IMPACT OF THREE DIFFERENT DAILY DOSES OF VITAMIN D SUPPLEMENTATION IN HEALTHY SCHOOL CHILDREN AND ADOLESCENTS FROM NORTH INDIA: A SINGLE BLIND PROSPECTIVE RANDOMIZED CLINICAL TRIAL

MAJ. GEN. (Dr) R K MARWAHA

Former Additional Director and Head, Dept of Endocrinology and Thyroid Research Centre

INMAS, DRDO, DELHI

Consultant Endocrinologist & Advisor projects, AIIMS, New Delhi

Consultant- Central council of Homeopathic Research, Ministry of AYUSH

Member of scientific panel on nutrition and Fortification, FSSAI

President, Society for Endocrine Health Care of Elderly, Adolescents and Children

Former President, Indian Society for Bone Mineral Research, India

INTRODUCTION

- Vitamin D is an important micronutrient required for not only maintaining Ca balance and safeguarding skeletal integrity but also overall health and well being of all age groups
- Presently, vitamin D deficiency (VDD) is recognized as a global epidemic *(Palacios C et al. 2014; Steroid Biochem Mol Biol, Cheng L et al. 2017; j Pediatr Nurs)*
- Despite adequate sunlight throughout the year, VDD has been reported among all age groups and both genders from different parts of India*(Marwaha R K et al. 2010; Vitami D : Physiology, Mol Biology and Clinical Applicationby M F Holick)*

CAUSES OF VITAMIN D DEFICIENCY IN INDIA

- **Primarily attributed to poor sun exposure due to cultural avoidance of skin exposure, crowded houses with limited exposure, work culture of staying indoors, dark skin complexion, atmospheric pollution, use of sunscreens, vegetarian food habits, absence of food fortification and poor intake of vitamin D supplements** *(Gupta R et al. 2014; Nutrients)*
- **Though vitamin D is synthesized in the skin on exposure to UV radiation, it is difficult to achieve sufficiency in all seasons solely through sun exposure.** *(Marwaha R K et al.2015; Br J Dermatol, Marwaha R K et al. 2016; Osteoporos Int.)*

OVERCOMING VITAMIN D DEFICIENCY

- Consumption of foods rich in vitamin D
- Sunlight
- Fortification
- Supplementation

Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle

- Prevalence of low serum 25(OH)D D was seen in 90.8 % of girls

- . Daily intake of Vitamin D through meals was 2-2.5 ug/day (80-100 IU/day) using vitamin D values in foods provided by US food Agricultural Dept.

- Significant correlation between serum 25-hydroxyvitamin D and estimated sun exposure (r 0.185, P = 0.001) and percentage body surface area exposed (r 0.146, P = 0.004)

Br J Nutr. 2008 Apr;99(4):876-82.

CONCLUSION

- In the absence of vitamin D fortification of foods, diet alone appears to have an insignificant role.

- Physical activity and adequate sun exposure are vital for attaining peak bone mass in Indian context.

Research Letter

Impact of Solar UVB radiation (290 – 320 nm) on vitamin D synthesis in children with Type IV and V skin

R.K. Marwaha[1], V. Sreenivas[2], D. Talwar[3,†], V.K. Yenamandra[2,‡], A. Challac[2,†], R. Lakshmy[4], V.K. Sharma[3] and G. Sethuraman[3,*]

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- **Inadequate exposure to sunlight is an important contributing factor for VDD**
- **Significant increase in serum 25(OH)D concentrations is observed with exposure to artificial source ultraviolet B irradiation**

Marwaha RK, Sreenivas V, Talwar D, Yenamandra VK, Challac A, Lakshmy R, *et al.* Impact of Solar UVB radiation (290 - 320 nm) on vitamin D synthesis in children with Type IV and V skin. *Br J Dermatol*. 2015.

