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Original Research Article

Correlation of Serum Vitamin D Level with Glycemic Status in Children with Type 1 Diabetes Mellitus at Tertiary Care Teaching Hospital

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Abstract

Introduction: Studies have identified Vitamin D deficiency (VDD) to be prevalent in children with Type1 Diabetes Mellitus (T1DM) and is associated with poor glycemic control (HbA1c).

Aim: To estimate serum vitamin D level (25(OH)D) and to evaluate its correlation with HbA1 c among children with T1DM at first visit.

Setting and Design: A cross sectional observation study was done in department of pediatrics over a period of one year.

Methods and Material: Newly diagnosed and established T1DM children of <12 years old were included. Children >12 years, on vitamin D supplementations, with renal disorder, endocrinal problems were excluded. 25(OH)D level and HbA1c estimation done for all children along with routine investigations.

Statistical analysis: Categorical variables and means were analyzed with Fisher's exact, unpaired t test and Analysis of Variance respectively. Association between variables were analyzed with Pearson correlation and multiple linear regression. P< 0.05 was considered statistically significant.

Results: Total 70 children were included, 74.28% had VDD (25 OHD < 15ng/ml). We observed significantly higher mean HbA1c in VDD children compared to children with vitamin D sufficiency and insufficiency(p-0.008) and 25(OH)D levels were inversely correlated with HbA1c ($p < 0.05$). Multiple linear regression analysis showed a link between HbA1c and 25(OH)D ($p<0.001$) when adjusted for age, sex, and duration of the disease.

Conclusion: The present study revealed high prevalence of VDD in children with T1DM. Considering the high prevalence, estimation of 25(OH)D to be considered routinely in T1DM children as improvement in vitamin D levels may improve glycemic control.

Keywords: Type 1 Diabetes Mellitus, Vitamin D, 25(OH)D, Glycemic Status.

Introduction

Type 1 diabetes mellitus (T1DM) is the most common form of diabetes in childhood. [1] The annual incidence of T1DM has been increasing worldwide, possibly due to increasing urbanization and higher socioeconomic status. [2]

Vitamin D is a fat-soluble vitamin, which plays an important role in bone mineralization and calcium homeostasis. Many other biological actions of vitamin D are shown in recent studies, suggesting a possible role of vitamin D deficiency in the pathogenesis of various metabolic conditions, including diabetes mellitus.

It has become evident that the β-cells of pancreas express the vitamin D receptor (VDR) and 1 alpha hydroxylase enzyme. [3] Vitamin D due to its diverse immunomodulatory properties seems to contribute to the suppression of chronic inflammation (insulitis) in islets of Langerhans. Variations in genes controlling vitamin D metabolism and expression of VDRs have been implicated in the pathogenesis of T1DM. [4] Studies in humans have indicated that vitamin D supplementation in early childhood decreases the risk of TIDM [5]

A recent meta-analysis showed that patients with T1DM have a lower level of serum 25OHD compared with healthy controls. [6] Previous studies done to estimate percentage of type 1 diabetic children who were vitamin D deficient, showed a wide variation. The highest rate of deficiency of vitamin D is 90.6%. On the other hand, the lowest rates of deficiency of vit. D are 15%. [7,8]

Studies have also revealed that reduced serum 25(OH) D levels had a close relationship with improper metabolic control among diabetic patients. [8.9] Studies also showed improved glucose tolerance and insulin resistance with vitamin D treatment. [10] Vitamin D deficiency is more prevalent in T1DM patients with poor glycemic control, while better glycemic control has been consistently related to higher 25 hydroxy vitamin D (25(OH)D) concentrations. [11]

The purposes of this study were to assess serum vitamin D (25OHD) levels in children with type 1 diabetes mellitus, and to evaluate the association between serum 25(OH)D and glycosylated hemoglobin (HbA1c) levels, to test the hypothesis that lower 25(OH)D levels are associated with poorer glycemic control in children with T1DM.

Materials and methods

A cross sectional study was done over period of one year from November 2018 to October 2019 in children diagnosed as T1DM as per American Diabetic Association criteria. [12]

Inclusion criteria:

70 children of Type 1 Diabetes Mellitus (Ages between 1month to 12 years) attending Out patient department and children admitted in the Intensive Care Unit / general ward of department of Pediatrics formed the study group.

