ISSN: 2581 – 3633

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: *https://www.ijmacr.com*

Volume – 9, Issue – 4, August – 2026, Page No.: 263 – 276

Correlation of Vitamin D Supplementation with Insulin Sensitivity, Glycaemic Control and Residual Beta-Cell Function in Children and Adolescents with Type 1 Diabetes Mellitus - A Prospective Interventional Study

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How to citation this article: Dr. Pavithra Shree B E, Dr. Yashwanth N S, "Correlation of Vitamin D Supplementation with Insulin Sensitivity, Glycaemic Control and Residual Beta-Cell Function in Children and Adolescents with Type 1 Diabetes Mellitus - A Prospective Interventional Study", IJMACR– August – 2026, Volume – 9, Issue –4, P. No. 263 – 276.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Indian children with type 1 diabetes mellitus, and the vitamin D receptor is expressed in pancreatic beta cells and in insulin - responsive tissue. Whether correcting deficiency improves insulin sensitivity, glycaemic control or residual beta-cell function in established type 1 diabetes remains uncertain. This study evaluated the correlation of vitamin D supplementation with these parameters.

Methods: Eighty children and adolescents aged 5 to 18 years with type 1 diabetes of at least six months duration and serum 25-hydroxyvitamin D below 30 ng/mL were allocated to receive oral cholecalciferol 60,000 IU monthly for six months in addition to standard insulin therapy (Group S, n = 40) or standard insulin therapy alone (Group C, n = 40). Serum 25-hydroxyvitamin D, glycated haemoglobin, fasting C-peptide, insulin dose-adjusted glycated haemoglobin and the estimated glucose disposal rate were measured at baseline and at six months.

Results: Serum 25-hydroxyvitamin D rose from 16.8 to 34.6 ng/ mL in the supplemented group and was unchanged in controls ($p < 0.001$).

The estimated glucose disposal rate improved modestly in the supplemented group (8.14 to 8.62 mg/kg/min versus 8.09 to 8.18, $p = 0.014$), as did fasting C-peptide (0.42 to 0.46 versus 0.41 to 0.34 ng/mL, $p = 0.002$). Glycated haemoglobin fell by 0.34 percentage points with supplementation and by 0.09 in controls, a difference that did not reach significance ($p = 0.152$).

Achieved 25-hydroxyvitamin D correlated weakly with the estimated glucose disposal rate (r = 0.312, p = 0.005).

Conclusion: Cholecalciferol supplementation corrected deficiency and was associated with a small improvement in insulin sensitivity and preservation of fasting C-peptide, but did not significantly improve glycated haemoglobin over six months. Supplementation is justified for the correction of deficiency itself; it should not be presented to families as a treatment that will improve glycaemic control.

Keywords: Diabetes Mellitus, Type 1, Vitamin D, Cholecalciferol, Insulin Resistance, C-Peptide, Glycated Haemoglobin A

Introduction

Type 1 diabetes mellitus is the commonest form of diabetes in childhood and results from immune-mediated destruction of the insulin-secreting beta cells of the pancreatic islets. Its incidence has risen steadily worldwide over recent decades, and the increase has been most marked in the youngest age groups, a pattern that cannot be accounted for by genetic drift and that has directed attention towards environmental determinants of disease. Among these, vitamin D has attracted sustained interest, both because its status varies with latitude and season in a manner that parallels the epidemiology of the disease and because the vitamin has well - characterised immune modulatory properties.

The biological rationale is substantial. The vitamin D receptor is expressed in pancreatic beta cells, in activated T lymphocytes, in monocytes and in dendritic cells, and the active metabolite calcitriol suppresses antigen presentation, shifts the T helper balance away from the Th1 phenotype and expands regulatory T cell populations. In insulin-responsive tissue, vitamin D influences the expression of the insulin receptor and modulates intracellular calcium flux, which is a determinant of insulin-mediated glucose transport. Experimental work has demonstrated impaired insulin biosynthesis in the vitamin D deficient rat pancreas with restoration on repletion. These observations generate two distinct hypotheses that are often conflated in the clinical literature: that vitamin D may preserve residual beta-cell function through immune modulation, and that it may improve peripheral insulin sensitivity through effects on the insulin receptor and on calcium handling.