Table 2: Changes in biochemical parameters following 4 weeks of sun-exposure in Summer

	Serum 25 (OH) D (ng/mL)			Calcium (mg%)			ALP (IU)		
	Pre	Post	*P* value	Pre	Post	*P* value	A	Post	*P* value
Overall n=71	9.3 ± 5.5	13.3 ± 6.9	< 0.001	9.8 ± 0.5	10.2 ± 0.5	< 0.001	270.2 ± 136.2	207.6 ± 107.5	< 0.001
Boys n=36	11.3 ± 4.9	14.6 ± 6.7	< 0.001	10.0 ± 0.2	10.3 ± 0.4	< 0.001	336.2 ± 89.1	263.3 ± 58.8	< 0.001
Girls n=35	7.2 ± 5.3	11.9 ± 6.9	< 0.001	9.6 ± 0.6	10.1 ± 0.6	< 0.001	200.3 ± 143.3	148.8 ± 116.4	< 0.001

Table 4:Change in biochemical parameters among school children with sun exposure in Winter

Characteristic	N	Pre Exposure Winter	Post exposure Winter	P
25(OH)D (ng/ml)		6.3 ± 4.6	5.1 ± 2.7	0.001
PTH (pg/ml)		82.1 ± 73.2	77.6 ± 68.6	0.20
Calcium (mg/dl)		10.2 ± 0.6	10.0 ± 0.7	0.004
Phosphate (mg/dl)		4.1 ± 0.7	4.1 ± 0.6	0.74
ALP (IU/ml)		197.5 ± 93.7	214.7 ± 111.0	0.02

FORTIFICATION OF FOODS WITH VITAMIN D

- Fortification of widely consumed staple foods offers a simple , practical, effective and safe alternative for combating VDD and is being practiced all over the world *(Black L J et al. 2012; J Nutr)*
- Food fortification program in India is still in the stage of infancy
- FSSAI has recently permitted voluntary fortification of milk and cooking oil with A & D (Ref)
- Our own study in Indian Children clearly showed that providing milk fortified with D is an effective and safe strategy to deal with this public health issue *(Khadgawat R & Marwaha R K et al. 2013; Osteporos Int)*

SUPPLEMENTATION

- **In view of poor availability of D3 from Indian Diets, limited sun exposure and absence of mandatory food fortification, vitamin D supplementation assumes an important role in alleviating the burden of vitamin D deficiency in Indians.**
- **Hence maintaining sufficient levels of 25(OH)D through supplementation is of utmost importance.**
- **ICMR recommends RDA of 400 IU/day for Indians of all age groups**
- **Indian Academy of Pediatrics and Institute of Medicine (IOM) US- 600 IU/day**
- **Several other associations and studies recommend RDA of 1000/2000 IU/day**

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Impact of three different daily doses of vitamin D_3 supplementation in healthy schoolchildren and adolescents from North India: a single-blind prospective randomised clinical trial

Raman K. Marwaha[1]*, Mahendra K. Garg[2], Gomathy Sethuraman[3], Nandita Gupta[4], Ambrish Mithal[5], Navin Dang[6], Mani Kalaivani[7], Mohd Ashraf Ganie[4], Archana Narang[8], Preeti Arora[9], Annie Singh[9], Aditi Chadha[8] and Raj Kumar Manchanda[9]

[1]*Department of Endocrinology and Thyroid Research Centre, Institute of Nuclear Medicine and Allied Sciences, DRDO, Timarpur, New Delhi 110054, India*
[2]*Department of Medicine, All India Institute of Medical Sciences, Jodhpur 432005, India*
[3]*Department of Dermatology, All India Institute of Medical Sciences, New Delhi 110029, India*
[4]*Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India*
[5]*Department of Endocrinology, Medanta Hospital, Gurgram 122006, India*
[6]*Dang Laboratories, New Delhi 110016, India*
[7]*Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India*
[8]*Dr B R Sur Homeopathic Medical College, New Delhi 110021, India*
[9]*Central Council of Homeopathic Research, Ministry of Ayush, New Delhi 110023, India*

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OBJECTIVE

- **In the absence of information about Recommended Daily Allowance (RDA) of vitamin D for prevention of vitamin D deficiency in Indian children, we undertook this study to evaluate the adequacy and efficacy of daily doses of 600, 1000 and 2000 IU of vitamin D.**

WHY WE CHOSE 600, 1000 AND 2000 IU/DAY FOR SUPPLEMENTATION?

