A study of 25-(OH)D_3 levels in children with type 1 diabetes mellitus and its influencing factors

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Abstract. The present study aimed to assess 25-(OH)D_3 levels, their influencing factors and their association in children with type 1 diabetes mellitus (T1DM). The medical records of children with T1DM were retrospectively collected from the Department of Endocrinology, Genetics and Metabolism, Shanxi Children's Hospital (Taiyuan, China), between January 2017 and December 2023, and designated as the T1DM group. The data of healthy children who underwent physical examinations as outpatients during the same period were collected and designated as the control group. Differences in 25-(OH)D_3 levels and the proportions of vitamin D deficiency and insufficiency between the two groups and among the subgroups [defined by age, sex, disease history, presence of diabetic ketoacidosis (DKA)/diabetic ketosis (DK), infection, and admission quarter] were analyzed, and the influencing factors were explored. The 25-(OH)D_3 levels in the T1DM group and its various subgroups (classified by age, sex, and residence) were lower than those in the control group and the corresponding subgroups, whereas the proportions of vitamin D deficiency and insufficiency were higher. The 25-(OH)D_3 level was negatively correlated with age. The 25(OH)D_3 levels and the proportions of vitamin D deficiency and insufficiency were significantly different among the T1DM subgroups, which were divided according to age, sex, whether newly diagnosed or complicated with DKA/DK or infection, and admission quarter Age, admission quarter, duration of disease, sex, place of residence and HbA_1C levels were identified as statistically significant factors affecting 25-(OH)D_3 levels. In conclusion, insufficiency or deficiency of vitamin D during childhood may be an important factor in the occurrence of T1DM and its complications. The 25-(OH)D_3 levels in the body are affected by several factors. Timely diagnosis and treatment of vitamin D deficiency in children may be helpful. However, due to the retrospective observational design of the present study and the absence of data on key confounders, prospective studies with standardized covariate collection are needed.

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Introduction

Type 1 diabetes mellitus (T1DM) is the most common type of DM in children. The pathogenesis of T1DM has not been elucidated, but it is considered to be mainly related to the destruction of pancreatic β cells by autoimmune responses and oxidative stress caused by genetic and environmental factors (1,2). The global incidence of T1DM has been increasing steadily at an average annual rate of 3-4% over the past 30 years, and the role of environmental factors in the occurrence of T1DM is increasingly being emphasized (1).

Vitamin D is a fat-soluble steroid hormone derivative. Under normal circumstances, 70-80% of vitamin D in the body is synthesized from 7-dehydrocholesterol in the human skin after ultraviolet irradiation and becomes biologically active after two hydroxylations. Serum 25-(OH)D_3 levels are typically used as an evaluation index of vitamin D levels *in vivo*. Vitamin D not only regulates calcium and phosphorus metabolism but also cell proliferation, differentiation, metabolism and immune functions (3,4). Vitamin D levels have been reported to be positively associated with the function of pancreatic β cells due to their immunoregulatory, anti-inflammatory and anti-oxidative effects, and vitamin D insufficiency or deficiency has been associated with the development of T1DM and its complications (3-5). In a meta-analysis, among children of different ethnicities and ages, those with T1DM had a higher incidence of vitamin D deficiency and lower 25-(OH)D_3 levels than healthy children (6). By contrast, vitamin D or active vitamin D supplementation has been suggested to be effective in preventing the incidence of T1DM (7). Therefore, the role of vitamin D in the onset, prevention and treatment of diabetes in children is receiving increasing attention.

In the present study, the 25-$(OH)D_3$ levels between children with T1DM and healthy children were collected and compared, and various factors that may affect 25-$(OH)D_3$ levels were analyzed to provide new ideas and a basis for the clinical prevention and treatment of T1DM in children.

