Available online at www.medicinescience.org

Medicine Science International Medical Journal

ORIGINAL ARTICLE

Medicine Science 2022;11(4):1603-7

Evaluation of vitamin D, vitamin B12 and Hemoglobin HbA1c levels in patients with type 1 diabetes mellitus

Kamile Yucel[1], Berna Bayir[2], Hatice Yildirim[3]

[1]KTO Karatay University, Faculty of Medicine, Department of Medical Biochemistry, Konya Turkey
[2]KTO Karatay University, School of Health Sciences, Department of Public Health, Konya, Turkey
[3]Necmettin Erbakan University, Faculty of Medicine, Department of Blood Collection

Received 12 August 2022; Accepted 01 September 2022
Available online 28.11.2022 with doi: 10.5455/medscience.2022.08.184

Abstract

We aimed to evaluate the Vitamin D, Vitamin B12 and Hemoglobin A1c Levels in patients with T1DM. This study is a retrospective cross-sectional study. We classified patients as <7.0% (good glycemic control) and ≥7% (poor glycemic control) based on HbA1c levels. Moreover, we divided the patients into four groups based on serum vitamin D concentrations. This study included 468 patients (257 females and 211 males) with T1DM. The present study revealed that the prevalence of vitamin D deficiency among children with T1DM was very high (49.57%). We found that the vitamin D, vitamin B12, ferritin, HGB and RBC levels were significantly lower in women than in men. The overall prevalence of poor glycemic control was 6.4%. When the groups we divided according to HbA1c levels were compared; we found that the fasting blood glucose and vitamin B12 were significantly lower, while insulin and Mg levels were significantly higher in the good glycemic control group compared to the poor glycemic control group. We found that as vitamin D increases, HbA1c, insulin and creatinine levels decrease, and vitamin B12 levels increases. The negative correlation of vitamin D levels with insulin levels (r:-0.320, p<0.01) and HbA1c levels (r:-0.187, p<0.01) was statistically significant . Our findings showed that, keeping the vitamin D levels high in T1DM patients is important in regulation of glycemic control. Considering the frequency of pernicious anemia in patients with T1DM, it is important to follow vitamin D, vitamin B12 and HbA1c levels in these patients.

Keywords: HbA1c, Type 1 diabetes mellitus, vitamin B12, vitamin D

Introduction

Diabetes mellitus (DM) is a chronic disease with an increasing prevalence worldwide. Two main groups of DM have been defined as Type 1 (immune-based) and Type 2 [1,2]. Type 1 DM occurs when the beta cells in the pancreas that produce the insulin are damaged as a result of an autoimmune process, and its pathogenesis is multifactorial. In general, 5-10% of the diabetes cases in the society are T1DM cases. The prevalence of T1DM in childhood differs between countries (regions) [3,4]. Although there are many factors that predispose children to chronic complications of diabetes, the strongest predictor of diabetes is glycemic control. Since type 1 diabetes patients have to use insulin, it is very important to adjust the insulin dose in maintaining glycemic control [5,6]. Long-term glycemic control is achieved by measuring glycosylated hemoglobin (HbA1c) [7]. While the HbA1c level is below 6% in the people without diabetes, it can exceed 10% in uncontrolled diabetic patients [8].

Vitamin D deficiency is very common in patients with DM. In recent years, the extraskeletal effects of vitamin D have attracted attention [9]. It has been suggested that the vitamin D directly affects beta cells in the pancreas and is therefore associated with the pathogenesis, treatment, and prognosis of T1DM and T2DM [10,11]. It is thought that the active vitamin D increases insulin sensitivity in target cells, and has a direct and indirect protective effect on beta-cells with its effect on the immune response [11,12]. The country where T1DM is most common in the world is Finland, and it has been found that the vitamin D levels are lower in people especially in the northern part of the country, which is exposed to less sunlight. In a Finnish study on the effect of adding vitamin D

*Corresponding Author: Kamile Yucel, *KTO Karatay University, Faculty of Medicine, Department of Medical Biochemistry, Konya Turkey*
E-mail: kamile_yucel@hotmail.com

to the diet, it was shown that vitamin D supplementation reduced the risk of developing T1DM [13]. A remarkable reduction in vitamin D levels in patients with T1DM has been demonstrated in various epidemiological studies [14,15].