Observational evidence for the first hypothesis is reasonably consistent. A systematic review and meta-analysis by Zipitis and Akobeng concluded that vitamin D supplementation in early childhood was associated with a reduced risk of subsequently developing type 1 diabetes, with a suggestion of a dose-response relationship.[1] Interventional evidence in established disease is less consistent. Gabbay and colleagues, in a randomised double-blind trial of cholecalciferol as adjunctive therapy in new-onset type 1 diabetes, reported a protective immunological profile and a slower decline in residual beta-cell function in the treated group.[2] Treiber and colleagues demonstrated restoration of the suppressive capacity of regulatory T cells with cholecalciferol in young patients with new-onset disease, although stimulated C-peptide did not differ significantly.[3] Against these, Walter and colleagues found no effect of calcitriol on beta-cell residual function or insulin requirement in adults with new-onset disease.[4] Panjiyar and colleagues, in an Indian randomised controlled trial in children, reported augmentation of residual beta-cell function and improvement in insulin secretion with oral vitamin D, but no significant reduction in glycated haemoglobin and

no reduction in exogenous insulin requirement, an important negative finding that is frequently omitted when this literature is summarised.[5]

Evidence for the second hypothesis, that vitamin D improves insulin sensitivity, derives predominantly from studies in type 2 diabetes and in prediabetes, where the pathophysiology is dominated by insulin resistance and where a benefit would be expected to be most readily demonstrable.

Even in that setting the results are mixed, with several randomised trials in type 2 diabetes failing to demonstrate improvement in insulin resistance or in long term glycaemic control following supplementation.[6,7]

The applicability of this literature to type 1 diabetes is limited, since insulin resistance is not the primary defect. It is nevertheless increasingly recognised that insulin resistance does occur in type 1 diabetes, that it worsens during puberty under the influence of growth hormone, and that it contributes materially to glycaemic instability and to cardiovascular risk in this population. Because the hyperinsulinaemic euglycaemic clamp is impracticable in routine paediatric practice, validated surrogate measures such as the estimated glucose disposal rate, derived from waist circumference, hypertension status and glycated haemoglobin, have been developed and applied in this context.

Two considerations make an Indian study worthwhile. First, vitamin D deficiency is exceptionally prevalent among Indian children despite abundant sunlight, a paradox attributable to skin pigmentation, limited sun exposure, atmospheric pollution and dietary patterns low in vitamin D, and the prevalence among Indian children with type 1 diabetes has been reported to exceed sixty percent.[5,8] A population with this baseline burden of deficiency offers greater scope for demonstrating a benefit of repletion than a replete population would. Second, most published interventional studies have been conducted in newly diagnosed patients, in whom preservation of residual beta-cell function is the natural outcome of interest, and comparatively few have examined children with established disease, in whom insulin sensitivity is arguably the more relevant endpoint. The present study was therefore designed to evaluate the correlation of oral cholecalciferol supplementation with insulin sensitivity, glycaemic control and residual beta-cell function in children and adolescents with established type 1 diabetes mellitus and biochemical vitamin D insufficiency.

Aims and Objectives

The study aimed to determine whether correction of vitamin D insufficiency by oral cholecalciferol supplementation was associated with measurable improvement in insulin sensitivity and in metabolic control in children and adolescents with established type 1 diabetes mellitus. The primary objective was to compare the change in insulin sensitivity, assessed by the estimated glucose disposal rate, over six months between participants receiving oral cholecalciferol in addition to standard insulin therapy and those receiving standard insulin therapy alone. The secondary objectives were to compare the change in glycated haemoglobin, the change in the total daily insulin dose expressed per kilogram of body weight, the change in the insulin dose-adjusted glycated haemoglobin, and the change in fasting serum C-peptide as an index of residual beta-cell function between the two groups.

Further objectives were to determine the prevalence and severity of vitamin D deficiency and insufficiency in the study population at baseline, to document the serum 25-hydroxyvitamin D concentration achieved on the

supplementation regimen employed, to examine the correlation between the achieved serum 25-hydroxy vitamin D concentration and each of the metabolic parameters studied, and to record the frequency of severe hypo glycaemic episodes, of diabetic ketoacidosis and of any adverse effect attributable to supplementation, including hyper calcaemia.

Materials and Methods

Study design and setting

This prospective interventional study with a parallel comparison group was conducted in the paediatric endocrinology and diabetes clinic of the Department of Paediatrics, Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Mandya District, Karnataka, over an eighteen-month period from January 2024 to June 2025. Approval of the Institutional Ethics Committee was obtained before the commencement of enrolment. Written informed consent was obtained from a parent or legal guardian of every participant, and written assent was obtained from children aged eight years and above. The study was conducted in accordance with the principles of the Declaration of Helsinki and with the National Ethical Guidelines for Biomedical and Health Research Involving Children issued by the Indian Council of Medical Research.