Exclusion criteria:

- Children above 12 years of age.
- Children with poor compliance to Insulin.
- Children who are already receiving supplementation of vitamin D.
- Children with other comorbid conditions like end stage renal disease/ liver disease, endocrine abnormalities like thyroid/parathyroid disorders, other chronic diseases, immunodeficiencies.
- Children with Anemia.
- Children with history of blood transfusions.

Institutional Ethical committee approval (IEC/GMC/2019/04/32) was taken. Children aged less than 12 years age who

were fulfilling the inclusion criteria were included after taking consent from parents. Children diagnosed to have T1DM for the first time taken as Newly diagnosed diabetes mellitus. Children diagnosed as T1DM previously and on insulin treatment taken as established diabetes mellitus cases. Detailed history and clinical examination were done in all children included in the study as per predesigned proforma. Detailed laboratory evaluation including Complete blood count, Reticulocyte count, Liver and kidney function test, serum electrolytes, serum calcium, thyroid profile, random blood sugars at the time of admission using glucometer, urinary ketones, arterial blood gases, serum 25(OH) D [25 hydroxy Vitamin D] levels and Hb A1 C [Hemoglobin A1C / Glycated hemoglobin] levels were done to all children at the first visit / admission.

Measurement of Serum vitamin D levels can be done by immunoassay and chemical assay. Immunoassays [Chemiluminescence Immunoassays (CLIA), Radio Immunoassay (RIA)] are sensitive, cost and time effective. The disadvantage is with reproducibility and inability to discriminate 25 hydroxy and 1,25 hydroxy forms of 25(0H) D metabolite. [13] Chemical assays are High Performance Liquid Chromatography (HPLC) and Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) etc. These are sensitive, accurate, reproducible and costly. [13,14] Serum 25-hydroxyvitamin D levels have been determined by using CLIA in the recent years because of it being a simple, cost-effective method when compared to LC-MS/MS systems. [15]

In this study Serum 25(OH)D levels were estimated using CLIA and American academy of pediatrics classification was used to categorize vitamin D status. [16]. 25(OH)D levels >20ng/dL taken as sufficiency, 25(OH)D level <15 ng/dL or less are considered as deficiency and Values in between 16 to 20 ng/dl considered as insufficiency.

HbA1c value was measured using Ion exchange High performance Liquid chromatography (IE-HPLC) based assay. Diabetes control and Complication Trial (DCCT) and National Glycohemoglobin Standardization Program (NGSP) certified IE-HPLC also a standardized reference method. [17] HbA1c measurement can be false low or false high in patients with Hb variants and less accurate for patients with iron deficiency anemia, hemolytic anemia and patients with bleeding. [18]

In children with diabetes, HbA1c values of 6-7.5% represent good metabolic control, values of 7.6-9.9% indicate fair control, and values of 10% or higher indicate poor control. [19]

Statistical analysis

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Frequencies were calculated for categorical Variables and analyzed by using fisher's exact test. Descriptive statistics such as mean and standard deviation (SD) were calculated for continuous variables. Comparison of mean between quantitative variables were analyzed using unpaired t test and ANOVA (Analysis of Variance) for variables having 2 and more than 2 categories respectively. The association between the variables were analyzed using Pearson correlation test and multiple linear regression analysis was used to detect independent predictors of HbA1c. P- value < 0.05 was considered as statistically significant.

Results

Total 70 children were included in the study. Characteristics of patients included in the study showed in table 1, the mean age was significantly lower in newly

diagnosed cases compared to established cases of T1DM (P value < 0.05). We did not find statistically significant difference in mean values of HbA1C, in vitamin D status of newly diagnosed and established cases of T1DM as shown in table 1 and 2.

Table 1: Characteristics of Patients included in the study

Parameter	Newly Diagnosed DM n=39			Established DM n=31			P-value
	Mean (SD)	Confidence interval		Mean (SD)	Confidence interval		
		UL†	LL‡		UL†	LL‡	
Age in years	7.358 (2.650)	8.217	6.499	9.435 (3.06)	10.558	8.312	0.004*
HbA1C	10.574 (1.733)	11.135	10.013	11.019 (1.818)	11.686	10.352	0.130
25(OH)D > 20 ng/dl	22.105 (1.365)	23.538	20.672	22.866 (2.327)	25.308	20.424	0.508
25(OH)D between 16-20 ng/dl	18.2 (1.840)	21.128	15.272	17.0 (1.414)	29.706	4.294	0.44
25(OH)D < 15 ng/dl	9.682 (3.336)	10.951	8.413	8.221 (2.563)	9.329	7.113	0.08