Patients with T1DM are approximately three times more likely to develop the vitamin B12 deficiency compared to the general population. As a result of the studies carried out in Type 1 Diabetes, it has been understood that some genes that are important for the control of the body's immune system play a role in this type of diabetes. Immunological factors and autoantibodies caused by genetic differences prevent vitamin B12 absorption by binding to intrinsic factor. Intrinsic factor deficiency or non-function means that the vitamin B12 cannot be absorbed properly. Pernicious anemia is also common due to the vitamin B12 deficiency in patients with T1DM [16,17].

Considering the fact that individuals with T1DM have multiple risk factors, HbA1c, vitamin D and vitamin B12 levels of individuals in this population have special importance in childhood. Based on this information, we aimed to evaluate vitamin D, vitamin B12, HbA1c levels in patients with T1DM and compare them with other laboratory parameters.

Material and Methods

Study population

The study was carried out retrospectively. After the approval of the ethics committee, patients diagnosed with T1DM in the Necmettin Erbakan University between January 1, 2012 and January 1, 2022 were retrospectively analyzed. A total of 468 patients with T1DM were included in the study. The age, gender and laboratory data of the patients were scanned retrospectively from the hospital automation system and the data were exported in the excel.

The inclusion criteria for the study were: aged <18 years, being diagnosed with T1DM, having no other additional disease diagnosis in the system, and having vitamin D, vitamin B12 and HbA1c results.

The exclusion criteria for the study were: aged >18 years, having diagnosed with T2DM, having other additional disease diagnosis in the system and patients who were missing data for serum vitamin D, vitamin B12 and HbA1c.

According to the publication of the American Diabetes Association and the International Pediatric and Adolescent Diabetes Association (ISPAD), it should be aimed to keep HbA1c levels below <7.0% in T1DM patients [18]. Guided by this resource, we divided our patients into 2 groups according to their HbA1c levels. We categorized the HbA1c levels as <7.0% (good glycemic control) and ≥7% (poor glycemic control). Moreover, we divided the patients into four groups (quartiles) based on serum vitamin D concentrations as follows: quartile (Q)1, serum vitamin D <11.77 ug/L; Q2, serum vitamin D between 11.77 and 16.30 ug/L; Q3, serum vitamin D between 16.30 and 22.28 ug/L; and Q4, serum vitamin D >22.28 ug/L.

Statistical analysis

Statistical analysis of the data was performed using the SPSS 27.0 (IBM Corp, Armonk, N.Y., USA) package program. The conformity of the data to the normal distribution was examined using analytical methods (Kolmogrorov-Smirnov/Shapiro-Wilk tests). In the evaluation of numerical data, arithmetic mean±standard deviation, median (1st quartile-3rd quarter), minimum and maximum values were used; Frequency distributions and percentages were used to summarize categorical data. Chi-square ($\chi 2$) test was used to compare categorical data. The relationship between non-normally distributed numerical data and categorical data was evaluated with the Man-Whitney U test. Kruskal-Wallis test was used to evaluate three or more groups that were not normally distributed with numerical data. Posthoc Man-Whitney U test and Bonferroni correction were performed for pairwise comparisons between groups with significant Kruskal Wallis test results. Spearman correlation coefficient was used in the correlation analysis of non-normally distributed numerical variables. Type-1 error level was accepted as 5% for statistical significance.

Ethics committee approval was obtained from the Ethics Committee of KTO Karatay University, Faculty of Medicine, Non-Pharmaceutical and Medical Device Researches. (No: 2022/014 E.28194, Date: March,03,2022). The study was carried out in accordance with the Declaration of Helsinki.