Participants

Children and adolescents aged 5 to 18 years with type 1 diabetes mellitus diagnosed according to International Society for Pediatric and Adolescent Diabetes criteria, of at least six months duration, receiving insulin therapy, with a serum 25-hydroxyvitamin D concentration below 30 ng/mL, and attending the clinic regularly with an expectation of continued follow-up for at least six months, were eligible for inclusion.

Participants were excluded if they had type 2 diabetes, monogenic diabetes or secondary diabetes, if they had received vitamin D or calcium supplementation within the preceding three months, or if the serum 25-hydroxyvitamin D concentration was 30 ng/mL or above at screening.

Further exclusions comprised chronic renal impairment with an estimated glomerular filtration rate below 60 mL per minute per 1.73 square metres, chronic liver disease, hyper calcaemia at screening, granulomatous disease including tuberculosis and sarcoidosis, primary hyper parathyroidism, malabsorptive disorders including untreated coeliac disease, uncontrolled thyroid disease, treatment with anticonvulsants, glucocorticoids, thiazide diuretics or any drug known to interfere with vitamin D metabolism, an episode of diabetic ketoacidosis within the preceding one month, pregnancy, and known hypersensitivity to cholecalciferol.

Sample size calculation

The sample size was calculated for the primary outcome, the change in the estimated glucose disposal rate. On the basis of previously published data, the standard deviation of the change in the estimated glucose disposal rate was taken as 0.65 mg/kg/min and the minimum clinically meaningful between-group difference as 0.45 mg/kg/min.

The formula for the comparison of two independent means was applied:

- n per group = $2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2 / d^2$
- Substituting $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$ for 80 percent power, $\sigma = 0.65$ and $d = 0.45$:
- $n = 2 \times (2.80)^2 \times (0.65)^2 / (0.45)^2$
- $n = 2 \times 7.84 \times 0.4225 / 0.2025$
- $n = 6.6248 / 0.2025 = 32.7$

Thirty-three participants per group were therefore required. Allowing for approximately twenty percent attrition over six months of follow-up, which is realistic in a paediatric diabetes clinic serving a dispersed rural catchment, the group size was increased to 40, giving a total sample of 80 participants.

Allocation and intervention

Eligible participants were allocated in a 1:1 ratio using a computer-generated random number sequence, with allocation concealed in sequentially numbered sealed opaque envelopes opened after consent had been obtained. Group S received oral cholecalciferol 60,000 IU administered as a single supervised dose once monthly for six consecutive months, in addition to their existing insulin regimen. Group C continued their existing insulin regimen without vitamin D supplementation. Blinding was not undertaken, since a placebo preparation was not available, and this limitation is acknowledged in the discussion. Laboratory personnel performing the biochemical assays were unaware of group allocation.

All participants in both groups received identical standard diabetes care comprising a basal-bolus insulin regimen or twice-daily premixed insulin according to the prevailing individual prescription, structured diabetes education at each visit, dietary counselling by a dietitian, instruction in self-monitoring of blood glucose, and screening for coeliac disease and thyroid autoimmunity according to unit protocol. Insulin doses were titrated by the treating physician on clinical grounds in both groups, without reference to group allocation.

Measurements

At baseline and at six months, participants underwent measurement of height, weight, body mass index, waist circumference and blood pressure, with anthropometry plotted against Indian Academy of Pediatrics reference charts and pubertal status assessed by Tanner staging. Fasting venous samples were obtained for serum 25-hydroxyvitamin D by chemiluminescent immunoassay, glycated haemoglobin by high-performance liquid chromatography, fasting plasma glucose, fasting serum C-peptide by chemiluminescent immunoassay, serum calcium, phosphorus and alkaline phosphatase, and a lipid profile. The total daily insulin dose was recorded from the diabetes diary and expressed in units per kilogram per day.

Vitamin D status was categorised according to conventional thresholds as deficiency where the serum 25-hydroxyvitamin D was below 20 ng/mL, insufficiency where it was 20 to 29 ng/mL, and sufficiency where it was 30 ng/mL or above. Insulin sensitivity was assessed using the estimated glucose disposal rate, a validated surrogate derived from waist circumference, the presence or absence of hypertension and the glycated haemoglobin, with higher values denoting greater insulin sensitivity. The insulin dose-adjusted glycated haemoglobin was computed as the glycated haemoglobin in percent plus four times the total daily insulin dose in units per kilogram per day, a composite in which a value of 9.0 or below denotes partial clinical remission. Severe hypoglycaemia was defined as an episode requiring third-party assistance, and diabetic ketoacidosis according to standard biochemical criteria.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 26.0. Normality was assessed by the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean with standard deviation and non-normally distributed

variables as median with interquartile range. Within-group changes from baseline to six months were compared by the paired t test or the Wilcoxon signed-rank test as appropriate, and between-group comparisons of the change from baseline by the independent samples t test or the Mann-Whitney U test. Categorical variables were compared by the chi-square test or the Fisher exact test. The correlation between the achieved serum 25-hydroxyvitamin D concentration and each metabolic parameter was examined by the Pearson correlation coefficient where both variables were normally distributed and by the Spearman rank correlation coefficient otherwise. Analysis followed the intention-to-treat principle with the last observation carried forward for participants lost to follow-up. A two-tailed p value below 0.05 was considered statistically significant.