**P*-value significant, †UL-upper limit, ‡LL- lower limit

Table 2: Vitamin D status in newly diagnosed and established cases of T1DM

Parameter	Newly diagnosed DM n=39 (%)	Established DM n=31(%)	Total T1DM cases n=70(%)	P-value
Number of children with 25(OH)D > 20 ng/dl	6(15.38)	6(19.35)	12(17.14)	0.7544
Number of children with 25(OH)D between 16-20 ng/dl	4(10.25)	2(6.4)	6 (8.57)	0.6867
Number of children with 25(OH)D < 15 ng/dl	29 (74.35)	23(74.19)	52 (74.28)	1

Metabolic parameters were represented in table 3, *P*-value found to be significant for glycemic status in study population in relation to Vitamin D status.

Table 3: Metabolic parameters in relation to Vitamin D status. Data expressed as mean ± Standard deviation

Metabolic parameter		Vitamin D deficiency (<15)	Vitamin D insufficiency (16-20)	Vitamin D sufficiency (>20)	p-value
Ph	Mean (SD)	7.125(0.136)	7.200(0.110)	7.148(0.122)	0.402
	CI† -UL‡	7.163	7.315	7.225	
	CI - LL§	7.087	7.085	7.071	
Bicarbonate (mEq / L)	Mean (SD)	8.176(4.371)	10.05 (6.41)	9.258(3.826)	0.517
	CI -UL	9.392	16.777	11.689	
	CI - LL	6.96	3.323	6.827	
Hb A1c (%)	Mean (SD)	11.196(1.655)	9.066(1.827)	9.783(1.406)	0.008*
	CI -UL	11.656	10.983	10.676	
	CI - LL	10.736	7.149	8.89	

Association between 25OHD levels and glycemic control (HbA1c): Correlation & regression Children with vit D deficiency had higher mean HbA1c (11.19 +/- 1.65) compared to children with vitamin D insufficiency (9.53 +/- 1.45) and vit D sufficiency (9.78 +/- 1.40) (p value 0.004).

A Pearson correlation coefficient was computed to assess the linear relationship between 25OHD and HbA1c levels in all cases, newly diagnosed and established cases of type 1 diabetes as shown in figure 1.

