Paediatrics Section

Does Vitamin D Supplementation Improve Glycaemic Control In Children With Type 1 Diabetes Mellitus? – A Randomized Controlled Trial

SHREYA SHARMA[1], NIRANJAN BISWAL[2], ADHISIVAM BETHOU[3], MEDHA RAJAPPA[4], SADISH KUMAR[5], VICKNESHWARAN VINAYAGAM[6]

ABSTRACT

Introduction: Vitamin D endocrine system is a potential immune system modulator and has been implicated in the pathogenesis of several autoimmune diseases including Type 1 Diabetes Mellitus (T1DM). Studies have demonstrated an inverse risk relationship between T1DM and Vitamin D levels and also, shown a reduced risk of the disease with its supplementation.

Aim: To evaluate the role of Vitamin D as an adjuvant in improving glycaemic control and residual pancreatic beta-cell function. Primary outcome was the mean change in HbA1c levels over a period of six months.

Materials and Methods: This double-blinded randomized controlled trial was done in a tertiary care hospital, Southern India and included 52 children aged 1-18 years with T1DM, with 26 participants each in the intervention and standard of care arm. Oral Vitamin D therapy was administered once a month for six months in addition to insulin in intervention arm while only insulin was continued for other arm. Plasma HbA1c, serum 25-Hydroxy vitamin D (25OHD), insulin dose and C-peptide were measured at baseline and repeated after 6 months.

Results: Prevalence of Vitamin D deficiency was as high as 63.5% i.e., 33 of total 52 children with T1DM. The mean C-peptide levels were significantly high in intervention arm as compared to standard of care after six months. However, there was no significant difference in HbA1c, and insulin requirement at six months between the two groups. No adverse events due to Vitamin D therapy were noted.

Conclusion: Oral Vitamin D may serve as an adjuvant to insulin therapy for children with T1DM by augmenting residual beta-cell function and improving insulin secretion. However, a significant decrease in HbA1c level and requirement for exogenous insulin was not achieved in our study.

INTRODUCTION

T1DM is a chronic inflammatory disease characterized by diminished insulin secretion due to damage to islets of Langerhans in the pancreas [1]. Approximately, 90% of diabetes in children and adolescents is of Type 1 [2]. The prevalence of vitamin D deficiency is as high as 50-90% in the Indian population and is attributed to increased melanin content of skin and increasing urbanization with an indoor lifestyle [3]. Moreover, children with T1DM have a predisposition towards vitamin D deficiency as compared to general population [4]. In addition to immunoregulatory functions, insulin gene expression in pancreatic beta-cells may also be modulated by Vitamin D, thereby regulating insulin secretion [5]. Similar intervention studies by Gabbay et al., Aljabri et al., have demonstrated favourable changes in HbA1c, C-peptide, insulin dose and insulin sensitivity in patients supplemented with Vitamin D [6,7]. However, Pitocco et al., and Bizzari et al., found no beneficial effect of Vitamin D on C-peptide or HbA1c levels [8,9].

This randomized controlled trial was conducted to further evaluate the role of Vitamin D as an adjuvant in improving glycaemic control and residual pancreatic beta-cell function in children with T1DM. Primary outcome was the mean change in HbA1c levels over a period of six months.

MATERIALS AND METHODS

This randomized controlled trial was conducted at JIPMER, a tertiary care teaching hospital, South India during the period of August 2014-15 for one year. Due approval from Institute Ethics Committee (IEC) was obtained and was registered in Clinical Trials Registry of India (CTRI/2014/07/004739), after informed consent from parents, children (1-18 years of age) with T1DM attending the

Paediatric endocrinology clinic were enrolled. Confirmation of Type 1 diabetes was based on: dependence on insulin for diabetes control from time of diagnosis, Diabetic ketoacidosis or marked ketonuria at time of clinical onset, lack of obesity, and Acanthosis Nigricans. However, those with one or more of the following criteria were excluded: children already on Vitamin D supplements for preceding one month, Malabsorption syndrome, primary or secondary immunodeficiency, Renal stones, Chronic kidney disease, Adrenal tumours and children on steroid therapy for more than 2 weeks. The same inclusion and exclusion criteria was followed for selection of both cases and controls. Stratified random sampling was done using age strata as follows: 1-3 years, 4-8 years, 9-18 years. Allocation concealment was done using pre-printed randomization sequences kept in opaque sealed envelopes. The principal investigator and lab personnel were blinded to the group allocation. The intervention and standard of care arm consisted of 26 participants each. Oral Vitamin D therapy was administered in addition to insulin in intervention arm while only insulin was continued for the other arm.