- We chose 600 IU/day as it the most widely recommended RDA (IOM)

- Higher dose of 1000 IU/day as per our earlier reported prediction equation as well as several other associations *(Garg M K & Marwaha R K et al. 2013; J pediatr Endocrinol Metab)*

- 2000 IU/day as 2098 IU of vitamin D were shown to needed to maintain serum levels of 20ng/ml or 50nmol/lit in 97.5% of US children *(Rajkumar K et al. 2015; JCEM)*

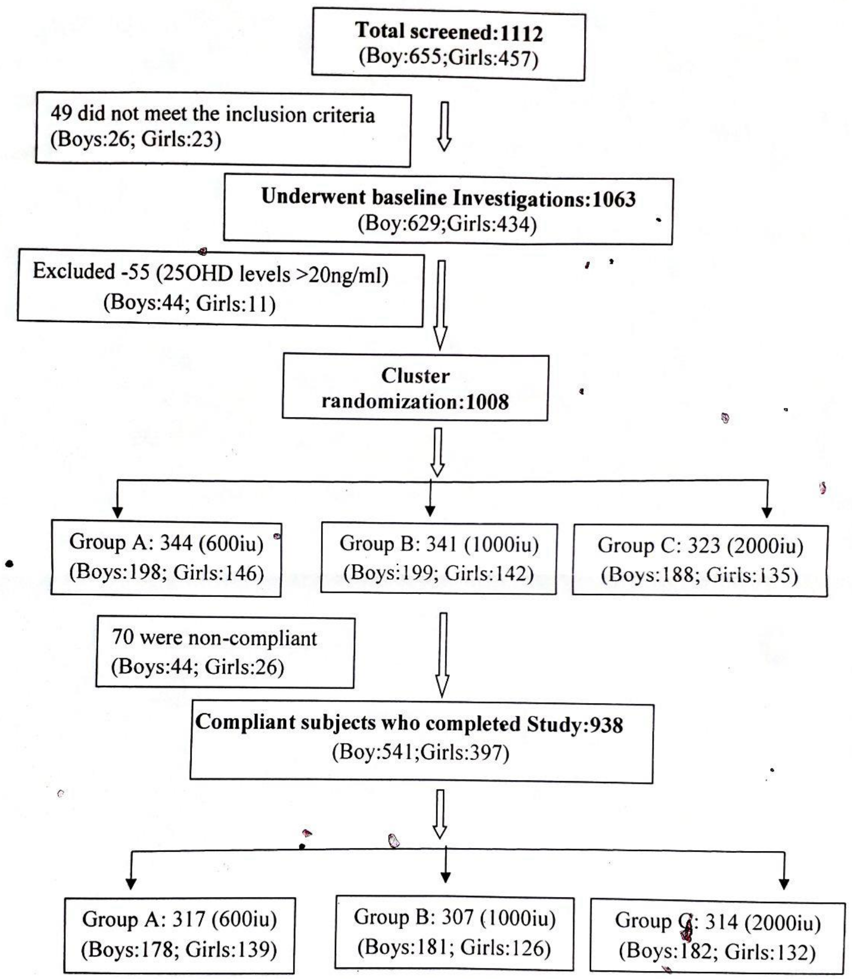
SAMPLE SIZE CALCULATION

- **Based on our earlier study, we expected 70, 80 & 90% children to achieve serum levels of 25(OH)D>50nmol/Lit or 20ng/ml after 6 months of supplementation with 600, 1000 & 2000 IU/Day of cholecalciferol.**
- **To detect a significant difference among the three groups in a two sided test with a 5% error and 80% power, 74 subjects per group were required.**
- **Considering 10% loss during follow up period, a sample size of 82 per group was considered.**

EXCLUSION CRITERIA

- **School children who were either on drugs affecting bone mineral metabolism such as Ca, vitamin D, glucocorticoids, antitubercular or anti-epileptics or suffering from any systemic illness were excluded from the study**

Figure 1: Consort Flow Diagram



METHODS

- 1008 children, aged 6-16 yrs with serum 25(OH)D <20ng/ml were cluster randomized into three groups for supplementation with daily 600, 1000 and 2000 IU of vitamin D3 under supervision for 6 months.

- 938/ 1008 subjects were compliant.

- Serum Ca, Po4, ALP, 25(OH)D & PTH and spot urine samples for calcium/ creatine ratio were evaluated at base and 6 months after intervention.

