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Vitamin D and vitamin D-binding protein in type 1 diabetes mellitus

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Abstract

Background and aim

Type 1 diabetes mellitus (T1DM) is an autoimmune disease caused by destruction of pancreatic islet βcells, leading to absolute insulin deficiency. The D vitamins are a group of sterols that have a hormone-like function, which bind to vitamin D receptor. Vitamin D (25(OH) D) deficiency is involved in the induction of autoimmune destruction of β-cells and onset of T1DM. The majority of circulating 25(OH) D is bound to vitamin D-binding protein (VDBP), which protects it from biodegradation, limits its access to target tissues, and helps its reabsorption from the kidneys. VDBP also binds fatty acids, activates macrophages, enhances the chemotactic activity of C5, and associates with immune cell surfaces. The aim of our work was to evaluate the levels of 25(OH) D and VDBP and their relation to each other in T1DM and comparing 25(OH) D level with some variables in children with T1DM.

Patients and methods

In this simple comparative study, 60 children with T1DM and 35 normal children were enrolled, and for them, we measured serum 25-hydroxyvitamin D, serum VDBP, and glycosylated hemoglobin (HbA1c).

Results

25(OH) D level was significantly lower in T1DM group than control (20.73 ± 5.69 and 41.16 ± 3.61 ng/ml, respectively) ($t = 8.3$ and $P < 0.0001$). Moreover, VDBP level was significantly lower in T1DM group than control group (203.96 ± 32.52 and 238.32 ± 34.82 μg/ml, respectively) ($t = 4.7$ and $P < 0.0001$). 25(OH)D level in T1DM had a significant positive correlation with age at onset of the disease (r=0.77) and a significant negative correlation with HbA1c % (r=-0.74) and no correlation with VDBP levels or disease duration.

Conclusion

25(OH)D and VDBP levels in T1DM were significantly lower than normal children. 25(OH)D level had no correlation with VDBP levels, a positive correlation with age at onset of the disease, a negative correlation with HbA1c %, and no correlation with disease duration.

Keywords: Diabetes mellitus, vitamin D-binding protein, vitamin D

Introduction

Type 1 diabetes mellitus (T1DM) accounts for 90% of diabetes cases in children and adolescents. The incidence in children and adolescents in three Egyptian governorates (Fayoum, North Sinai, and Suez) is 4.01/100 000 per year [1]. There is formation of T1DM-associated autoantibodies, leading to loss of β-cells [2]. Specific antibodies that are detected in patients with T1DM include islet cell antibodies, glutamic acid decarboxylase antibodies (GAD-65), insulin autoantibodies (IAA), and protein tyrosine phosphatase and zinc transporter [3]. The disease process begins months to years before the onset of hyperglycemia, and clinical symptoms become apparent when approximately more than or equal to 90% of pancreatic β cells are destroyed [4].

T1DM has a strong association with genetic susceptibility and different environmental factors such as short-term exclusive breast-feeding [5], early introduction of cows'

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milk or cereals [6], enterovirus infections [7], and vitamin D deficiency [8].

The D vitamins are a group of sterols that have a hormone-like function. The two main forms of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) [8].

Vitamin D3 is hydroxylated twice to the active form, generating 1α, 25-dihydroxyvitamin D3 (1α,25-(OH) 2D3) [9], which binds to vitamin D receptor (VDR) at target cells, and subsequently binding to the specific DNA called vitamin D responsive elements (VDREs) to exert its effects at the transcriptional level [10]. Additionally, VDR and 1, 25-(OH) 2D3 complex also intervene in the function of nuclear transcriptional factors in a dose-dependent manner. All the genes with VDREs in the promoter regions play a crucial role in immunoregulation, and abnormal expression may lead to autoimmune diseases [11]. VDR are expressed in human T and B lymphocytes, and vitamin D is thought to modify the Th1/Th2 cytokine profile [12] and inhibit lymphocyte proliferation [13]. It also counteracts cytokine-induced expression of Fas, which regulates cell death in human islet cells, so 1, 25(OH) 2D3 plays an immunomodulatory role in the prevention of T1DM [14], and thus, VDR gene polymorphisms may be related to T-cell-mediated autoimmune diseases [15].