Results

Participant flow and baseline characteristics

Ninety-four children and adolescents with type 1 diabetes were screened. Fourteen were excluded, six because the serum 25-hydroxyvitamin D was 30 ng/mL or above, four because of recent vitamin D supplementation, two because of untreated coeliac disease and two because consent was declined. Eighty participants were allocated, 40 to each group. Three participants in Group S and four in Group C were lost to follow-up before the six-month assessment, and their baseline values were carried forward.

The two groups were comparable at baseline. The mean age was 12.4 ± 3.2 years in Group S and 12.8 ± 3.4 years in Group C (t = 0.54, p = 0.591), and the mean duration of diabetes was 3.6 ± 2.1 years and 3.9 ± 2.3 years respectively (t = 0.61, p = 0.545). Twenty-two participants (55.0 percent) and 21 participants (52.5 percent) were female (χ^2 = 0.05, p = 0.823). Mean body mass index was 17.8 ± 2.6 kg/m² and 18.1 ± 2.8 kg/m² (t = 0.50, p = 0.620). Baseline glycated haemoglobin was 9.24 ± 1.42 percent and 9.31 ± 1.38 percent (t = 0.22, p = 0.824), and the baseline total daily insulin dose was 0.94 ± 0.22 and 0.96 ± 0.24 units per kilogram per day (t = 0.39, p = 0.700). Baseline characteristics are presented in Table 1.

Vitamin D status

Vitamin D deficiency with a serum 25-hydroxyvitamin D below 20 ng/mL was present in 27 participants (67.5 percent) in Group S and 26 participants (65.0 percent) in Group C, and insufficiency in the remainder of each group by virtue of the inclusion criterion (χ^2 = 0.06, p = 0.812). The mean baseline serum 25-hydroxyvitamin D was 16.8 ± 5.4 ng/mL in Group S and 17.2 ± 5.6 ng/mL in Group C (t = 0.32, p = 0.747).

At six months the mean serum 25-hydroxyvitamin D had risen to 34.6 ± 8.2 ng/mL in Group S, a within-group increase of 17.8 ng/mL (paired t = 14.62, p < 0.001), while in Group C it was essentially unchanged at 17.9 ± 5.8 ng/mL (paired t = 1.24, p = 0.223). The between-group difference in the change from baseline was highly significant (t = 12.84, p < 0.001). Sufficiency, defined as a concentration of 30 ng/mL or above, was achieved by 29 participants (72.5 percent) in Group S and by 2 participants (5.0 percent) in Group C (χ^2 = 39.51, p < 0.001). Vitamin D data are set out in Table 2.

Insulin sensitivity and glycaemic parameters

The estimated glucose disposal rate rose from 8.14 ± 1.12 mg/kg/min to 8.62 ± 1.08 mg/kg/min in Group S, a within-group increase of 0.48 mg/kg/min (paired t = 4.86, p < 0.001), and from 8.09 ± 1.18 to 8.18 ± 1.14 mg/kg/min in Group C, a non-significant increase of 0.09 mg/kg/min (paired t = 0.92, p = 0.363). The between-group difference in the change from baseline

was 0.39 mg/kg/min and was statistically significant (t = 2.51, 95 percent confidence interval 0.08 to 0.70, p = 0.014).

Glycated haemoglobin fell from 9.24 ± 1.42 percent to 8.90 ± 1.36 percent in Group S, a reduction of 0.34 percentage points (paired t = 2.68, p = 0.011), and from 9.31 ± 1.38 percent to 9.22 ± 1.41 percent in Group C, a reduction of 0.09 percentage points (paired t = 0.71, p = 0.482). The between-group difference in the change was 0.25 percentage points and did not attain statistical significance (t = 1.45, 95 percent confidence interval −0.09 to 0.59, p = 0.152).

The total daily insulin dose fell from 0.94 ± 0.22 to 0.89 ± 0.21 units per kilogram per day in Group S and from 0.96 ± 0.24 to 0.97 ± 0.23 units per kilogram per day in Group C, with a between-group difference in the change of 0.06 units per kilogram per day that reached significance (t = 2.14, p = 0.036). The insulin dose-adjusted glycated haemoglobin fell from 13.00 ± 1.68 to 12.46 ± 1.58 in Group S and from 13.15 ± 1.72 to 13.10 ± 1.66 in Group C (between-group difference in change t = 2.28, p = 0.025). These data are detailed in Table 3.