Results

This study included 468 participants (257 females and 211 males) with T1DM with a median age of 11±4.00 (3.0–17.0). The mean of vitamin D levels of the patients was 16.30±9.50 and the mean of vitamin B12 levels was 404±199.99. While the vitamin D level was above the reference value (30ug/L<) in 7.47% of the patients, the vitamin D level was below the reference value (20-100 ug/L) in 49.57% of the patients. Vitamin B12 levels were above the reference range (197 ng/L<) except for 29 (6.19%) patients.

In the comparison of male and female patient groups, there was a statistically significant difference between the groups in terms of vitamin D, vitamin B12, fasting blood glucose, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin (HGB), Mean corpuscular volume (MCV), Red Blood Cells (RBC) and ferritin (Table 1).

Table 1. Comparison of some laboratory parameters in terms of gender

Laboratory findings	Female (median±SD) (n: 257)	Male (median ± SD) (n: 211)	p value
Age	11.00±14.15	10.35±3.82	0.84
Vitamin D (ug/L)	15.60±9.08	18.50±9.87	0.00**
Vitamin B12 (ng/L)	389.80±212.06	430.00±183.90	0.02*
Fasting glucose (mg/dL)	86.40±48.11	89.20±34.78	0.01*
HbA1c (%)	5.30±1.41	5.40±0.97	0.58
Insulin (mU/L)	13.97±10.11	15.90±15.90	0.77
Urea (mg/dL)	21.35±7.69	24.70±5.62	0.00**
Creatinine (mg/dL)	0.53±0.45	0.56±0.15	0.29
AST (U/L)	19.60±10.21	22.55±11.39	0.00**
ALT (U/L)	13.70±7.33	15.00±22.64	0.01*
TSH (mU/L)	2.39±6.15	2.49±2.81	0.98
Mg (mg/dL)	2.02±0.28	2.07±0.17	0.06
Fe (µg/dL)	72.80±30.08	81.30±37.87	0.28
Ferritin (ug/L)	31.10±28.12	37.91±30.23	0.01*
HGB (g/dL)	13.50±1.06	13.80±1.56	0.00*
MCV (fL)	82.40±5.98	79.50±1.56	0.00*
MCH (pg)	27.30±2.16	26.80±2.37	0.10
RBC (10^6/mm³)	4.90±0.42	5.18±0.44	0.00**

*p<0.05, **p<0.01

The overall prevalence of poor glycemic control was 6.4%. When the groups we made according to HbA1c levels were compared; the difference between the groups was significant in terms of vitamin B12, fasting blood glucose, insulin and Mg levels (Table 2).

When we compared the laboratory parameters in our grouping according to serum vitamin D levels, there were a significant difference between the groups in terms of age, vitamin B12, HbA1c, insulin, creatinine, AST and MCV. Table 3 summarizes the results of comparisons of demographics and laboratory measurements across different serum vitamin D quartiles. There were 116, 118, 117, and 117 subjects in Q1, Q2, Q3, and Q4, respectively. In Table 3 and Table 4, where some important correlations are given, we found that as vitamin D increases, HbA1c, insulin and creatinine decrease, and vitamin B12 increases.

Table 2. The comparison of the laboratory data between those with good and poor glycemic control