The majority of circulating 25-hydroxyvitamin D (25OHD) and 1,25(OH) 2D is tightly bound to vitamin D-binding protein (VDBP), 10–15% is bound to albumin, and less than 1% is in free form. Serum 25OHD is the standard indicator of vitamin D status, composed of vitamin D3 and vitamin D2 [16].

VDBP is a 58-kDa glycoprotein that serves as the main carrier for circulating vitamin D and its metabolites. Its role is maintaining the total levels of vitamin D and regulating the amounts of free vitamin D available for utilization [17]. It is relatively stable and should be considered in the interpretation of 25(OH) D levels [18].

The VDBP+25OHD complex is freely filtered across the glomerulus allowing transport to the proximal tubule, where its reabsorption facilitates the generation of 1, 25(OH) 2D [19] and reduces the urinary excretion of 1, 25(OH) 2D to trace [20].

There are three main roles of VDBP in vitamin D physiology: protecting it from biodegradation, limiting its access to target tissues, and its reabsorption from the kidneys. The VDBP/25(OH)D complex is filtered in the glomerulus and then reabsorbed by megalin-cubilin receptors of the proximal tubular epithelial cells. VDBP is degraded in lysosomes, whereas 25(OH) D is converted into biologically active 1, 25(OH) 2D, which is resecreted into the circulation [21].

Aside from its main function of 25 (OH) D transport and preservation, VDBP binds fatty acids, activates macrophages, stimulates osteoclasts, enhances the chemotactic activity of C5, and is associated with immune cell surfaces such as T and B cells [22]. Only ~4% of VDBP is bound to 25 (OH) D at any time and has a half-life of 2.5–3 days [23].

The plasma concentration of VDBP is stable from birth and is ~0.2–0.5 g/l [24].

Aim

The aim of this study was to evaluate the serum levels of 25 (OH) D and VDBP and their relation to each other in children with T1DM and to compare the serum level of 25 (OH) D with some variables such as age at onset, glycosylated hemoglobin (HbA1c) level, and disease duration in those patients.

Patients and methods

This case–control study was performed on 60 children with T1DM from the outpatient department of Banha Teaching Hospital scheduled for insulin treatment. This study was conducted between June 2017 and March 2018.

A total of 35 children of nearly matched age, sex, and socioeconomic status were incorporated as the control group.

Ethical considerations:

(1) The study purpose and procedures were explained to the parents and written consents were obtained before the study.
(2) The authors declared no potential conflict of interest with respect to the research and publication of this article.
(3) All data of the patients and results of the study are confidential, and the patient has the right to keep them.
(4) The authors received no financial support for the research and publications of the article.

Inclusion criteria: type 1 diabetic children irrespective of age or sex were included.

Exclusion criteria: patients having malnutrition [includes wasting (low weight-for-height), stunting (low height-for-age), and underweight (low weight-for-age)], malabsorption (frequent, bulky, offensive, or abnormal colored stool associated with malnutrition and/or manifestations of vitamin deficiency), liver disease (abnormal liver function tests), end-stage renal disease, metabolic bone disease (clinical and laboratory abnormalities) or vitamin D supplementation, corticosteroid therapy or hypercortisolism, malignancy, immobility for more than 1 week, and medications influencing bone metabolism.

The studied groups were subjected to the following:

(1) Complete history taking, including age, sex, residence, dietetic history, vitamin supplementations, activity and family history of diabetes, metabolic diseases, and metabolic bone diseases. Diabetic history, including disease duration, age at onset, insulin dose, and compliance.
(2) Complete thorough clinical examination.
(3) Laboratory data, including the following:

(a) Serum 25OHD.
(b) Serum VDBP.
(c) HbA1c level.

Method of obtaining human 25-hydroxy vitamin D

Blood samples were taken and allowed to coagulate; serum was separated and stored at −70°C until biochemical analysis was performed.