Residual beta-cell function

Fasting serum C-peptide rose marginally from 0.42 ± 0.18 ng/mL to 0.46 ± 0.19 ng/mL in Group S (paired t = 2.14, p = 0.039) and fell from 0.41 ± 0.17 ng/mL to 0.34 ± 0.15 ng/mL in Group C (paired t = 3.42, p = 0.001), reflecting the expected natural decline. The between-group difference in the change from baseline was 0.11 ng/mL and was statistically significant (t = 3.21, 95 percent confidence interval 0.04 to 0.18, p = 0.002). The proportion of participants with a detectable fasting C-peptide above 0.20 ng/mL at six months was 31 of 40 (77.5 percent) in Group S and 24 of 40 (60.0 percent) in Group C (χ^2 = 2.87, p = 0.090). Partial clinical remission, defined by an insulin dose-adjusted glycated haemoglobin of 9.0 or below, was present in 3 participants (7.5 percent) and 1 participant (2.5 percent) respectively (Fisher exact test, p = 0.615). Beta-cell function data appear in Table 4.

Correlation analysis

Across the whole cohort at six months, the achieved serum 25-hydroxyvitamin D concentration correlated positively but weakly with the estimated glucose disposal rate (r = 0.312, p = 0.005) and with fasting C-peptide (r = 0.268, p = 0.016), and correlated negatively and weakly with glycated haemoglobin (r = −0.241, p = 0.031) and with the total daily insulin dose (r = −0.226, p = 0.044). The correlation with body mass index standard deviation score was not significant (r = −0.118, p = 0.297), nor was that with the duration of diabetes (r = −0.094, p = 0.407). It should be emphasised that a correlation coefficient of 0.312 corresponds to a coefficient of determination of approximately 0.097, indicating that under ten percent of the variance in insulin sensitivity was accounted for by the achieved vitamin D concentration. Correlation data are presented in Table 5.

Safety and adverse events

No participant in either group developed hyper calcaemia, defined as a corrected serum calcium above 10.8 mg/dL, at any assessment. The mean corrected serum calcium at six months was 9.42 ± 0.38 mg/dL in Group S and 9.28 ± 0.41 mg/dL in Group C (t = 1.58, p = 0.118). Severe hypoglycaemia requiring third-party assistance occurred in 4 participants (10.0 percent) in Group S and 6 participants (15.0 percent) in Group C (χ^2 = 0.46, p = 0.499), and diabetic ketoacidosis in 2 participants (5.0 percent) and 4 participants (10.0 percent) respectively (Fisher exact test, p = 0.675). No

participant discontinued supplementation because of an adverse effect, and adherence to the monthly supervised dose exceeded ninety percent. Safety data are shown in Table 6.

Tables

Table 1: Baseline demographic, anthropometric and diabetes-related characteristics (N = 80)

Variable	Group S (n = 40)	Group C (n = 40)	Test statistic	p value
Age, years (mean ± SD)	12.4 ± 3.2	12.8 ± 3.4	t = 0.54	0.591
Female sex, n (%)	22 (55.0)	21 (52.5)	χ^2 = 0.05	0.823
Duration of diabetes, years (mean ± SD)	3.6 ± 2.1	3.9 ± 2.3	t = 0.61	0.545
Age at diagnosis, years (mean ± SD)	8.8 ± 3.4	8.9 ± 3.6	t = 0.13	0.899
Body mass index, kg/m² (mean ± SD)	17.8 ± 2.6	18.1 ± 2.8	t = 0.50	0.620
Waist circumference, cm (mean ± SD)	62.4 ± 7.8	63.1 ± 8.2	t = 0.39	0.697
Tanner stage III or above, n (%)	23 (57.5)	24 (60.0)	χ^2 = 0.05	0.820
Basal-bolus regimen, n (%)	26 (65.0)	25 (62.5)	χ^2 = 0.05	0.816
Total daily insulin, U/kg/day (mean ± SD)	0.94 ± 0.22	0.96 ± 0.24	t = 0.39	0.700
Glycated haemoglobin, % (mean ± SD)	9.24 ± 1.42	9.31 ± 1.38	t = 0.22	0.824
Fasting plasma glucose, mg/dL (mean ± SD)	184 ± 62	191 ± 66	t = 0.49	0.626
Fasting C-peptide, ng/mL (mean ± SD)	0.42 ± 0.18	0.41 ± 0.17	t = 0.26	0.799
Estimated glucose disposal rate, mg/kg/min	8.14 ± 1.12	8.09 ± 1.18	t = 0.19	0.847
Corrected serum calcium, mg/dL (mean ± SD)	9.24 ± 0.42	9.21 ± 0.44	t = 0.31	0.756
Coeliac disease on treatment, n (%)	3 (7.5)	2 (5.0)	Fisher exact	1.000
Autoimmune thyroid disease, n (%)	5 (12.5)	4 (10.0)	Fisher exact	1.000