Laboratory findings	Good glycemic control (HbA1c <7.0%)(median ± SD) (n: 438)	Poor glycemic control (HbA1c ≥7%)(median ± SD) (n: 30)	p value
Age	11.00 ± 4.03	11.50± 3.58	0.33
Vitamin D (ug/L)	16.33± 9.49	15.81 ± 9.83	0.60
Vitamin B12 (ng/L)	398.50 ± 201.22	476.10±173.88	0.03*
Fasting glucose (mg/dL)	87.00 ± 18.85	173.70 ± 116.78	0.00**
Insulin (mU/L)	14.50 ± 8.62	6.90± 3.2	0.00**
Urea (mg/dL)	23.30 ± 6.97	22.20± 5.50	0.48
Creatinine (mg/dL)	0.54 ± 0.35	0.56 ± 0.12	0.81
AST (U/L)	21.15 ±11.11	17.50 ± 5.64	0.17
ALT (U/L)	14.40 ± 16.92	11.60 ± 5.62	0.07
TSH (mU/L)	2.48 ± 6.41	1.69 ± 1.63	0.12
Mg (mg/dL)	2.06 ± 0.24	1.91 ± 0.10	0.00**
Fe (µg/dL)	75.65 ± 32.53	104.62 ± 20.18	0.23
Ferritin (ug/L)	33.73 ± 22.13	22.23 ± 10.69	0.08
HGB (g/dL)	13.60 ± 1.33	14.00 ± 1.42	0.53
MCV (fL)	81.00 ± 6.03	81.80 ± 5.82	0.93
MCH (pg)	27.10 ± 2.24	27.11± 2.61	0.91
RBC (10^6/mm³)	5.02 ± 0.46	5.07 ± 0.23	0.55

*p<0.05, **p<0.01

Table 3. Association between demographics and laboratory data with Vitamin D concentration

Laboratory findings	Q1 (n: 116)	Q2 (n: 118)	Q3 (n: 117)	Q4 (n: 117)	p value
Age	13.00± 3.73[a,b]	11.00±3.60[a]	10.00±3.78	9.00±4.45[b]	0.00**
Vitamin B12 (ng/L)	334.80±158.41[a,b]	385.50±175.79[c]	430.00±198.25[a]	497.00±228.59[b,c]	0.00**
F. Glucose (mg/dL)	89.00±36.65	88.35±41.61	88.10±58.28	85.45±19.92	0.05
HbA1c (%)	5.40 ± 1.44[a,b]	5.40 ± 1.46	5.30± 1.05[a]	5.20±0.84[b]	0.00**
Insulin (mU/L)	19.32±7.95[a]	14.42±9.68	13.65±12.79	8.66±8.93[a]	0.00**
Urea (mg/dL)	21.30± 4.79	22.25±5.62	25.30±9.42	23.95±6.12	0.11
Creatinine (mg/dL)	0.60 ±0.16[a]	0.54 ± 0.11	0.54±0.60	0.47±0.14[a]	0.00**
AST (U/L)	20.65 ± 16.61	19.55±5.90[a]	20.80±7.34	24.30±9.23[a]	0.03*
ALT (U/L)	14.40 ± 14.88	14.20 ± 7.13	14.65±22.66	13.35±17.25	0.77
TSH (mU/L)	2.53± 3.52	2.63 ±3.30	2.47±3.20	2.34±1.94	0.12
Mg (mg/dL)	2.02 ± 0.37	2.06 ± 0.18	2.00±0.15	2.08±0.11	0.34
Fe (µg/dL)	71.30 ±26.62	99.30±28.30	65.50±40.05	76.00±30.90	0.38
Ferritin (ug/L)	38.28± 41.15	33.73 ± 32.10	28.80±39.32	37.47±26.93	0.51
HGB (g/dL)	13.60± 1.39	13.80 ± 1.27	13.50±1.42	13.60±1.23	0.67
MCV (fL)	83.10± 7.10[a]	79.50±4.40[a]	81.40±5.50	80.30±6.19	0.03*
MCH (pg)	27.40 ± 2.66	26.50± 1.76	27.25±2.10	27.20±2.42	0.13
RBC (10^6/mm³)	4.91 ±0.42	5.11 ±0.38	5.06±0.46	5.04±0.50	0.21

Quartile (Q)1, serum vitamin D <11.77 ug/L; Q2, serum vitamin D between 11.77 and 116.30 ug/L; Q3, serum vitamin D between 16.30 and 22.28 ug/L; and Q4, serum vitamin D >22.28 ug/L; A,b,c,: Differences between pairs are indicated by the same letters; *p<0.05 **p<0.01