Human serum 25-OH-D (kit from Wkea Med Supplies. Jilin China) concentration was determined by solid-phase enzyme-linked immunosorbent assay method [25], where the microtiter plate wells were coated with a purified human 25-OH-D antibody, which captures the 25-OH-D from the samples. The combination of the 25-OH-D antibody with the labeled enzyme becomes antibody–antigen–enzyme–antibody complex, and after washing completely, a substrate was added, forming blue color, and the HRP enzyme–catalyzed reaction was terminated by the addition of sulfuric acid solution, and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of 25-OH-D in the samples is determined by comparing the optical density of the samples to the standard curve.

Method of obtaining human vitamin D-binding protein

Human serum VDBP (kit from AssayPro) concentration was determined by a double-antibody sandwich (enzyme-linked immunosorbent assay) method [25]. VDBP of the tested samples is added to the monoclonal antibody enzyme well, which was precoated with human VDBP monoclonal antibody. After incubation for 60 min at 37°C, VDBP antibody labeled with biotin and combined with streptavidin–HRP was added to form an immune complex. Then, washing was done, and a substrate was added. The color changed to blue, and then yellow with the effect of addition of an acid. The color was measured spectrophotometrically at a wavelength of 450 nm. The concentration of VDBP was determined by comparing the optical density of samples to the standard curve.

Methods of assay of HbA1c: the kit was obtained from Crystal Chem, which is a high-quality enzymatic assay for the quantification of HbA1c in the whole blood, in which lysed whole blood samples are subjected to extensive protease digestion. Then, the released amino acids, including glycated valines from the hemoglobin beta chains, in turn, are measured [26].

Statistical analysis

The gathered data were statistically analyzed using the SPSS program for Windows (version 24; SPSS Inc., Chicago, Illinois, USA), and variables were presented as mean ± SD. The relationship between vitamin D and different laboratory parameters was determined using the Spearman correlation analysis and the linear regression method. *P* value less than 0.05 was considered statistically significant.

Results

The characteristics of studied groups were found as follows:

(1) Age range of patients with T1DM was 62–155 months, with mean ± SD of 115 ± 38.1 months and for the control group was 59–157 months, with mean ± SD of 113 ± 34.54 months ($P = 0.35$). Male/female ratio for T1DM was 26/34 and for control group was 15/20 ($P > 0.05$). Age at onset for diabetes ranged from 37 to 137, with mean ± SD of 88.91 ± 28.65 months. Duration of diabetes ranged from 4 to 39, with mean ± SD of 21 ± 5.82 months. HbA1c % levels in T1DM ranges from 5.8 to 9%, with mean ± SD of 7.19 ± 0.81%, and in control group, it ranges from 3.9 to 5.8%, with mean ± SD of 4.77 ± 0.82% ($P > 0.001$) [Table 1].

(2) The levels of 25 (OH) D and VDBP for T1DM ranged from 12 to 31, with mean ± SD of 20.73 ± 5.69 ng/ml and for control group ranged from 35 to 52, with mean ± SD of 41.16 ± 3.61 ng/ml [Table 2].

VDBP level for T1DM ranged from 148 to 289, with mean ± SD of 203.96 ± 32.52 µg/ml, and for control group ranged from 196 to 382, with mean ± SD of 238.32 ± 34.82 µg/ml [Table 2].

Moreover, the 25 (OH) D level of T1DM group was significantly lower ($t = 8.3$ and $P < 0.0001$) than control group. In addition, level of VDBP of T1DM group is significantly lower ($t = 4.7$ and $P < 0.0001$) than control group [Table 2].