Group S, cholecalciferol supplementation plus standard insulin therapy; Group C, standard insulin therapy alone; SD, standard deviation.

Table 2: Serum 25-hydroxyvitamin D status at baseline and at six months (N = 80)

Parameter	Group S (n = 40)	Group C (n = 40)	Test statistic	p value
Baseline 25(OH)D, ng/mL (mean ± SD)	16.8 ± 5.4	17.2 ± 5.6	t = 0.32	0.747
Six-month 25(OH)D, ng/mL (mean ± SD)	34.6 ± 8.2	17.9 ± 5.8	t = 10.51	<0.001
Change from baseline, ng/mL (mean ± SD)	+17.8 ± 7.6	+0.7 ± 3.4	t = 12.84	<0.001
Within-group paired test	t = 14.62	t = 1.24	—	<0.001 / 0.223
Baseline status, n (%)			χ^2 = 0.06	0.812
Deficiency (<20 ng/mL)	27 (67.5)	26 (65.0)		
Insufficiency (20–29 ng/mL)	13 (32.5)	14 (35.0)		
Six-month status, n (%)			χ^2 = 39.51	<0.001
Deficiency (<20 ng/mL)	2 (5.0)	25 (62.5)		
Insufficiency (20–29 ng/mL)	9 (22.5)	13 (32.5)		
Sufficiency (≥30 ng/mL)	29 (72.5)	2 (5.0)		

25 (OH) D, 25-hydroxyvitamin D; SD, standard deviation. Group S received oral cholecalciferol 60,000 IU once monthly for six months.

Table 3: Insulin sensitivity and glycaemic parameters at baseline and at six months (N = 80)

Parameter	Group S baseline	Group S 6 months	Group C baseline	Group C 6 months	p*
Estimated glucose disposal rate, mg/kg/min	8.14 ± 1.12	8.62 ± 1.08	8.09 ± 1.18	8.18 ± 1.14	0.014
Glycated haemoglobin, %	9.24 ± 1.42	8.90 ± 1.36	9.31 ± 1.38	9.22 ± 1.41	0.152
Total daily insulin, U/kg/day	0.94 ± 0.22	0.89 ± 0.21	0.96 ± 0.24	0.97 ± 0.23	0.036
Insulin dose-adjusted HbA1c	13.00 ± 1.68	12.46 ± 1.58	13.15 ± 1.72	13.10 ± 1.66	0.025
Fasting plasma glucose, mg/dL	184 ± 62	172 ± 58	191 ± 66	188 ± 64	0.318
Body mass index, kg/m²	17.8 ± 2.6	18.2 ± 2.7	18.1 ± 2.8	18.4 ± 2.9	0.712
Total cholesterol, mg/dL	168 ± 32	162 ± 30	171 ± 34	169 ± 33	0.421
Triglycerides, mg/dL	108 ± 38	102 ± 36	112 ± 41	110 ± 39	0.516

Values are mean ± standard deviation. HbA1c, glycated haemoglobin. *p value refers to the between-group comparison of the change from baseline by independent samples t test. Insulin dose-adjusted HbA1c = HbA1c (%) + [4 × total daily insulin dose (U/kg/day)].

Table 4: Residual beta-cell function at baseline and at six months (N = 80)

Parameter	Group S (n = 40)	Group C (n = 40)	Test statistic	p value
Baseline fasting C-peptide, ng/mL	0.42 ± 0.18	0.41 ± 0.17	t = 0.26	0.799
Six-month fasting C-peptide, ng/mL	0.46 ± 0.19	0.34 ± 0.15	t = 3.13	0.002
Change from baseline, ng/mL	+0.04 ± 0.12	−0.07 ± 0.13	t = 3.21	0.002
Within-group paired test	t = 2.14 (p = 0.039)	t = 3.42 (p = 0.001)	—	—
Detectable C-peptide >0.20 ng/mL at 6 months, n (%)	31 (77.5)	24 (60.0)	$\chi^2 = 2.87$	0.090
Partial remission (IDAA1c ≤9.0), n (%)	3 (7.5)	1 (2.5)	Fisher exact	0.615
Insulin dose reduction ≥10%, n (%)	11 (27.5)	4 (10.0)	$\chi^2 = 4.02$	0.045

Values are mean ± standard deviation unless stated. IDAA1c, insulin dose-adjusted glycated haemoglobin.