Materials and methods

Subjects. The present study was retrospective in nature. Data were collected from electronic medical records, covering the period between January 2017 and December 2023. The study was approved by the Ethics Committee of Shanxi Medical University (Taiyuan, China; approval no. 2020sll003-3) and the Ethics Committee of Shanxi Children's Hospital/Shanxi Maternal and Child Health Hospital (Taiyuan, China; approval no. IRB-WZ-2024-032). The ethics committees approved the waiver of informed consent due to the retrospective nature of the study. All research was performed in accordance with relevant guidelines and regulations.

Inpatients with T1DM from the Department of Endocrinology, Genetics and Metabolism of Shanxi Children's Hospital who were treated between January 2017 and December 2023 were included in the T1DM group, and outpatients who underwent health examinations in the same location in the same period were included in the control group. The inclusion criteria for control subjects were: i) No history of diabetes or other metabolic diseases; ii) no chronic diseases affecting vitamin D metabolism, including chronic liver disease, chronic kidney disease, parathyroid disorders, inflammatory bowel disease or malabsorption syndromes; iii) no long-term use of medications known to affect vitamin D metabolism, such as glucocorticoids, anticonvulsants or antiretroviral agents; and iv) no acute illnesses at the time of inclusion. The inclusion criteria for patients with T1DM were inpatients who met the diagnostic criteria for T1DM, and who had no diseases or long-term use of drugs that affect calcium and vitamin D metabolism. For variables with missing data, a complete-case analysis was performed, and only patients with full data on all study variables were included. No imputation was used for missing data. A total of 86 patients were excluded from the T1DM group due to incomplete clinical data or the presence of other conditions affecting vitamin D metabolism. The diagnosis of T1DM was made according to the 1999 and 2019 World Health Organization diagnostic criteria for T1DM (8,9). The main data collected from children with T1DM included sex, age, place of residence, duration of disease, 25-$(OH)D_3$ level, random blood glucose (RBG) level, glycated hemoglobin (HbA1C) levels, and the presence of diabetic ketoacidosis (DKA), diabetic ketosis (DK) and infections. DKA and DK were diagnosed according to the 2014 guidelines issued by the International Society for Pediatric and Adolescent Diabetes (10). Data on sex, age, place of residence and 25-$(OH)D_3$ levels were collected from healthy children in the control group.

According to the medical history of the inpatients with T1DM, children who were hospitalized for the first time and newly diagnosed were divided into the newly diagnosed group, and those hospitalized more than once were divided into the established group. According to the recommendations for the prevention and treatment of the vitamin D deficiency and rickets released by the National Rickets Prevention and Treatment Research Collaboration Group in 2015 (11), children were divided into the following five subgroups based on 25-$(OH)D_3$ levels: Excess (>250 nmol/l), normal (≥50 and ≤250 nmol/l), insufficient (37.5-50 nmol/l), deficiency (≤37.5 nmol/l) and severe deficiency (≤12.5 nmol/l). The patients were also divided into corresponding subgroups based on age (<5 years old, 5-10 years old and ≥10 years old), sex (male and female), place of residence (city and rural), presence of DKA/DK or infections, and the admission quarter. The differences between or among the control and T1DM groups or different subgroups for T1DM, HbA1C, RBG and 25-$(OH)D_3$ levels, and the composition ratio of children with vitamin D insufficiency plus deficiency [25-$(OH)D_3$ below the normal level of 50 nmol/l] were compared, and the factors that may affect the 25-$(OH)D_3$ levels were analyzed.