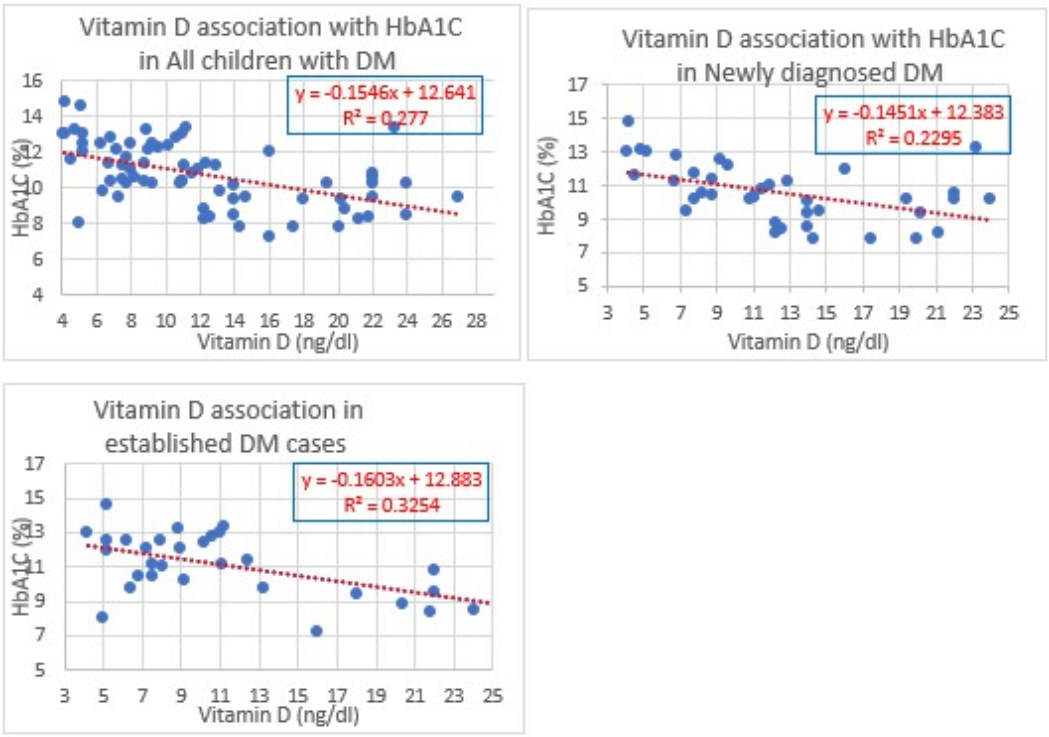


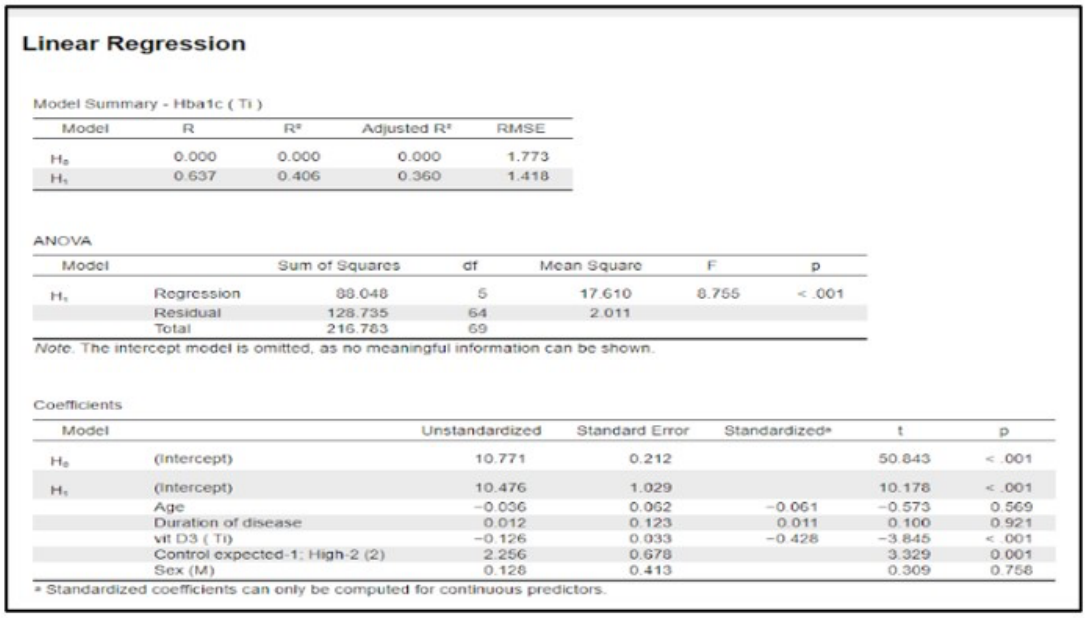
Figure 1. Scatter plots to show association between Vitamin D and HbA1c in children with T1DM. Significant inverse correlations between vitamin D and HbA1c in total children (n=70) with r = -0.526, *P*- 0.00000291*, newly diagnosed cases (n=39) with r = -0.4791, *P*-0.00203* and in established cases (n=31) of T1DM with r = -0.5704, *P*- 0.00081*.

There was a significant negative correlation between the two variables as shown in table 4.

Table 4: Vitamin D Association with metabolic parameters with Pearson correlation.

Variable	Pearson correlation coefficient (r)	p-value
Vitamin D in Newly diagnosed T1DM &HbA1C	-0.4791	0.00203*
Vitamin D in Established T1DM &HbA1C	-0.5704	0.00081*
Vitamin D in total T1DM &HbA1C	-0.526	0.00000291*
Vitamin D in total T1DM &Ph	0.048	0.69314299
Vitamin D in total T1DM & Bicorbonate	0.0711	0.55861810

A multiple linear regression analysis (R-square: 0.406) showed that 30% variance in HbA1c can be accounted for by vitamin D levels, age, sex and duration of diabetes collectively. ($p < 0.01$ f (5,64) = 8.755). Results showed a link between 25OHD levels and HbA1c (β: -0.291; t= -3.845 $p<0.001$). Age, sex or duration of diabetes did not show any significant correlation with HbA1c levels as shown in figure 2.