The primary outcome variable taken was the decrease in HbA1c levels at 6 months after the intervention, for sample size calculation. A similar study from Saudi Arabia [7] showed that Vitamin D supplementation for 12 weeks reduced HbA1c by 10% with a standard deviation of 2.4. It was estimated that 24 patients in each group would be required to achieve 80% power; $\alpha=0.05$ and two sided 95% CI to detect a mean difference of 2 % in HbA1c between the 2 groups. Adjusting for an attrition of 20%, a total of 56 patients were required to be enrolled.

The demographic parameters, body mass index, details regarding insulin therapy including daily requirement and compliance to insulin therapy and Self Monitoring of Blood Glucose (SMBG) were noted

for all children. Oral Vitamin D therapy was administered once a month for 6 months in addition to insulin in intervention arm while only insulin was continued for other arm. Vitamin D (cholecalciferol) 60,000 IU tablets (Mfd. by Mankind, India) were used. Vitamin D dosage was calculated using upper limit of Vitamin D intake as per American Association of Paediatrics guidelines, 2011 [10] i.e., 1-3 years-60,000 IU, 4-8 years-90,000 IU, 9-18 years-1,20,000 IU. An adequate dietary calcium intake was ascertained through dietary recall. Plasma HbA1c, serum 25-OHD and C-peptide were measured at baseline and repeated after 6 months. Serum 25-OHD levels were measured by ELISA (Mfd. MicroVue - California, USA) Plasma HbA1c (normal range 4%-6.5%) was measured by High Performance Liquid Chromatography (Bio-Rad D-10™ Haemoglobin A1c analyser, USA). Serum C-Peptide was measured using ELISA kits (Mfd. DRG International, Inc., USA).

Parents and older children were counselled regarding importance of compliance to insulin therapy and SMBG at home. A free glucometer and a blood glucose monitoring notebook were issued to each parent, along with a diabetic diet chart and a diabetes information handout for the parents. Compliance to SMBG was defined as five point monitoring i.e. monitoring blood glucose five times on one specific day of the week i.e., pre breakfast, pre-lunch, pre-dinner, two hours post dinner, and 2 am. Insulin doses were titrated by a team of paediatricians and endocrinologists not involved in the study. All children followed up monthly for a total duration of 6 months. Parents were contacted over phone if the monthly follow up was missed. Pill adherence was assessed by a self-report on the basis of pill counts. All children in intervention arm were monitored for symptoms and signs of Vitamin D toxicity (vomiting, polyuria and gastritis) at each follow up. Serum Calcium and Urinary Calcium/ creatinine ratio was done at 3 and 6 months follow-up. Urinary calcium/ creatinine ratio less than 0.2mg/dl was considered normal.

Per-protocol analysis was done. Quantitative data like 25-OHD levels, HbA1c, C-peptide, Insulin dose/day were represented using mean±SD. Analysis of quantitative data between two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney test if data failed 'Normality test'. A p-value<0.05 was considered significant. SPSS Version 17 was used for data analysis.

RESULTS

In our study, 56 children were found eligible and were randomized to the two arms (intervention and standard of care). In view of failure to adhere to protocol, two children were removed from each arm and data of 52 children were analysed [Table/Fig-1]. The baseline characteristics of children in both arms are described in [Table/Fig-2]. As high as 63.5% children with T1DM (33 of total 52) were Vitamin D deficient i.e., serum 25 OHD < 20 ng/ml [11]. Six months supplementation of Vitamin D caused significant rise in serum vitamin D levels to sufficient range in intervention arm with mean serum 25-OHD level of 68.64 ng/ml. The outcome variables observed after 6 months are depicted in [Table/Fig-3]. The mean C-peptide levels showed a significant rise in the intervention arm as compared to standard of care arm (p <0.05) at the end of 6 months. No adverse events due to Vitamin D therapy were noted.