TABLE 1: SHOWING BASELINE DEMOGRAPHIC DETAILS AND BIOCHEMICAL PARAMETERS

Baseline Characteristics	Vitamin D Supplementation Groups			p-value
	600IU (n=344)	1000IU (n=341)	2000IU (n=323)	
Age (year)	11.5±2.4 (11.3-11.8)	11.5±2.4 (11.2-11.7)	12.1±2.4 (11.8-12.4)	0.0008
BMI (kg/m^2)	18.0±3.5 (17.7-16.4)	17.9±4.0 (17.5-18.3)	18.2±3.6 (17.8-18.6)	0.531
Serum 25OHD (ng/ml)	9.6±3.8	9.7±3.9	9.8±3.8	0.823
Serum PTH (pg/ml)*	53.2 (12.6-764.3)	51.5 (15.0-613.4)	52.7 (16.8-845.5)	0.911
Serum calcium (mg/dl)	9.9±0.5 (9.8-9.9)	9.9±0.4 (9.8-9.9)	9.8±0.5 (9.7-9.8)	0.010
Serum phosphates (mg/dl)	4.8±0.7 (4.7-4.9)	4.8±0.6 (4.7-4.9)	4.7±0.6 (4.6-4.7)	0.041
Serum ALP (U/L)	275.3±100.1 (263.3-285.8)	274.0±109.7 (264.9-289.5)	273.4±121.6 (259.0-285.9)	0.975
UCaCrR* (mg/mg)	0.027(0.0006-0.129)	0.022 (0.0004-0.125)	0.020 (0.0008-0.151)	0.126

RESULTS CONT.

Primary outcome	600 IU (A)	1000 IU (B)	2000 IU (C)	p-for trend
Per Protocol (N=938)	N=317	N=307	N=314	
Serum 25OHD (ng/ml)/nmol/L				
Baseline	9.7±3.8 (ng/ml) (24.3±9.5 nmol/L)	9.6±3.9 (ng/ml) (24.0±9.8 nmol/L)	9.8±3.9 (ng/ml) (24.5±9.8 nmol/L)	0.796
End of Study	24.3±7.1 (60.8±17.8 nmol/L)	28.3±8.7 (70.8±21.8 nmol/L)	37.8±11.8 (94.5±24.5 nmol/L)	<0.0001
P-Value	<0.0001	<0.0001	<0.0001	
Mean Increase	14.6±7.4 ng/ml (13.8-15.4) 36.5 nmol/L (34.5-38.5)	18.7±9.0 ng/ml(17.719.8) 46.8 nmol/L (44.3-49.5)	28.0±12.0 ng/ml (26.6-29.3) 70.0 nmol/L (66.6-73.3)	<0.0001
Percentage Increase	192 (175.3-209.2)	251 (228.7-272.9)	351 (323.8-372.3)	<0.0001

DISCUSSION

- **Supplementation is an effective alternate strategy to improve serum25(OH)D status in India, as it has greater specificity of intervention and permits dose adjustment.**
- **There are very few studies assessing the adequacy and efficacy of different daily doses of vitamin D3 in children and adolescents with VDD** *(Talib H J et al. 2016; J pediatr, (Rajkumar K et al. 2015; JCEM) &Dong Y et al. 2010; JCEM)*
- **A report from expert group from ICMR recommended 400 IU/day for Indians of all age groups as against 600 IU/day by IAP and IOM, US and several other countries***(Sesikeran B et al. 2010; Report of expert group from NIN, Khadilkar A et al. 2017; Indian Pediatr, Rosen CJ et al. 2011; JCEM& Balvers M G et al. 2015; J Nutr Sci)*
- **Since there is no definite data on how much daily vitamin D is required to prevent VDD and whether recommended daily allowance of 400 or 600 IU/day will suffice to combat widely prevalent VDD in India, we undertook this study**

IMPACT OF SUPPLEMENTING VITAMIN D ON SERUM 25(OH)D

- **A significant rise in serum25(OH)D following supplementation was observed in all three groups.**

- **The dose-dependent increase of 36.5, 44.3 & 70 nmol/lit in serum 25(OH)D following daily supplementation of 600, 1000 and 2000 IU/day in the present study is consistent with the reports in literature with VDD** ***(Talib H J et al. 2016; J pediatr, (Rajkumar K et al. 2015; JCEM & Dong Y et al. 2010; JCEM)***

- **Dong et al compared 400 and 2000 IU for 16 weeks to forty nine blackboys and girls aged 16.3±1.4 years with VDD also did show higher increase with 2000 than 400 IU/day.**

CONT.