Statistical analysis. GraphPad Prism 6.0 software (Dotmatics) was used for the statistical analysis. Measurement data with normal or approximate normal distribution are expressed as the mean ± standard deviation. For two-group comparisons, the unpaired t-test was used when variances were equal, and Welch's corrected t-test was used when variances were unequal. For multiple-group comparisons, one-way ANOVA followed by Tukey's test was applied when variances were equal; otherwise, the Kruskal-Wallis test was used, followed by Dun's post hoc test for pairwise comparisons. Skewed data are expressed as the median (interquartile range). The Mann-Whitney test was used for two-group comparisons, and the Kruskal-Wallis test was used for multiple-group comparisons, followed by Dun's post hoc test for pairwise comparisons. Qualitative data are expressed as n (%), and the differences in composition ratios were compared using the χ^2 test. For multiple comparisons, P-values were adjusted using Bonferroni's correction to control for Type I errors. Pearson correlation analysis was used to analyze the linear correlation between 25-$(OH)D_3$ levels and quantitative variables such as age, HbA1C and RBG in the T1DM group, and multiple linear regression was used to screen the variables affecting the 25-$(OH)D_3$ level. To evaluate the association between T1DM status and vitamin D status, logistic regression analysis was performed. Vitamin D status was dichotomized as insufficiency/deficiency [25-$(OH)D_3$ <50 nmol/l] vs. normal (≥50 nmol/l). Both crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All subgroup analyses were exploratory. No adjustment for multiple testing was applied, and results should be interpreted accordingly. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General information of the study subjects. As shown in Table I, 757 inpatients with T1DM and 136 healthy outpatients were included in the present study. The age distribution was consistent between the control group and the newly-diagnosed diabetes subgroup ($P>0.05$; data not shown), whereas the age distribution in the overall T1DM group differed from that in the control group ($P<0.0001$). No significant differences were observed in terms of sex or place of residence between the control and T1DM groups ($P>0.05$). Due to the significant age

Table I. General information of children in the control and T1DM groups.

		Sex		Place of residence		Age				
Groups	n	Male/female, n	P-value	City/rural, n	P-value	Median (IQR), years	P-value	<5 years, n	5-10 years, n	≥10 years, n
Control	136	67/69	0.1049[a]	73/63	0.6629	8.0 (5.0-11.0)	<0.0001[a]	25	77	34
T1DM	757	433/324		425/332		10.0 (7.0-12.0)		101	241	415
Newly diagnosed	324	157/167	<0.0001[b]	201/123	0.0058	8.0 (5.0-11.0)	<0.0001[b]	77	126	121
Established	433	276/157		224/209		11.0 (8.5-13.0)		24	115	294

[a]Comparison between control and TIDM groups; [b]comparison between newly-diagnosed and established groups. Skewed data are presented as median (IQR) and were analyzed using the Mann-Whitney U test. T1DM, type 1 diabetes mellitus.

difference, further analyses were adjusted for age to minimize potential confounding. Most newly-diagnosed children with T1DM were aged >5 years.

Lower 25-(OH)D_3 levels are present in inpatients with T1DM, especially in those newly diagnosed or in those cases complicated with DKA/DK or infection. As shown in Table II, 54.4% of the inpatients with T1DM had vitamin D insufficiency or deficiency, compared to only 13.2% in the control group (χ^2 test; P<0.0001), and as shown in Fig. 1A, the 25-(OH)D_3 level of the T1DM group was significantly lower than that of the control group (Mann-Whitney test, P<0.01). The 25-(OH)D_3 level in each age subgroup in the T1DM group was also significantly lower than that in the same age subgroup in the control group (all Mann-Whitney test with Bonferroni correction, P<0.01; Table II and Fig. 1B). Notably, the 25-(OH)D_3 levels in both T1DM and control groups decreased with age, and children <5 years had the highest 25-(OH)D_3 levels in both groups, whereas the proportion of patients with <50 nmol/l 25-(OH)D_3 was the lowest in the <5 years subgroup (all Kruskal-Wallis test with Bonferroni correction, P<0.05; Table II and Fig. 1B). Compared with those of the control group, the 25(OH)D_3 levels of the same sex or place of residence subgroups in the T1DM group were significantly lower, while the proportion of patients with <50 nmol/l 25(OH)D_3 was significantly higher in the T1DM group than in the control group (all Mann-Whitney test or χ^2 test with Bonferroni correction, P<0.01; Table II; Fig. 1C and D). No significant differences were observed in 25(OH)D_3 levels and the proportion of patients with <50 nmol/l 25(OH)D_3 between different sex or place of residence subgroups in the control group, whereas the 25(OH)D_3 level of females was lower and the proportion of patients with <50 nmol/l 25(OH)D_3 was higher in the T1DM group (all Mann-Whitney test or χ^2 test with Bonferroni correction, P<0.01; Table II; Fig. 1C and D). Even in the same subgroups with normal 25-(OH)D_3 levels, the 25-(OH)D_3 levels in the children with T1DM were significantly lower than those in the control group (Mann-Whitney test, P<0.01; Table II; Fig. 1E).