DISCUSSION

This is one of the few intervention studies using Vitamin D as adjuvant for children with T1DM especially in the Indian context. Children recruited in both arms of this study were similar in terms of the mean age, sex, body mass index, duration of disease, diabetes medication, daily insulin requirement, Vitamin D status, mean HbA1c levels and C-peptide levels at baseline. Vitamin D deficiency was noted in 63.5% of the study population. Higher prevalence of Vitamin D deficiency in T1DM patients has been documented in similar studies [4]. As Vitamin D deficiency is very common among
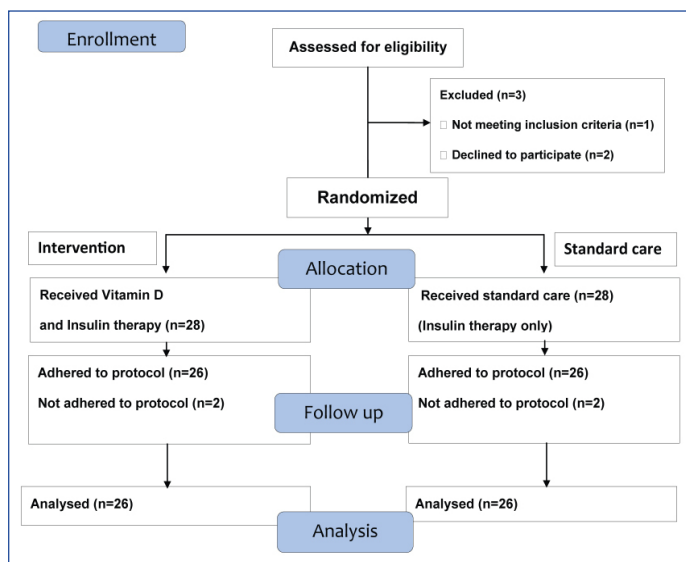
[Table/Fig-1]: CONSORT Flow Diagram.

Characteristics	Intervention arm	Standard of care arm	p-value
Mean Age (years) (SD)	9.5 (3.9)	9.0 (4.4)	0.67
Male: Female	14:12	13:13	
Duration of diabetes (years) (SD)	4.75 (3.0)	4.0(2.5)	0.84
BMI (kg/m²)	22.6	24.2	0.57
Compliance to SMBG (%)	38.5%	42.5%	0.92
Type of Insulin			
Pre-mixed (70:30 NPH :Regular)	61.5%	53.8%	0.62
NPH with Regular (Basal-bolus)	19.2%	30.8%	0.24
Glargine with Regular (Basal-bolus)	19.2%	15.4%	0.48
Mean 25-OHD levels (ng/ml) (SD)	20.7(10.5)	19.7(11.8)	0.75
Mean HbA1c (%)(SD)	10.2 (2.5)	10.7 (3.3)	0.58
Mean Insulin requirement (U/kg/day) (SD)	1.19 (0.3)	1.03 (0.3)	0.15
Mean C-peptide levels (ng/ml) (SD)	0.3 (0.1)	0.4 (0.3)	0.057

[Table/Fig-2]: Baseline characteristics of children in both arms.

paediatric population, its supplementation may be useful in general for all children including those with T1DM.

The mean change in HbA1c trends towards a greater reduction in the intervention arm than the standard of care arm after 6 months. However, the reduction was not statistically significant. In a similar study in Saudi Arabia, significantly lower HbA1c was achieved in Vitamin D deficient T1DM patients when 25OHD level reached >75 nmol/L at end of 12 weeks [7]. A recent study from Egypt found that better glycaemic control was achieved when Vitamin D was supplemented for 3 months in Vitamin D deficient T1DM patients, albeit no reduction in insulin requirement [12]. Another study from Iran demonstrated a lower mean HbA1c after Vitamin D deficient T1DM patients received a mega dose of Vitamin D (3 Lac IU) intramuscularly [13].

In our study, the mean C-peptide levels showed a significant rise in the intervention arm as compared to standard of care arm (p <0.05) at the end of 6 months, indicating improved beta-cell function. Gabbay et al., have demonstrated a slower rate of decline in C–peptide levels, significant fall of HbA1C levels in 6 months, and a significant decrease in GAD65 antibody titres in T1DM patients after supplementing 2000 IU/ day Vitamin D for18 months [6].