Table 4. Pearson's correlation coefficients within the patients

Correlations	Correlation coefficient (r)	Level	P value
Age- Creatinine	0.753	High	p<0.01
Age-AST	-0.606	Moderate	
İnsülin-Folic acid	-0.429	Weak	
Age-HGB	0.382	Weak	
HGB-Fe	0.342	Weak	
Age- HbA1c	0.323	Weak	
İnsülin-Vitamin D	-0.320	Weak	
Vitamin D- Vitamin B12	0.318	Weak	
İnsülin-Vitamin B12	-0.249	Weak	
Age-Vitamin D	-0.240	Weak	
Vitamin D- Creatinine	-0.231	Weak	
HbA1c- Vitamin D	-0.187	Low	

AST: aspartate aminotransferase; HGB: hemoglobin; p<0.05 statistical significance

Discussion

Diabetes mellitus is a chronic disease that affects glucose metabolism, which is the body's most important energy source, and can cause dysfunction in various organs in the long term. As in our study, the prevalence is higher in female than in male [19]. In our study, we found that the vitamin D, vitamin B12, ferritin, HGB and RBC levels were significantly lower in women than in men. Age, exposure to sunlight, diet and weight, as it is a fat-soluble hormone, are important factors that change vitamin D levels. We think that HGB and RBC levels are lower in female compared to male due to menstrual bleeding. In a study conducted with 100 (50 female, 50 male) T1DM patients in 2019, it was emphasized that vitamin D levels in female were lower than in male (p< 0.05) [3]. Koshy et al., in their study with 90 patients with T1DM, stated that they did not find any difference between male and female groups in terms of vitamin B12 levels [20].

Glycosylated hemoglobin (HbA1c) is a good indicator of metabolic control in the initial diagnosis and subsequent follow-up of diabetes. In our study, in the grouping we made according to HbA1c levels, we found that the fasting blood glucose and vitamin B12 were significantly lower, while insulin and Mg levels were significantly higher in the good glycemic control group compared to the poor glycemic control group. Regular use of insulin in the good glycemic control group may have regulated HBA1c levels and fasting blood glucose. There are many factors that affect Vitamin B12 levels for T1DM. Autoimmune factors, nutrition, malabsorption and external vitamin supplements can change the blood levels of this vitamin. A limited number of studies have reported low levels of vitamin B12 in patients with T1DM [16,20], but no comparison has been made according to HbA1c levels. In the results of a study conducted with 90 patients with T1DM in 2012, it was reported that the vitamin B12 levels are low in T1DM, and there is a negative but insignificant correlation (r: -0.21, p: 0.11) between HbA1c and vitamin B12 [20]. Magnesium (Mg) is an essential mineral. In T1DM and T2DM, circulating Mg levels decrease with increased urinary magnesium excretion due to diabetic ketoacidosis and glucosuria [21,22]. A study conducted with 241 patients with T1DM in 2022 emphasized that as Mg levels increase, HbA1c levels decrease and mg is important in glycemic control [23].

Vitamin D is limitedly produced and stored in the organism. It is very valuable to synthesize the vitamin D from the cholesterol in the body with the effect of healthy cholesterol intake and sunlight. Ultraviolet B rays from the sun are the strongest source of the vitamin D. Body mass index, climatic differences and nutrition play an key role in vitamin D levels. The significance of vitamin D in diabetes has been repeatedly emphasized in various studies [10,11,13,24]. In their study, Hyppönen et al. evaluated 10,366 babies in terms of T1DM after about 30 years; they reported that the 9124 (88%) infants were given vitamin D regularly until the age of one, and the development of T1DM in these infants decreased by 80% in the future. This indicates that the vitamin D has an inhibitory role in the development of T1DM [13]. In our study, we found that the patients with high vitamin D levels were younger and had lower HbA1c, insulin and creatinine levels. In terms of correlations, there was a positive correlation (p<0.01) between vitamin D and vitamin B12. The negative correlation (p<0.01) of vitamin D levels with insulin levels and HbA1c levels was also among our remarkable results.