- **The mean increase of 60 nmol/L with 2000 IU/day shown by Dong et al in his study was almost similar to the rise in the present study (70 nmol/d).**

- **Similar rise of 53.3 nmol/d was observed by AL-Shaar et al in 336 Lebanese adolescents aged 13 years supplemented with 2000IU/day of vitamin D as against only 9nmol/L with 200 IU/day.**

- **In contrast, the rise was not that large with 2000IU/Day in recent studies by Sacheck et al and Lewis et al (26.8nmol/L and 38nmol/L) in VDD subjects**

IMPACT OF 1000 IU ON SERUM 25(OH)D

- **The rise in serum 25(OH)D post supplementation with 1000 IU/day was significantly higher than those reported in literature (46.8 nmol/L vs 15.5 & 17.3 nmol/L by Talib HJ et al & Rajkumar K et al)**
- **This is because the baseline serum 25(OH)D in the present study were markedly lower than the those quoted above.**
- **The other possible explanation is the difference in the BMI of subjects between the studies as the serum 25(OH)D response is dependent on the vitamin D dose per unit of weight.**
- **The BMI of our subjects in the present study was markedly lower than that reported in other studies.**

COMPARISON OF MILK FORTIFICATION AND SUPPLEMENTATION WITH VITAMIN D

	Increase in Serum 25 (OH) D following Fortified Milk with Vitamin D (3 Months)	Increase in Serum 25 (OH) D following Supplementation with Vitamin D capsule (6 Months)
Baseline	**28.5 – 29.75 nmol/L**	**24 – 24.5 nmol/L**
600 IU	**28.75 nmol/L (138 % rise)**	**36.5 nmol/L (192 % rise)**
1000 IU	**39.25 nmol/L (177 % rise)**	**46.8 nmol/L (251 % rise)**
% of Subjects with Vitamin D sufficiency post supplementation	**With 600 IU : ~ 70 % 1000 IU : ~ 82 %**	**With 600 IU : ~ 72 % 1000 IU : ~ 86.6 %**

CONT.

- **The overall increase of 4.5 (SD±2.5)nmol/L in serum 25(OH)D per 100 IU of vitamin D supplementation in the present study was significantly greater than that of 1.8 ±2.5nmol/L reported in literature** *(Rosen C J. 2011; JCEM)*

- **The increment in serum 25(OH)D levels following vitamin D supplementation is inversely correlated with the dose per unit weight,** *(Garg M K & MarwahaR K et al. 2013; JPEM)* **baseline serum 25(OH)D** *(Talib H J et al. 2016; J pediatr, Marwaha R K et al. 2010;Indian Pediatr)* **and dose and duration of the study** *(Shab-Bidar S et al. 2014; Nutrition)*

PERCENTAGE OF CHILDREN ACHIEVING VITAMIN D SUFFICIENCY WITH 2000 IU/DAY

- **2000 IU/d of vitamin D for 6 months were required to achieve serum levels of >50nmol/L in 94% of participants.**
- **Consistent with what was reported by Raj Kumar et al who showed that 2098 IU of vitamin D/day were needed to maintain serum levels of >50 nmol/day in 97.5% of US children** ***(Rajakumar K et al2016;Pediatr Res)***
- **A systemic review and meta-analysis from middle east and North Africa also suggested that daily dose of 1000-2000 IU of vitamin D will be required to obtain serum 25(OH)D levels of >50nmol/L in majority of pediatric population** ***(Chakatoura M et al. 2017; Metabolism)***

% OF SUBJECTS ACHIEVING SERUM 25(OH)D OF > 20NG/ML FOLLOWING SUPPLEMENTATION

- **Overall, 84.1% participants achieved serum levels of > 50nmol/L or 20ng/ml (B - 86.7% & G - 80.6%)**
- **Group A (600IU/day) : 72%**
- **Group B (1000IU/day) : 86.6%**
- **Group C (2000IU/day) : 94%**

WHY 15.9% SUBJECTS IN THE PRESENT STUDY DID NOT ACHIEVE DESIRED LEVELS OF >50NMOL/L?