Vitamin D level in T1DM had significant positive correlation with age at onset of the disease ($r = 0.77$) and

Table 1 Characteristics of the studied groups

	T1DM (*n*=60)	Control group (*n*=35)
Age (months)		
Range	62-155	59-157
Mean±SD	115±38.1	113±34.54
Age at onset (months)		
Range	37-137	
Mean±SD	88.91±28.65	
Sex [*n* (%)]		
Male	26 (43.3)	15 (42.8)
Females	34 (56.7)	20 (57.2)
Duration (months)		
Range	4-39	
Mean±SD	21±5.82	
HbA1c %		
Range	5.8-9	3.9-5.8
Mean±SD	7.19±0.81	4.77±0.82

Table 2 Vitamin D and vitamin D-binding protein levels of the studied groups

	T1DM (*n*=60)	Control group (*n*=35)	*t*	*P*
Vitamin D				
Range (ng/ml)	12-31	35-52	8.3	<0.0001*
Mean±SD	20.73±5.69	41.16±3.61		
VDBP (µg/ml)				
Range	148-289	196-382	4.7	<0.0001*
Mean±SD	203.96±32.52	238.32±34.82		

*Significant results

significant negative correlation with HbA1c % (r=−0.74) and no correlation with VDBP levels or disease duration. The 25 (OH) D levels in T1DM and control group are presented in Fig 1. It also shows that 25 (OH) D levels are lower in T1DM than in the control group.

Moreover, the VDBP levels in T1DM and control group are presented in Fig 2, and it is seen that VDBP level is lower in T1DM than in the control group.

(3) The correlation between 25 (OH) D and the different parameters is presented in Table 3, and it shows that 25 (OH) D level for T1DM group had a significant positive correlation with age at onset of the disease (r = 0.77), a significant negative correlation with HbA1c % (r=−0.74), and no correlation with disease duration or VDBP levels.

The correlation between 25 (OH) D level and HbA1c in T1DM is shown in Fig 3, and it shows that there is a negative correlation between 25 (OH) D and HbA1c (r=−0.74) in T1DM.

The correlation between 25 (OH) D level and age at onset in T1DM is shown in Fig 4, showing that there is a positive correlation between 25 (OH) D and age at onset in T1DM (r = 0.77).

The correlation between 25 (OH) D level and VDBP in T1DM is presented in Fig 5, illustrating that there is no correlation between 25 (OH) D and VDBP in T1DM (r = 0.03).

Table 3 Correlation between vitamin D and different parameters

Variables	*r*	*P*
Age at onset	0.77	<0.001**
25 (OH) vitamin D3 (ng/ml)		
Duration (years)	0.23	0.07
HbA1c %	−0.74	<0.001**
VDBP (µg/ml)	0.03	0.82

**Significant results

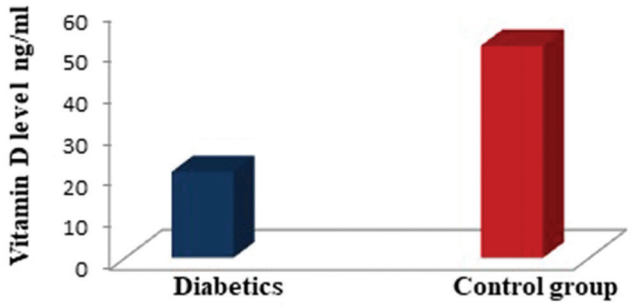

Figure 1: Vitamin D levels in T1DM and control group. T1DM, type 1 diabetes mellitus

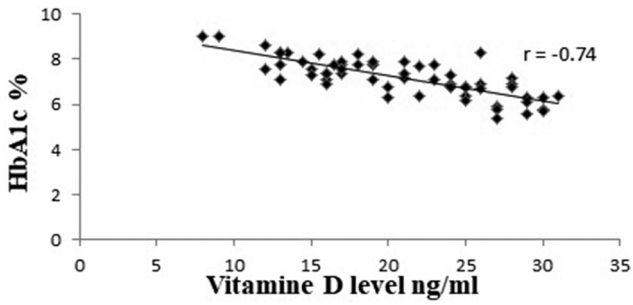

Figure 3: Correlation between vitamin D level and HbA1c in T1DM. This figure shows that there is a negative correlation between vitamin D and HbA1c (r=−0.74) in T1DM. HbA1c, glycosylated hemoglobin; T1DM, type 1 diabetes mellitus

Discussion

T1DM is an autoimmune disorder caused by the progressive T-cell-mediated destruction of pancreatic β-cells. It is triggered by a combination of genetic and environmental factors, including viral infections, dietary antigens, and 25 (OH) D deficiencies [27].