Linear Regression

Model Summary - Hba1c (Ti)

Model	R	R²	Adjusted R²	RMSE
H_0	0.000	0.000	0.000	1.773
H_1	0.637	0.406	0.360	1.418

ANOVA

Model		Sum of Squares	df	Mean Square	F	p
H_1	Regression	88.048	5	17.610	8.755	< .001
	Residual	128.735	64	2.011		
	Total	216.783	69			

Note. The intercept model is omitted, as no meaningful information can be shown.

Coefficients

Model		Unstandardized	Standard Error	Standardized*	t	p
H_0	(Intercept)	10.771	0.212		50.843	< .001
H_1	(Intercept)	10.476	1.029		10.178	< .001
	Age	−0.036	0.062	−0.061	−0.573	0.569
	Duration of disease	0.012	0.123	0.011	0.100	0.921
	vit D3 (Ti)	−0.126	0.033	−0.428	−3.845	< .001
	Control expected-1; High-2 (2)	2.256	0.678		3.329	0.001
	Sex (M)	0.128	0.413		0.309	0.758

* Standardized coefficients can only be computed for continuous predictors.

Figure 2: Linear regression analysis

Discussion

Vitamin D status in children T1DM: Management of T1DM is very challenging issue in developing countries due to various factors including insulin initiation, insulin storage, cost, adherence to treatment, availability of glucometer, cost of glucometer strips and parental education levels etc. Optimizing good glycemic control is the main stay of treatment in diabetes to avoid long term complications. Hence study was undertaken to assess the vitamin D status and its association with glycemic control in children with T1DM.

We found high prevalence of vitamin D deficiency (74%) in newly diagnosed and established cases of T1DM. This finding confirms the widespread vitamin D deficiency in children with T1DM, as recently suggested by a meta-analysis of pediatric subjects with T1DM. [6] The prevalence of vitamin D deficiency is higher in newly diagnosed and established cases of T1DM than the study done by Liu C et al in 296 children with T1DM. [20] There is evidence in literature about potential role of Vitamin D deficiency in pathogenesis of DM and improving glycemic status with its supplementation.

Association of vitamin D levels with glycemic status: Children with vitamin D sufficiency had better glycemic control (lower HbA1c) when compared to children with vit D insufficiency and deficiency. Similar result was seen in prospective observational study done in type 1 and type 2 DM patients over a period of 9 months and improvement in glycemic status noted with vitamin D supplementation. [21]

This study identified a moderate inverse correlation between vitamin D and HbA1C among the all children, newly diagnosed cases, and established cases of T1DM consistent with studies done in T2DM and T1DM. [21,22,23] When the correlation adjusted for age, sex, duration of diabetes, we found that 25(OH)D was an independent risk factor for glycemic status in all children with T1DM. A cross sectional observational study done in adults with type 1& 2 DM to investigate association of 25(OH)D levels with glycemic status and fasting blood sugar. In this study, multiple variables including age, weight, height, BMI, duration of DM, 25 (OH)D were analyzed in linear regression analysis to identify the

correlation with glycemic status. It showed that HbA1C was inversely associated with 25(OH)D and directly associated with fasting blood sugar. [9]

Limitation of the study

Our study was limited by small sample size and absence of a control group to compare the prevalence of vitamin D deficiency in type 1 diabetics with that of general population.

One more limitation being cross sectional study, we could not able to identify the role of vitamin D supplementation in glycemic control. Factors that affect vitamin D status like variations in exposure to sunlight, seasonal variations, dietary habits, economic status, nutritional condition of child and Factors influencing the glycemic status of children like insulin dose, type of insulin, educational status of parents, family support were also not analyzed in this study.

Most of the studies to assess the association between 25(OH)D and HbA1C were done in adult patients with DM. Only few studies are available in literature which examined association between vitamin D levels and glycemic status, with variable results. Hence studies having large sample size and factors effecting the metabolic status to be studied to impart the result to general population.

Conclusion

In this study, we found high prevalence of vitamin D deficiency in T1DM. Children with Vitamin D deficiency had poor glycemic status when compared to children with sufficient vitamin D levels. There is an inverse association between HbA1C and 25(OH)D when adjusted for other independent risk factors.