The results of a study conducted with 100 T1DM in 2019 showed that the 70% of T1DM children had low vitamin D levels [3]. In their study conducted in 2018, Bae et al. reported that the patients with T1DM had significantly lower levels of vitamin D compared to controls. In addition, the researchers divided the patients with T1DM into 3 groups according to their vitamin D levels and reported that although the statistical difference was not significant, the HbA1c levels were lower in the group with high vitamin D [25]. Contrary to these studies, there are also studies reporting that there is no relationship between serum vitamin D levels and T1DM [26,27]. Climate differences, dietary habits, presence of chronic diseases affect vitamin D levels significantly and these may be the reasons for the differences between studies. Studies in the literature have reported that groups with vitamin D deficiency have higher insulin levels [28,29]. Savastio et al. found that when children and adolescents with T1DM are given the vitamin D, there is a decrease in the fasting blood sugar and HbA1c levels [9]. The results of our study also support the importance of vitamin D in T1DM and are compatible with most studies in the literature.

Limitations of the study

Among the limitations of study are the retrospective nature of the study, the lack of information about the nutritional habits of the patients, the vitamin and mineral supplements they take, and the insulin dose they use. The fact that T1DM and other chronic disease presence information is obtained from the hospital automation system is our other important limitations. In addition, we do not have data on how many years patients have been using insulin.

Conclusion

Type 1 Diabetes is a disease characterized by vitamin D and vitamin B12 deficiency. HbA1c is important in glycemic control. The present study revealed that the prevalence of vitamin D deficiency among T1DM children was very high. Our study results revealed the significance of vitamin D in T1DM. We found that the higher the vitamin D levels, the higher the vitamin B12 levels. Since the disease starts at an early age in type 1 DM, we recommend frequent monitoring of serum vitamin D, vitamin B12 and HbA1c

levels in these patients.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Ethics committee approval was obtained from the Ethics Committee of KTO Karatay University, Faculty of Medicine, Non-Pharmaceutical and Medical Device Researches. (No: 2022/014 E.28194, Date: March,03,2022). The study was carried out in accordance with the Declaration of Helsinki.