Table 5: Correlation of achieved serum 25-hydroxyvitamin D at six months with metabolic parameters (N = 80)

Parameter correlated with 25(OH)D	r	r²	Direction	p value
Estimated glucose disposal rate	0.312	0.097	Positive	0.005
Fasting C-peptide	0.268	0.072	Positive	0.016
Glycated haemoglobin	−0.241	0.058	Negative	0.031
Total daily insulin dose	−0.226	0.051	Negative	0.044

Insulin dose-adjusted HbA1c	−0.259	0.067	Negative	0.020
Fasting plasma glucose	−0.184	0.034	Negative	0.102
Body mass index standard deviation score	−0.118	0.014	Negative	0.297
Duration of diabetes	−0.094	0.009	Negative	0.407
Age	−0.076	0.006	Negative	0.503

25(OH) D, 25-hydroxyvitamin D; r, Pearson correlation coefficient; r^2, coefficient of determination; HbA1c, glycated haemoglobin. The coefficient of determination indicates the proportion of variance in the parameter accounted for by the achieved 25(OH)D concentration.

Table 6: Safety parameters and adverse events over six months (N = 80)

Parameter	Group S (n = 40)	Group C (n = 40)	Test statistic	p value
Corrected serum calcium at 6 months, mg/dL	9.42 ± 0.38	9.28 ± 0.41	t = 1.58	0.118
Hypercalcaemia (>10.8 mg/dL), n (%)	0 (0.0)	0 (0.0)	—	—
Serum phosphorus at 6 months, mg/dL	4.32 ± 0.56	4.24 ± 0.58	t = 0.63	0.532
Alkaline phosphatase at 6 months, IU/L	246 ± 68	258 ± 72	t = 0.77	0.446
Severe hypoglycaemia, n (%)	4 (10.0)	6 (15.0)	$\chi^2 = 0.46$	0.499
Diabetic ketoacidosis, n (%)	2 (5.0)	4 (10.0)	Fisher exact	0.675
Hospital admission for any cause, n (%)	5 (12.5)	8 (20.0)	$\chi^2 = 0.83$	0.361
Nephrolithiasis, n (%)	0 (0.0)	0 (0.0)	—	—
Discontinuation due to adverse effect, n (%)	0 (0.0)	—	—	—
Lost to follow-up, n (%)	3 (7.5)	4 (10.0)	Fisher exact	1.000
Adherence ≥90% to supervised dose, n (%)	37 (92.5)	—	—	—

Values are mean ± standard deviation unless stated. Severe hypoglycaemia was defined as an episode requiring third-party assistance.

Discussion

This prospective interventional study found that oral cholecalciferol 60,000 IU administered monthly for six months corrected vitamin D insufficiency in the great majority of children and adolescents with established type 1 diabetes, and was associated with a small but statistically significant improvement in insulin sensitivity as measured by the estimated glucose disposal rate, with preservation of fasting C-peptide against the expected natural decline, and with a modest reduction in the total daily insulin dose. It was not associated with a statistically significant improvement in glycated haemoglobin.

The pattern of these results deserves careful interpretation, because it would be easy to overstate them. The improvement in the estimated glucose disposal rate of 0.39 mg/kg/min relative to controls, while statistically significant, is of modest magnitude, and the correlation between achieved vitamin D concentration and insulin sensitivity, at r = 0.312, accounts for under a tenth of the variance in that parameter. The finding that glycated haemoglobin did

not improve significantly is arguably the most clinically informative result in the study, since glycated haemoglobin is the parameter that determines long-term complication risk and is the one about which families and clinicians care most. This negative finding is directly concordant with the Indian randomised controlled trial of Panjiyar and colleagues, who reported augmentation of residual beta-cell function with oral vitamin D but explicitly noted that a significant decrease in glycated haemoglobin and a reduction in exogenous insulin requirement were not achieved.[5] The convergence of two Indian studies on this point is worth emphasising.

The preservation of fasting C-peptide is consistent with the immune modulatory hypothesis and with the body of interventional work in new-onset disease. Gabbay and colleagues reported a slower decline in residual beta-cell function with cholecalciferol as adjunctive therapy, together with a protective immunological profile.[2] Treiber and colleagues demonstrated restoration of regulatory T cell suppressive capacity, although without a corresponding effect on stimulated C-peptide, a dissociation that suggests the immunological effect may be real while its functional consequence is small.[3] It should be noted that the present participants had established rather than new-onset disease, with a mean duration exceeding three and a half years, by which time the majority of beta-cell mass has already been destroyed.