25 (OH) D has nonclassic role in many autoimmune diseases, as it shows potent antiproliferative and immunomodulatory properties [28].

Circulating 25 (OH) D is carried mainly by VDBP, which is thought to have immune regulatory properties itself [29].

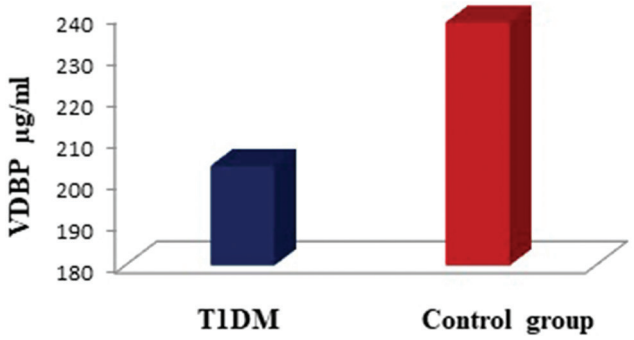

Figure 2: VDBP levels in T1DM and control group. T1DM, type 1 diabetes mellitus; VDBP, vitamin D-binding protein

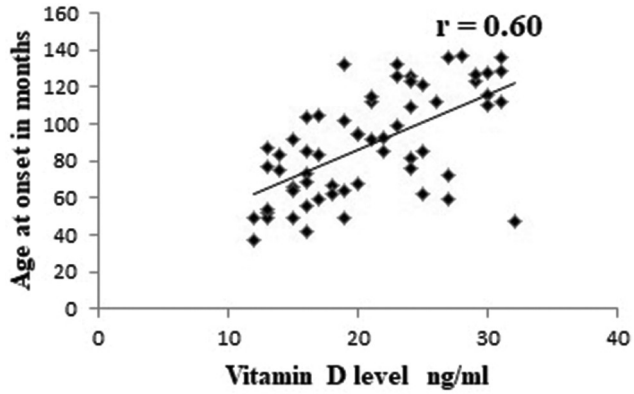

Figure 4: Correlation between vitamin D level and age at onset in T1DM. This figure shows that there is a positive correlation between vitamin D and age at onset in T1DM (r = 0.77). T1DM, type 1 diabetes mellitus

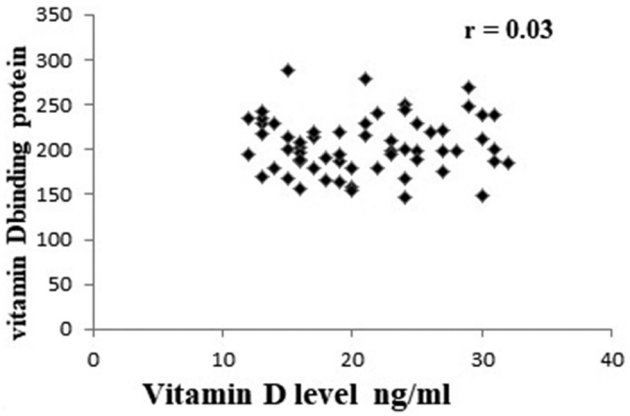

Figure 5: Correlation between vitamin D level and VDBP in T1DM. This figure shows that there is no correlation between vitamin D and VDBP in T1DM (r = 0.03). T1DM, type 1 diabetes mellitus; VDBP, vitamin D-binding protein

To evaluate the level of 25 (OH) D and VDBP and their relation to each other and compare 25 (OH) D levels with the glycemic control in patients with T1DM, we measured 25 (OH) D and VDBP levels in 60 patients with T1DM and compare their levels with 35 normal children of nearly matched age, sex, and socioeconomic status.

