** Vitamin D level is quantitated by Enzyme linked immunosorbent assay (ELISA) method using ELISA kit from Epitope Diagnostics INC **(KT 715, Lot(s) L 220-L225).** Vitamin D status will be defined according to the serum concentration of 25-hydroxy cholecalciferol [25(OH) D]. Vitamin D deficiency will be defined to exist, when the serum 25 (OH) D levels is lower than 10ng/mL, and vitamin D insufficiency; 10–20ng/mL and level above 20ng/mL was taken as normal.[9]

Statistical analysis: SPSS version 20.0 was used for data entry and analysis. Independent sample t-test, Mann-Whitney U- test, Chi-square and Fisher exact test were used to compare continuous and Categorical variables between groups. ANOVA was used to find out the significant difference among multiple groups. A P-value of less than <0.05 will be considered statistically significant.

Results

Our study included 72 cases of Down syndrome (DS) confirmed by Karyotyping, who visited OPD or admitted in pediatrics ward were categorized in group (I) and 72 healthy age and sex match children were taken as control in group (II).Out of 72 cases, 46(63.98%) were male and 54(75%) of them were less than 5 years but above 0ne year of age, 14(19.44%); 5-10 years and only 4(10%) were above 10 years of age. History of developmental delay was observed in 93% of DS cases.

The mean level of hemoglobin in DS (Group-I) was 10.97±2.56 and in control 11.60±2.08. Twenty one (29.16%) had hemoglobin level less than 10 gm/dL Thrombocytopenia was observed in 13(18.05%) and thrombocytosis in 9(12.5%). Twenty two (30.56%) had microcytosis and 12(16.66%); macrocytosis. The peripheral blood smear examination of one case revealed acute lymphoblastic leukemia. Out of 72 cases of Group-I, mean iron, TIBC and ferritin were 52.7±26.54, 387.67±90.8 and 53.8±40.46 respectively at enrollment (Table 1).

Table 1 Hematological and biochemical parameters of children with Trisomy 21 at enrollment

Parameters	Group 1(n=72)	Group 2(n=72)	t-value	p-value
Hb (gm./dL)	10.97±2.563	11.60±2.086	-1.629	0.305
TLC	12284.5±10484.853	8928.18±2674.523	2.632	0.009
DLC				
N (%)	50.19±13.832	49.93±14.570	0.111	0.911
L (%)	37.04±14.201	39.28±12.467	-1.004	0.317
PLT (lakh/cumm^3)	2.9557±1.48476	3.1599±1.62379	-0.787	0.435
MCV (fL)	85.512±13.4354	85.331±9.2022	0.095	0.925
MCHC (gm./dL)	29.324±3.9601	31.938±2.4450	-4.766	0
MCH (pg.)	28.161±5.1009	25.743±3.6295	3.277	0.001
Urea(mg/dL)	32.43±19.17	29.75±12.12	1.005	0.317
Creatinine(mg/dL)	0.53±0.21	0.53±0.18	0.129	0.897
Sodium(meq/L)	138.25±5.17	138.15±5.85	0.103	0.918
Potassium(meq/L)	4.21±0.77	4.35±0.64	-1.245	0.215
ALT(I.U.)	102.33±407.24	42.69±42.52	1.236	0.219
AST(I.U.)	118.70±473.25	46.49±28.3	1.292	0.198
Iron(µg/dL)	52.7±22.5	56.4±20.2	1.04	0.149
TIBC	387.7±90.8	346.6 ±85.6	2.7	0.01
Ferritin (ng/mL)	53.8±20.5	28.7±12.3	8.9	<0.001

Calcium, and 25(OH) D *level in cases (Group-I) were found significantly low as compared to control (Group-II). There was no significant difference in level of alkaline phosphatase in between two groups (Table 2).* During six months of vitamin D supplementation in cases (group I), 8 had died, 1 case left against medical advice (LAMA) and 6 were lost follow up. In remaining 57 cases, statistically significant difference was observed in calcium, phosphates, alkaline phosphates and vitamin D levels. Before vitamin D supplementation, out of 72 DS cases, 6 (8.33%) had 25(OH) D less than 10ng/dL, 33 (45.83%) had levels between 10-20 ng /dL, 33 (45.83%) had levels more than 20ng/dL. After 6 months of supplementation, none had 25(OH) D level less than 10ng/dL, 15 cases had levels between 10-20 ng /dL and remaining i.e. 42(73.68%) had levels more than 20ng/dL (Table 3).

Table 2 calcium, phosphate, alkaline phosphatase and vitamin D in enrolled children

Parameters	Group-I(n=72)	Group-II(n=72)	t-value	p-value
Calcium	8,76±0.94	9.51± 0.97	-4.764	<0.001
Phosphate	4.85±1.38	4.10±1.02	3.714	<0.001
Alkaline phosphatase	319.94±147.54	315.85±140.87	0.17	0.865
25(OH) cholecalciferol	22.8±11,39	34.63±20.11	0.001	<0.001

Table 3 Effect of vitamin D supplementation on cases of Trisomy 21

Parameters	Before treatment (n=72)	After 6 months of treatment (n=57)	t-value	p-value
CALCIUM	8.756±.9378	9.39±.727	0.203	<0.001
PO_4	4.85±1.385	4.242±.9684	0.064	<0.001
Alk. PO_4	319.94±147.537	243.43±92.361	0.555	<0.001
Vit-D	22.2858±.11.39706	28.926±10.0970	0.001	<0.001
	<10 ng/dl	10-20ng/dl	>20 ng/dl	
Before vitamin D supplementation (72 case)	6 (8.33%)	33 (45.83%)	33 (45.83%)	
After 6 month vitamin D supplementation (57*control)	……	15 (26.31%)	42 (73.68%)	

*6 lost follow-up, 8 expired, 1- LAMA

Echocardiography of DS (Group-I) children showed cardiac disease (CHD) in 26 (36.1%) of which VSD alone was found in 13(18.05%), followed by AVSD in 10 (13.86%), ASD; 3(4.17%), and PDA; 2(2.77%). None of DS cases had cyanotic congenital heart disease.