Possible explanations:

- **Higher baseline BMI**
- **Lower baseline serum 25(OH)D**
- **Higher baseline PTH levels**

when compared to those subjects who achieved vitamin D sufficiency

Effect of Vitamin D supplementation on Serum Levels of PTH in the per protocol analysis group

Per protocol (N=938)	600 IU (A)	1000 IU (B)	2000 IU (C)	P - for Trend
Serum PTH (pg/ml)				
Baseline	52.2 (12.6-764.3)	51.5 (15.0-613.4)	52.1 (16.8-845.5)	0.934
End of the study	37.8 (12.3-126.3)	34.1 (12.3-159.7)	34.5 (9.8-109.0)	0.049
P- value	< 0.0001	< 0.0001	< 0.0001	
Median decrease	15.7 (-6.1-170.4)	16.6 (-3.6-362.9)	17.8 (-4.3-753.6)	0.223
Percentage decrease	27.1 ± 21.7 (24.7-29.5)	31.3 ± 22.3 (28.8-33.8)	31.3± 22.2 (28.8-33.8)	0.012

PTH values are expressed as median (range)
PTH : parathyroid hormone

IMPACT ON SERUM PTH

- **Significant decrease in median serum PTH levels from 52.3 pg/ml to 39.8 pg/ml as well as decline in the prevalence of Secondary hyperparathyroidism from 31.7% at baseline to 8.4% observed in the present study was also reported from Middle East** ***(Al-Shar L et al.2014; Jbone Miner Res)*** **and in one of our earlier studies** ***(Marwaha R K et al. 2016;JPEM).***
- **In contrast, no significant decrease in serum PTH levels was recorded in studies carried out in subjects without VDD and lower serum PTH levels when compared to the present study**
- **The significant decrease was noted in all three groups**
- **The median decrease in serum PTH was not significant but the % decrease was significant among three groups**

Table 3: Parameters affecting changes in 25OHD and PTH

Parameters	Number	25OHD increase	PTH Decrease
Age			
Prepubertal (<10 years)	232	22.3±13.6 (20.5-24.0)	15.0±23.7 (12.0-18.1)
Post pubertal (>10 years)	706	19.8±10.3 (19.1-20.6)	31.0±64.3 (26.3-35.8)
P-value		0.004	<0.0001
Gender			
Boys	541	19.8±10.9 (18.8-20.7)	21.0±45.0 (17.2-24.8)
Girls	397	21.3±11.6 (20.2-22.5)	35.4±70.1 (28.4-42.3)
P-value		0.033	<0.0001
Weight Categories			
Normal	689	20.8±11.6 (19.9-21.6)	28.8±64.1 (24.1-33.6)
Overweight	170	19.9±10.5 (18.3-21.5)	20.9±24.5 (17.2-24.6)
Obese	79	18.5±9.5 (16.4-20.6)	24.7±43.7 (14.9-34.5)
P-value		0.181	0.748
VDD			
Mild	356	17.8±11.4 (16.6-19.0)	12.0±15.5 (10.4-13.7)
Moderate	444	21.1±10.8 (20.1-22.1)	26.6±52.2 (21.8-31.5)
Severe	138	25.0±10.3 (23.2-26.7)	67.2±104.4 (49.6-84.7)
P-value		<0.0001	<0.0001
SPTH			
Present	79	14.5±6.5 (13.0-16.00	65.3±129.4 (36.3-94.3)
Absent	859	20.9±11.4 (20.2-21.7)	23.5±43.5 (20.6-26.5)
P-value		<0.0001	<0.0001

* VDD – Vitamin D deficiency, SPTH - Secondary hyperparathyroidism

Decrease in serum PTH was higher in:

1. **Post pubertal adolescents than in pre-pubertal children**
2. **Higher in girls than boys**
3. **In severe than in mild VDD**
4. **Those with secondary hyperparathyroidism**

- **Since the mean decrease in serum PTH was significantly higher in participants with severe VDD and those with secondary hyperparathyroidism, it may be hypothesized that children in the present study were truly represented VDD as opposed to those from the west who either did not truly have VDD or had Subclinical VDD** *(Garg MK et al. 2013; Med Hypotheses).*

- **These studies from the west were probably conducted to raise the serum 25(OH)D levels to > 75nmol/L to derive controversial extra-skeletal benefits particularly in pediatric population.**