Our results showed that 25 (OH) D of T1DM group was statistically significantly lower than control group ($P < 0.0001$). This finding was in accordance with many studies conducted by other authors such as Hewison [30], who stated that the autoimmune pathology of T1DM can be affected by the deficiency of 25 (OH) D, and 25 (OH) D deficiency precedes the onset of type 1 diabetes. Moreover, Raab *et al*. [31], stated that in the case of prediabetic children, we must be mindful of the risk of 25 (OH) D deficiency and consider recommending 25 (OH) D supplementation at an early stage of type 1 diabetes. Setty-Shah *et al*. [32], suggested that T1DM may be dependent on 25 (OH) D receptor variants. Many researchers found low 25 (OH) D concentrations in children with T1DM, as in the UK by Giri *et al*. [33], in Finland by Miettinen *et al*. [34], in Korea by Nam *et al*. [35], and in Egypt by Abd-Allah *et al*. [15]. On the contrary, Kim *et al*. [36], found that there was no significant difference in the frequency of 25 (OH) D deficiency between healthy and pediatric patients with T1DM in Seoul.

Our results also showed that 25 (OH) D of T1DM group had a statistically significant positive correlation with age at onset, and this may be owing to lack of 25 (OH) D vitamin D function in promotion of insulin secretion and beta cell survival by inactivation of NF-κb and downregulation of Fas-Ligand [37]. This was in accordance with Svoren *et al*. [16], who found that although glycemic control, duration of DM, and age were associated with 25 (OH) D inadequacy, only age remained a significant predictor.

We also found that there was a negative correlation between 25 (OH) D levels and HbA1c in diabetic patients, as 25 (OH) D regulates intracellular calcium, so it increases insulin secretion and promotes insulin sensitivity [38]. This finding was similar to Kositsawat *et al*. [39], who stated that decreased levels of 25OHD lead to increased levels of glucose and hence increased levels of glycated hemoglobin. Moreover, Soliman *et al*. [40], found that 25 (OH) D was lower in T1D Egyptian children and had significant strong negative correlations with fasting blood sugar and HbA1c %.

Our results showed that VDBP of T1DM group was statistically significantly lower than control group ($t = 4.7$, $P < 0.0001$). This finding was in accordance with Blanton *et al*. [22], who reported that serum VDBP levels are decreased in those with type 1 diabetes. In addition, Thrailkill *et al*. [41], found that there is increased urinary VDBP loss secondary to diminished availability of megalin (receptor of reabsorption of VDBP from proximal tubule) owing to its loss with proteinuria. Moreover, Kirac *et al*. [29], demonstrated a significant decrease in VDBP diabetic patients.

Our data found no significant correlation between 25 (OH) D and VDBP levels in T1DM. This may be owing to the fact that VDBP has many other functions other than carrying 25 (OH) D [22], and only about 4% of VDBP is bound to 25 (OH) D at any one time [23]. Similar finding was shown by Kim *et al*. [36], who stated that in pediatric type 1 diabetic patients, urinary VDBP excretion did not contribute to low serum 25(OH) D level in the setting of normoalbuminuria. In addition, Sollid *et al*. [42], found that 25 (OH) D supplementation for 12 months did not affect serum VDBP but increased 25 (OH) D levels in normal individuals.

Conclusion

Serum levels of 25 (OH) D and VDBP levels in T1DM are significantly lower than normal children, and 25 (OH) D levels have no correlation with VDBP levels.

Serum levels of 25 (OH) D have a positive correlation with age at onset of the disease, a negative correlation with HbA1c %, and no correlation with disease duration.

Recommendation

Low levels of 25(OH) D could be considered a potential risk factor for the development of T1DM. Moreover, 25(OH) D levels were related to glycemic control in diabetic patients, thus vitamin D supplementation could have a therapeutic potential in prevention and management of T1DM. Further studies of including vitamin D supplements in treatment protocol of T1DM are needed.

Conflicts of interest

None declared.