The mean level of T3, T4, and TSH in cases was 75.53 (±53.68), 7.65 (±2.50) and 4.50 (±4.17) respectively, however 103.61 (±48.75), 7.15 (±1.85), 2.96 (±.65) respectively were observed in control. T3 and TSH were significantly increased and decreased respectively in cases. Among cases, 19 had hypothyroidism and 2 had congenital hypothyroidism, which is significantly higher than control i.e. 4 had subclinical hypothyroid. There was no significant difference in intact parathyroid hormone (iPTH) level between these two groups (Table 4).

Table 4 Serum T3, T4, TSH and i PTH level in enrolled children

Variables	Group-I	Groyp-II	t-value	p-value
T3(ng/dl)	75.53±53.68	103.61±48.75	-3.286	0.001
T4(µg/dl)	7.65±2.50	7.15±1,85	1.365	0.175
TSH(µIU/ml)	4.50±4.17	2.96±1.65	2.91	0.005
TSH>5 µIU/ml*	21	4	7**	0.0007
I PTH (pg/ml)	25.94±12.07	45.28±6.75	0.107	0.686

*2 children had congenital hypothyroidism

**Odd's ratio

Eight cases had died and the primary causes of deaths were bronchopneumonia with respiratory failure (3), ventricular septal defect with refractory congestive heart failure (2), patent ductus arteriosus with pulmonary artery hypertension and congestive cardiac failure (1), septicemia (1), and acute lymphoblastic leukemia (1).

Discussion

In our study, mean calcium and vitamin D before supplementation of Vitamin D were significantly lower in cases as compared to control. After 6 months of 400 IU vitamin D supplementation in cases, statistically significant difference of calcium and Vitamin D levels were observed. Prior to vitamin D supplementation, out of 72 DS cases, 6 (8.33%) had vitamin D <10ηg/dL, 33 (45.83%) had between 10-20 ηg/dL, 33 (45.83%) had levels more than 30ηg/dL. Four children were lost to follow up and six cases had died, of which cases which one had vitamin D level below 10 ng/dL and 5; 10-20 ng/dL.

No correlation was found between the mean serum vitamin D level and serum calcium, phosphorus, ALP, and iPTH in our study as reported by Stagi et al.,[10] However Abu shady et al.,[11] observed that serum 25(OH)D levels were inversely related to iPTH and serum phosphorus and low serum calcium is not a risk factor for vitamin D deficiency or insufficiency as observed in our study. Vitamin D deficiency in adults with Down syndrome that can be corrected by vitamin D supplementation.[12]

El-Hawary et al.,[13] also reported significantly lower serum vitamin D in DS cases than in the control group. Moreover, iPTH, phosphates, alkaline phosphates were in the reference range as in our study. However, Del Arco et al.,[14] observed normal vitamin D metabolites or in the other parameter of calcium metabolism in children with Down syndrome. Poor physical activity, inadequate intake of vitamin D, associated hypogonadism and thyroid dysfuntion contribute to low bone density.[6,7]

Hematological disorders are more common in children with down syndrome than in normal children. Thrombocytosis, thrombocytopenia, polycythemia, anemia, macrocytosis are the most common disorders. In present study, the incidence of macrocytosis,

thrombocytosis, and anisocytosis was significantly higher as compared to control as reported by David et al.,[15] and Dixon et al.,[16] Macrocytosis is a common in children with DS and not related to vitamin B12 or folic acid deficiencies, and may be due to some metabolic or genetic reasons.[15–17] children with DS have higher risk of developing acute leukemia and myelodysplastic syndrome.[16,18]

Cardiac abnormalities were present in 26 (36.11%) children, of which 13 had VSD, 8 endocardial cushion defect, 3 ASD, 2 PDA, 1 both VSD and ASD and 1 with VSD and endocardial cushion defect. VSD was found as the most common cardiac defect followed by endocardial cushion defect. Our findings are contrary to findings of Sanna et al.,[19] who reported atrioventricular septal defect as the most common cardiac abnormality followed by VSD. CHD in DS have been reported as high as 40 to 63 % in DS[20,21] and a major cause of morbidity and early mortality as observed in our study.

Thyroid dysfunction is also more common in DS children, in our study 19 cases (26.38%) had subclinical hypothyroidism and 2 (2.77%) had congenital hypothyroidism, which is similar to observation of Tuysuz et al.,[22] but Cebeci et al.,[23] had reported high prevalence of thyroid dysgenesis in DS.

Conclusion

Our study showed high prevalence of vitamin D insufficiency and deficiency among DS children compared with the control group. Besides this, thyroid dysfunction, congenital heart disease and hematological disorder are also more common in children with DS. 400 IU vitamin D supplementation is not sufficient to correct vitamin D deficiency and insufficiency in all DS cases.

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Conflict of interest

The authors declare that they have no conflicts of interest in the conduct of this study.

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