- **Persistence of secondary hyperparathyroidism in 8.4% subjects despite serum levels of > 50nmol/L may be indicative of either persistent low dietary intake of calcium in them or inability of parathyroid gland to return to it's normal functioning within 6 months despite achieving adequate levels of serum 25(OH)D.**

- **Possibility of primary hyperparathyroidism was ruled out as none of these subjects had hypercalcemia.**

Table 4: **showing effect of Vitamin D supplementation on serum levels of Serum calcium, phosphate ALP and Urinary Ca/Cr ratio in the three groups in Per protocol analysis group**

Primary outcome	600IU (A) **N=317**	1000IU (B) **N=307**	2000IU (C) **N=314**	p-value
Serum Calcium (mg/dl)				
Baseline	9.9±0.5 (9.8-9.9)	9.9±0.4 (9.8-9.9)	9.8±0.5 (9.7-9.8)	0.015
Post-Supplementation	9.7±0.3 (9.7-9.8)	9.7±0.3 (9.6-9.7)	9.8±0.3 (9.7-9.8)	0.107
P-Value	<0.0001	<0.0001	0.090	
Serum Phosphates (mg/dl)				
Baseline	4.8±0.7 (4.7-4.9)	4.8±0.6 (4.7-4.9)	4.7±0.6 (4.6-4.7)	0.013
Post-Supplementation	4.9±0.6 (4.9-5.0)	4.9±0.6 (4.8-4.9)	4.8±0.6 (4.8-4.9)	0.068
P-Value	<0.0001	0.008	<0.0001	
Serum ALP (U/L)				
Baseline	274.5±101.3 (263.3-285.8)	277.2±108.7 (264.8-289.5)	272.4±119.9 (259.0-285.9)	0.867
Post-Supplementation	258.1±85.6 (248.6-267.6)	260.7±83.0 (251.3-270.0)	256.7±102.8 (245.3-268.1)	0.861
P-Value	<0.0001	<0.0001	<0.0001	
UCaCrR (mg/mg)				
Baseline	0.0261 (0.001-0.130)	0.0219 (0.003-0.125)	0.0204 (0.001-0.152)	0.108
Post-Supplementation	0.0337 (0.001-0.184)	0.0315 (0.002-0.245)	0.0345 (0.002-0.212)	0.703
P-Value	<0.0001	<0.0001	<0.0001	

* ALP=Alkaline phosphatase, UCaCrR – Urinary calcium creatinine ratio

EFFECT OF VITAMIN D SUPPLEMENTATION ON SERUM CA, PO4 AND ALP

- **Statistically but not clinically significant decrease in serum Ca, ALP and increase in serum Po4 as observed following supplementation could possibly be due to improvement in secondary hyperparathyroidism**

ADVERSE EFFECTS

- **Though hypercalcemia and hypercalciuria always remains a possibility with vitamin D supplementation as reported by Talib et al in three children following supplementation, there was no case of hypercalcemia in the present study**

- **However, two cases of hypercalciuria were detected following supplementation**

- **It is well known that hypercalcemia and hypercalciuria are unrelated with the dose and duration of vitamin D supplementation**

STRENGTH AND WEAKNESS OF THE STUDY

- Strengths:
- Large cohort of school children recruited for vitamin D supplementation
- Evaluation of urinary calcium/creatinine ratio to detect hypercalciuria was done for the first time in Indian children
- No change in life style was advised during the study as it could be an important confounding factor and affect the results of vitamin D supplementation

Weakness:

- Inability to carry out individual randomization and evaluate bone markers were possible weaknesses.

CONCLUSIONS

- **Supplementation of vitamin D with all three daily doses of 600, 1000 & 2000 IU/day resulted in significant increase in serum 25(OH)D levels in school children with VDD.**
- **Children seem to benefit maximum with the daily dose of 2000 IU/day with 94% achieving serum levels of 50nmol/L following supplementation.**
- **The rise in serum 25(OH)D was inversely proportion toage, BMI and serum 25(OH)D levels.**
- **Whether daily allowance of 400 IU/d as recommended by ICMR or 600 IU by IAP and IOM, US would suffice in children and adolescents with VDD to achieve serum levels of >50nmol/L remains debatable.**


Thank You!