Considering the high prevalence of vitamin D deficiency, Estimation of Vitamin D levels to be considered as part of routine workup. Hence early identification and improvement in vitamin D levels controls the glycemic status in children

References

1. Harrison LC, Honeyman MC, Morahan G, Wentworth JM, Elkassaby S, Colman PG et al., Type 1 diabetes: Lessons for other autoimmune diseases? Journal of Autoimmunity. 2008; 31(3): 306–310.
2. L. Moroni, I. Bianchi, and A. Lleo, Geoepidemiology, gender and autoimmune disease, Autoimmunity Reviews, 2012; 11: A386–A392, 2012.
3. Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE et al. Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. J Steroid Biochem Mol Biol. 2004;89-90(1-5):121-5.
4. Bailey R, Cooper JD, Zeitels L, Smyth DJ, Yang JH, Walker NM, et al. Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes. Diabetes. 2007;56(10):2616-21.
5. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001 Nov 3;358(9292):1500-3.
6. Feng R, Li Y, Li G, Li Z, Zhang Y, Li Q, et al. Lower serum 25 (OH) D concentrations in type 1 diabetes: A meta-analysis. Diabetes Res Clin Pract. 2015;108(3):e71-5.
7. Bener A, Alsaied A, Al-Ali M, Al-Kubaisi A, Basha B, Abraham A, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. Acta Diabetol. 2009 Sep;46(3):183-9.
8. Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatr. 2009;154(1):132-4.
9. Alkhatatbeh MJ, Abdul-Razzak KK. Association between serum 25-hydroxyvitamin D, hemoglobin A1c

and fasting blood glucose levels in adults with diabetes mellitus. Biomed Rep. 2018;9(6):523-530.
10. Parekh D, Sarathi V, Shivane VK, Bandgar TR, Menon PS, Shah NS. Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes mellitus. Endocr Pract. 2010;16(4):600-8.
11. Savastio S, Cadario F, Genoni G, Bellomo G, Bagnati M, Secco G, et al. Vitamin D Deficiency and Glycemic Status in Children and Adolescents with Type 1 Diabetes Mellitus. PLoS One. 2016;11(9): e0162554.
12. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018 Jan;41(Suppl 1): S13-S27.
13. Grebe SK, Singh RJ. LC-MS/MS in the Clinical Laboratory - Where to From Here? Clin Biochem Rev. 2011 Feb;32(1):5-31.
14. Atef S H. Vitamin D assays in clinical laboratory: Past, present and future challenges. J Steroid Biochem Mol Biol. 2018;175: 136–137.
15. Farrell CJ, Martin S, McWhinney B, Straub I, Williams P, Herrmann M. State-of-the-art vitamin D assays: a comparison of automated immunoassays with liquid chromatography-tandem mass spectrometry methods. Clin Chem. 2012 Mar;58(3):531-42.
16. Lee JY, So TY, Thackray J. A review on vitamin d deficiency treatment in pediatric patients. J Pediatr Pharmacol Ther. 2013 Oct;18(4):277-91.
17. American Diabetes Association. Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1(Suppl 1): S11-61.
18. Khan MI, Weinstock RS. Chapter 16: Carbohydrates. In: McPherson RA, Pincus MR, editors. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Philadelphia, PA: Saunders Elsevier. 2011; 210–25.
19. Svoren BM, Jospe N. Nelson textbook of paediatrics. 20th ed. Elsevier Publishing. Type 1 Diabetes Mellitus (Immune Mediated). In: Kliegman R, Behrman R, Nelson W. 2015; 2777.
20. Liu C, Wang J, Wan Y, Xia X, Pan J, Gu W, et al. Serum vitamin D deficiency in children and adolescents is associated with type 1 diabetes mellitus. Endocr Connect. 2018 ;7(12):1275-1279.
21. Buhary BM, Almohareb O, Aljohani N, Alrajhi S, Elkaissi S, Sherbeeni S, et al. Association of Glycosylated Hemoglobin Levels with Vitamin D Status. J Clin Med Res. 2017;9(12):1013-1018.
22. Kostoglou-Athanassiou I, Athanassiou P, Gkountouvas A, Kaldrymides P. Vitamin D and glycemic control in diabetes mellitus type 2. Ther Adv Endocrinol Metab. 2013;4(4):122-128.
23. Zhao H, Zhen Y, Wang Z, Qi L, Li Y, Ren L, et al. The Relationship Between Vitamin D Deficiency and Glycated Hemoglobin Levels in Patients with Type 2 Diabetes Mellitus. Diabetes Metab Syndr Obes. 2020; 13:3899-3907.