C-peptide acts as a surrogate marker of residual β-cell function as it is coupled with insulin release [14]. A boost to insulin synthesis

Variables	Intervention arm	Standard of care arm	p-value
Mean 25-OHD levels (ng/ml) (SD)	68.64 (24.2)	19.13 (7.9)	<0.01
Mean HbA1c (%) (SD)	9.82 (1.8)	10.69 (2.4)	0.147
Mean Insulin requirement (U/kg/day) (SD)	1.15 (0.49)	1.01 (0.36)	0.19
Mean C-peptide levels (ng/ml) (SD)	0.51 (0.29)	0.33 (0.24)	<0.05

[Table/Fig-3]: Outcome variables after 6 months.

and secretion by Vitamin D can be explained by the presence of the vitamin D response element in the human insulin gene promoter region and activation of transcription of the human insulin gene by 1,25- dihydroxyvitamin D [15]. Even a slight increase in C-peptide levels has been shown to reduce long-term complications of T1DM [16].

The daily insulin dose requirement did not show a significant difference between the two groups at 6 months follow up.

LIMITATION

Major limitations of this study were the non-standardized insulin regimen, use of different types of insulin analogs, relatively small sample size, and the short duration of the study.

The role of Vitamin D as an immunomodulator needs to be further researched in T1DM patients, preferably in a larger sample size and for a longer duration.

CONCLUSION

This study shows that oral Vitamin D may serve as an adjuvant for insulin therapy in children with T1DM by the augmentation of beta cell function and insulin secretion. However, tangible results in the form of better glycaemic control and decreased requirement for exogenous insulin were not achieved.

REFERENCES

[1] Gale EAM. The rise of childhood type 1 diabetes in the 20th century. Diabetes. 2002;51(12):3353–61.

[2] Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes. 2009;10Suppl 12:3–12.

[3] Harinarayan CV, Joshi SR. Vitamin D status in India--its implications and remedial measures. J Assoc Physicians India. 2009;57:40–48.

[4] Borkar VV, Devidayal null, Verma S, Bhalla AK. Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr Diabetes. 2010;11(5):345–50.

[5] Bourlon PM, Billaudel B, Faure-Dussert A. Influence of vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. J Endocrinol. 1999;160(1):87–95.

[6] Gabbay MAL, Sato MN, Finazzo C, Duarte AJS, Dib SA. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual β-cell function in new-onset type 1 diabetes mellitus. Arch PediatrAdolesc Med. 2012;166(7):601–07.

[7] Aljabri KS, Bokhari SA, Khan MJ. Glycaemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. Ann Saudi Med. 2010;30(6):454–58.

[8] Pitocco D, Crinò A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, et al. The effects of calcitriol and nicotinamide on residual pancreatic beta-cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI). Diabet Med J Br Diabet Assoc. 2006;23(8):920–23.

[9] Bizzarri C, Pitocco D, Napoli N, Di Stasio E, Maggi D, Manfrini S, et al. No protective effect of calcitriol on beta-cell function in recent-onset type 1 diabetes: the IMDIAB XIII trial. Diabetes Care. 2010;33(9):1962–63.

[10] Abrams SA. Dietary guidelines for calcium and vitamin D: a new era. Pediatrics. 2011;127(3):566–68.

[11] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.

[12] Hafez M, Hassan M, Musa N, Abdel AS, Azim SA. Vitamin D status in Egyptian children with type 1 diabetes and the role of vitamin D replacement in glycaemic control. J Pediatr Endocrinol Metab. 2016;30(4):389–94.

[13] Mohammadian S, Fatahi N, Zaeri H, Vakili MA. Effect of vitamin d3 supplement in glycaemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. J Clin Diagn Res JCDR. 2015;9(3):SC05–07.

[14] Greenbaum CJ, Mandrup-Poulsen T, McGee PF, Battelino T, Haastert B, Ludvigsson J, et al. Mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. Diabetes Care. 2008;31(10):1966–71.

[15] Maestro B, Molero S, Bajo S, Dávila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). Cell Biochem Funct. 2002;20(3):227–32.

[16] Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care. 2003;26(3):832–36.

PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Paediatrics, JIPMER, Puducherry, India.
2. Professor, Department of Paediatrics, JIPMER, Puducherry, India.
3. Associate Professor, Department of Paediatrics, JIPMER, Puducherry, India.
4. Associate Professor, Department of Biochemistry, JIPMER, Puducherry, India.
5. Associate Professor, Department of Endocrinology, JIPMER, Puducherry, India.
6. MSc PhD Scholar, Department of Paediatrics, JIPMER, Puducherry, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shreya Sharma,
C2-903, Hyde Park, Sector-35, Kharghar, Navi Mumbai-410210, Maharashtra, India.
E-mail: dr.shreya24@gmail.com