References

1. Hassan FM, Khatab AA, Abo El-Fotoh WM, Ganh IN. Prevalence of diabetes mellitus among school-age children. Menoufia Med J 2019 32:305–310.
2. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, *et al*. Type 1 diabetes mellitus. Nat Rev Dis Primers

2017; 3:17016.
3. Ling Q, Lu J, Li J, Xu Q, Zhu D, Bi Y. Risk of beta-cell autoimmunity presence for progression to type 1 diabetes: A systematic review and meta-analysis. J Autoimmun 2018; 86:9–18.
4. Karges B, Meissner T, Icks A, Kapellen T, Holl RW. Management of diabetes mellitus in infants. Nat Rev Endocrinol 2012; 8:201–211.
5. Holmberg H, Wahlberg J, Vaarala O, Ludvigsson J. Short duration of breast-feeding as a risk-factor for beta-cell autoantibodies in 5-year-old children from the general population. Br J Nutr 2007; 97:111–116.
6. Virtanen SM, Takkinen HM, Nevalainen J, Uusitalo L. Early introduction of root vegetables in infancy associated with advanced β-cell autoimmunity in young children with human leukocyte antigen-conferred susceptibility to Type 1 diabetes. Diabet Med 2011; 28:965–971.
7. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: Systematic review and meta-analysis of observational molecular studies. BMJ 2011; 342:d35.
8. Li JB, Xiao B, Xiang Y. Immune function of vitamin D in type 1 diabetes mellitus. Int J BioMed 2014; 4:67–71.
9. Meyer MB, Goetsch PD, Pike JW. A downstream intergenic cluster of regulatory enhancers contributes to the induction of CYP24A1 expression by 1alpha, 25-dihydroxyvitamin D3. J Biol Chem 2010; 285:599–610.
10. Smolders J, Peelen E, Thewissen M, Hupperts R. The relevance of vitamin D receptor gene polymorphisms for vitamin D research in multiple sclerosis. Autoimmun Rev 2009; 8:621–626.
11. Bouillon R, Carmeliet G, Verlinden L, Mathieu C. Vitamin D and human health: Lessons from vitamin D receptor null mice. Endocr Rev 2008; 29:726–776.
12. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev 2012; 12:127–136.
13. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: New etiological and therapeutic considerations. Ann Rheum Dis 2007; 66:1137–1142.
14. Riachy R, Vandewalle B, Moerman E. 1,25-dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. Apoptosis 2006; 11:151–159.
15. Abd-Allah SH, Pasha HF, Hagrass HA, Alghobashy AA. Vitamin D status and vitamin D receptor gene polymorphisms and susceptibility to type 1 diabetes in Egyptian children. Gene 2014; 536:430–434.
16. Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes. J Pediatr 2009; 154:132–134.
17. Chun RF. New perspectives on the vitamin D binding protein. Cell Biochem Funct 2012; 30:445–456.
18. Yousefzadeh *P* , Shapses SA, Wang X. Vitamin D binding protein impact on 25-hydroxyvitamin D levels under different physiologic and pathologic conditions. Int J Endocrinol 2014; 981581:6.
19. Negri AL. Proximal tubule endocytic apparatus as the specific renal uptake mechanism for vitamin D-binding protein/25-(OH) D3 complex. Nephrology 2006; 11:510–515.
20. Chaykovska L , Heunisch F, von Einem G, Alter ML. Urinary vitamin D binding protein and KIM-1 are potent new biomarkers of major adverse renal events in patients undergoing coronary angiography. PLoS ONE 2016; 11:e0145723.
21. Jassil NK, Sharma A, Bikle D, Wang X. Vitamin D binding protein and 25-hydroxyvitamin D levels: Emerging clinical applications. Endocrine Pract 2017; 23:605–613.
22. Blanton D, Han Z, Bierschenk L, Wang H. Reduced serum vitamin D-binding protein levels are associated with type 1 diabetes. Diabetes 2011; 60:2566–2570.