The scope for preservation is correspondingly narrow, and the absolute C-peptide values observed here, of the order of 0.4 ng/mL, are low in absolute terms. A difference of 0.11 ng/mL between groups, though statistically significant, is unlikely to translate into a clinically perceptible difference in glycaemic stability.

Contrary evidence must be given its due weight. Walter and colleagues found no effect of calcitriol on beta-cell residual function or on insulin requirement in adults with new-onset type 1 diabetes, in a population and at a disease stage where a benefit might have been most detectable.[4]

In the type 2 diabetes literature, where insulin resistance is the dominant pathophysiology and where an effect on insulin sensitivity should be easiest to demonstrate, several randomised trials have similarly failed to show improvement in insulin resistance or in long-term glycaemic control following supplementation.[6,7] Taken together with the modest effect sizes observed here, the reasonable synthesis is that vitamin D repletion exerts a real but small metabolic effect, that this effect is most plausibly mediated through the insulin receptor and intracellular calcium handling rather than through any dramatic immunological rescue of beta cells, and that it does not constitute a therapy for diabetes in any meaningful sense.

The high baseline prevalence of deficiency observed here, with two thirds of participants below 20 ng/mL, is consistent with reports from Indian paediatric diabetes populations and with the wider Indian literature on vitamin D status, which has repeatedly documented widespread deficiency despite abundant sunlight.[5,8] This finding carries its own clinical implication independent of any effect on glycaemia.

Children with type 1 diabetes are at increased risk of reduced bone mineral density, and vitamin D deficiency of this severity warrants correction on skeletal grounds alone. The supplementation regimen employed, of 60,000 IU monthly, achieved sufficiency in 72.5 percent of participants without a single instance of

hypercalcaemia, and can therefore be regarded as both effective and safe in this population.

Limitations

This study has important limitations. It was not blinded and did not employ a placebo, so the possibility that participants in the supplemented group altered their diet, activity or adherence to insulin in response to being in the intervention arm cannot be excluded, and this may account for part of the observed benefit. Insulin sensitivity was assessed by the estimated glucose disposal rate, a surrogate that incorporates glycated haemoglobin in its derivation, which introduces a degree of mathematical coupling between the primary and a secondary outcome and inflates the apparent consistency between them; the hyperinsulinaemic euglycaemic clamp would be required to measure insulin sensitivity definitively and was not feasible. Fasting rather than stimulated C-peptide was measured, which is less sensitive as an index of residual beta-cell function. The follow-up period of six months is short relative to the natural history of beta-cell decline.

The study was conducted at a single centre in a population with a high baseline prevalence of deficiency, and the findings should not be extrapolated to vitamin D replete populations, in whom no benefit would be expected. Puberty exerts a major influence on insulin sensitivity and, although Tanner staging was recorded, the study was not powered for stratified analysis by pubertal stage.

Finally, the sample size was calculated to detect a difference of 0.45 mg/kg/min in the estimated glucose disposal rate and was not powered for the glycated haemoglobin comparison, so the absence of a significant difference in that parameter should not be read as evidence that no difference exists.

Conclusion

Vitamin D deficiency or insufficiency was universal by design and severe in two thirds of children and adolescents with type 1 diabetes screened in this study. Oral cholecalciferol 60,000 IU monthly for six months raised the mean serum 25-hydroxyvitamin D from 16.8 to 34.6 ng/mL and achieved sufficiency in 72.5 percent of participants without hypercalcaemia or any other adverse effect. Supplementation was associated with a small improvement in insulin sensitivity, with preservation of fasting C-peptide against the natural decline seen in controls, and with a modest reduction in the total daily insulin dose, but not with a statistically significant improvement in glycated haemoglobin.

The appropriate conclusion is a measured one. Screening for vitamin D deficiency and correcting it in children with type 1 diabetes is justified on its own merits, given the very high prevalence in this population, the established consequences of deficiency for skeletal health, and the demonstrated safety and low cost of the regimen used. The associated metabolic benefits observed here were real but small, and under ten percent of the variance in insulin sensitivity was accounted for by achieved vitamin D concentration. Vitamin D should therefore not be presented to families as a treatment that will improve diabetes control, and it must not displace attention from insulin titration, structured education, dietary management and self-monitoring, which remain the determinants of glycaemic outcome. Adequately powered, placebo-controlled trials of longer duration, using stimulated C-peptide and a direct measure of insulin sensitivity, are required before any stronger claim can be advanced.

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