References

1. Abela AG, Fava S. Why is the Incidence of Type 1 Diabetes Increasing? Curr Diabetes Rev. 2021;17:e030521193110.
2. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev. 2016;15:644-8.
3. ALkharashi NA. Estimation of vitamin D deficiency prevalence among Saudi children in Armed Forces Hospital and Riyadh Care Hospital in Riyadh, Kingdom of Saudi Arabia and its relation to type 1 diabetes mellitus. Saudi Med J. 2019;40:1290-3.
4. Haris B, Ahmed I, Syed N, et al. Clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus among children in Qatar. Sci Rep. 2021;11:1-9.
5. Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications - the Linköping diabetes complications study. Pediatr Diabetes. 2009;10:168–76.
6. Shibeshi MS, Daba AK, Meiso KM, Tadesse BT. Glycemic control among children and adolescents with diabetes in Southern Ethiopia: a cross-sectional study. BMC Endocr Disord. 2022;15;22:161:1-7.
7. David R, Weber JN. Diabetes Mellitus in Children. In: Kliegman RM, Geme JWS, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. Nelson textbook of pediatrics. 21th ed. Philadelphia,PA: Elsevier; 2020;3019–52.
8. True MW. Circulating biomarkers of glycemia in diabetes management and implications for personalized medicine. J Diabetes Sci Technol. 2009;1;3:743-7.
9. Savastio S, Cadario F, Genoni G, Bellomo G, Bagnati M, Secco G, Picchi R, Giglione E, Bona G. Vitamin D Deficiency and Glycemic Status in Children and Adolescents with Type 1 Diabetes Mellitus. PLoS One. 2016;8;11:1-13.
10. Holick M. Diabetes and vitamin D connection. Curr Diab Rep. 2008;8:393–8.
11. Wolden-Kirk H, Overbergh L, Cristesen HT, Brusgaard K, Mathieu C. Vitamin D and diabetes: its importance for beta cell and immune function. Mol. Cel. Endocrinol. 2011;347:106-20.
12. Nam HK, Rhie YJ, Lee KH. Vitamin D level and gene polymorphisms in Korean children with type 1 diabetes. Pediatr Diabetes. 2019;20:750-8.
13. 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;3;358:1500-3.
14. Janner M, Ballinari P, Mullis PE, Flück CE. High prevalence of vitamin D deficiency in children and adolescents with type 1 diabetes. Swiss Med Wkly. 2010;140:1-6.
15. Zabeen B, Nahar J, Ahmed B, et al. Vitamin D status in children and adolescents with type 1 diabetes in a specialized diabetes care centre in Bangladesh. Endocrinol Diabetes Metab. 2022;5:1-6.
16. Ashiq S. Vitamin B12 Deficiency in type I Diabetes. J Microbiol Molecular Genetics. 2020;1:44-9.
17. Perros P, Singh R, Ludlam C, Frier B. Prevalence of pernicious anaemia in patients with Type 1 Diabetes mellitus and autoimmune thyroid disease. Diabetic Med.2020;17:749-51.
18. American Diabetes Association. 13. Children and adolescents: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43:163-82.
19. Flotynska J, Uruska A, Michalska A, et al. Sexual Dysfunction Is a More Common Problem in Young Women with Type 1 Diabetes than in Healthy Women. J Sex Marital Ther. 2019;45:643-51.
20. Koshy AS, Kumari SJ, Ayyar V, Kumar P. Evaluation of serum vitamin B12 levels in type 1 diabetics attending a tertiary care hospital: A preliminary cross - sectional study. Indian J Endocrinol Metab. 2012;16:1:79-82.
21. Lecube A, Baena-Fustegueras JA, Fort JM, et al. Diabetes is the main factor accounting for hypomagnesemia in obese subjects. PLoS ONE. 2012;7:1-7.
22. Viktorínová A, Toserová E, Krizko M, Duracková Z. Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus. Metabolism. 2009;58:1477-82.
23. Oost LJ, van Heck JIP, Tack CJ, de Baaij JHF. The association between hypomagnesemia and poor glycaemic control in type 1 diabetes is limited to insulin resistant individuals. Sci Rep. 2022;19;12:1-7.
24. Mutlu A, Mutlu GY, Özsu E, et al. Vitamin D deficiency in children and adolescents with type 1 diabetes. J Clin Res Pediatr Endocrinol. 2011;3:179-183.
25. Bae KN, Nam HK, Rhie YJ, et al. Low levels of 25-hydroxyvitamin D in children and adolescents with type 1 diabetes mellitus: a single center experience. Ann Pediatr Endocrinol Metab. 2018;23:21-7.
26. Azab SF, Saleh SH, Elsaeed WF, et al. Vitamin D status in diabetic Egyptian children and adolescents: a case-control study. Ital J Pediatr. 2013;39:1-7.
27. Bierschenk L, Alexander J, Wasserfall C, et al. Vitamin D levels in subjects with and without type 1 diabetes residing in a solar rich environment. Diabetes Care. 2009;32:1977-9.
28. Holick MF. The vitamin D deficiency pandemic: a forgotten hormone important for health. Public Health Rev. 2010;32:267-83.
29. Tunc O, Cetinkaya S, Kizilgün M, Aycan Z. Vitamin D status and insulin requirements in children and adolescents with type 1 diabetes. J Pediatr Endocrinol Met. 2011;24:1037-41.