23. Luebbering N, Abdullah S, Chowdhury CS, Lane A. Vitamin D binding protein and complement factor C5a influence neutrophil chemotaxis following HSCT. Biol Blood Marrow Transplant 2019; 25:S162–S163.
24. Gomme PT, Bertolini J. Therapeutic potential of vitamin D-binding protein. Trends Biotechnol 2004; 22:340–345.
25. Kim HJ, Ji M, Song J, Moon HW, Hur M, Yun YM. Clinical utility of measurement of vitamin D-binding protein and calculation of bioavailable vitamin D in assessment of vitamin D status. Ann Lab Med 2017; 37:34–38.
26. Penttilä I, Penttilä K, Holm P, Laitinen H, Ranta P, Torronen J, Rauramaa R. Methods, units and quality requirements for the analysis of haemoglobin A1c in diabetes mellitus. World J Methodol 2016; 6:133–142.
27. Knip M, Simell O. Environmental triggers of type 1 diabetes. Cold Spring Harb Perspect Med 2012; 2:a007690.
28. Nagpal SN, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 2005; 26:662–687.
29. Kirac D, DincerY C, Gezmis H, Haklar G. VDBP, VDR mutations and other factors related with vitamin D metabolism may be associated with type 1 diabetes mellitus. Cell Mol Biol (Noisy-le-grand) 2018; 64:11–16.
30. Hewison M. Vitamin D and the immune system: New perspectives on an old theme. Endocrinol Metab Clin North Am 2010; 39:365–379.
31. Raab J , Giannopoulou EZ, Schneider S, Ziegler KAG. Prevalence of vitamin D deficiency in pre-type 1 diabetes and its association with disease progression. Diabetologia 2014; 57:902–908.
32. Setty-Shah N, Maranda L, Nwosu BU. Increased risk for vitamin D deficiency in obese children with both celiac disease and type 1 diabetes. Gastroenterol Res Pract 2014; 2014:561351.
33. Giri D, Pintus D, Burnside G, Mehta F. Treating vitamin D deficiency in children with type I diabetes could improve their glycaemic control. BMC Res Notes 2017; 10:465.
34. Miettinen ME, Smart MC, Kinnunen L, Reinert-Hartwall L. Genetic determinants of serum 25-hydroxyvitamin D concentration during pregnancy and type 1 diabetes in the child. PLoS ONE 2017; 12:e0184942.
35. Nam HK, Rhie YJ, Lee KH. Vitamin D level and gene polymorphisms in Korean children with type 1 diabete. Pediatr Diabetes 2019; 20:750–758.
36. Kim HY, Lee YA, Jung HW, Gu MJ. A lack of association between vitamin D-binding protein and 25-hydroxyvitamin D concentrations in pediatric type 1 diabetes without microalbuminuria. Ann Pediatr Endocrinol Metab 2017; 22:247–252.
37. Harinarayan CV. Vitamin D and diabetes mellitus. Hormones (Athens) 2014; 13:163–181.
38. Dunlop TW, Väisänen S, Frank C, Molnár F. The human peroxisome proliferator-activated receptor delta gene is a primary target of 1alpha, 25-dihydroxyvitamin D3 and its nuclear receptor. Mol Biol 2005; 349:248–260.
39. Kositsawat J, Freeman VL, Gerber BS, Geraci S. Association of A1C levels with vitamin D status in U.S. adults: Data from the National Health and Nutrition Examination Survey. Diabetes Care 2010; 33:1236–1238
40. Soliman GT, Ali BA, Mohamed AA, Mahmoud AM, Abdellatif AA. Assessment of vitamin D status in Egyptian children with type-1 diabetes mellitus. J Diabetes Metab 2015; 6:573.
41. Thrailkill KM, Jo CH, Cockrell GE. Enhanced excretion of vitamin D binding protein in type 1 diabetes: A role in vitamin D deficiency?. J Clin Endocrinol Metab 2011; 96:142–149.
42. Sollid ST, Hutchinson MY, Berg V, Fuskeva OM. Effects of vitamin D binding protein phenotypes and vitamin D supplementation on serum total 25(OH) D and directly measured free 25(OH) D. Eur J Endocrinol 2016; 174:445–452.