As shown in Table III and Fig. 2A, in children with T1DM who were newly diagnosed or in those cases complicated with DKA/DK or infection, lower 25(OH)D_3 levels, and higher RBG and HbA1c levels were noted, as well as higher proportions of patients with vitamin D insufficiency or deficiency (all Mann-Whitney test with Bonferroni correction, P<0.01; Table III). The proportions of patients with vitamin D insufficiency or deficiency were 63.0, 62.5 and 65.9% in newly diagnosed children, those cases complicated with DKA/DK and those with infection, respectively, compared with 48.0% in established T1DM inpatients, 46.1 in those without DKA/DK and 52.0% in those without infection (all Mann-Whitney test or χ^2 test with Bonferroni correction, P<0.01, Table III). In addition, the 25(OH)D_3 level in patients admitted to the hospital in the third quarter was higher than that in other quarters (Table III and Fig. 2B), meanwhile, RBG, HbA1c and the proportion of patients with vitamin D insufficiency or deficiency were lower (all Mann-Whitney test or χ^2 test with Bonferroni correction, P<0.0001; Table III).

Analysis of factors influencing 25-(OH)D_3 levels. As shown in Table IV, 25-(OH)D_3 level was negatively associated with age,

Table II. Between-group and within-group comparisons of the proportion of children with 25-(OH)D_3 levels <50 nmol/l.

Grouping basis subgroups	Control group, n (%)	T1DM group, n (%)	P-value
25-(OH)D_3 levels			
Excess	0 (0.0)	0 (0.0)	
Normal	118 (86.8)	345 (45.6)	
Insufficient	16 (11.8)	194 (25.6)	
Deficiency	2 (1.5)	216 (28.5)	
Severe deficiency	0 (0.0)	2 (0.3)	
25-(OH)D_3 <50 nmol/l	18 (13.2)	412 (54.4)	<0.0001[a]
Age, years			
<5	0 (0.0)	31 (30.7)	0.0034[a]
5-10	9 (11.7)	115 (47.7)	<0.0001[a]
≥10	9 (26.5)	266 (64.1)	<0.0001[a]
P-value	0.0103[b]	<0.0001[b]	
Sex			
Male	9 (13.4)	266 (61.4)	<0.0001[a]
Female	9 (13.0)	146 (45. 1)	<0.0001[a]
P-value	0.8625[b]	<0.0001[b]	
Residence			
City	11 (15.1)	217 (51.1)	<0.0001[a]
Rural	7 (11.1)	195 (58.7)	<0.0001[a]
P-value	0.8065[b]	0.0424[b]	

Percentages for age, sex, and residence were calculated within each group (T1DM or control) separately. For any given subgroup, the percentage with vitamin D insufficiency/deficiency [25-(OH)D_3 < 50 nmol/l]=(number of participants in that subgroup with 25-(OH)D_3 < 50 nmol/l/total number of participants in that subgroup) x100%. [a]Between-group comparisons of the proportion of patients with 25-(OH)D_3 level <50 nmol/l; [b]within-group comparisons of the proportion of patients with 25-(OH)D_3 level <50 nmol/l. T1DM, type 1 diabetes mellitus. The χ^2 test was used for comparisons of proportions. P<0.05 was considered to indicate a statistically significant difference.

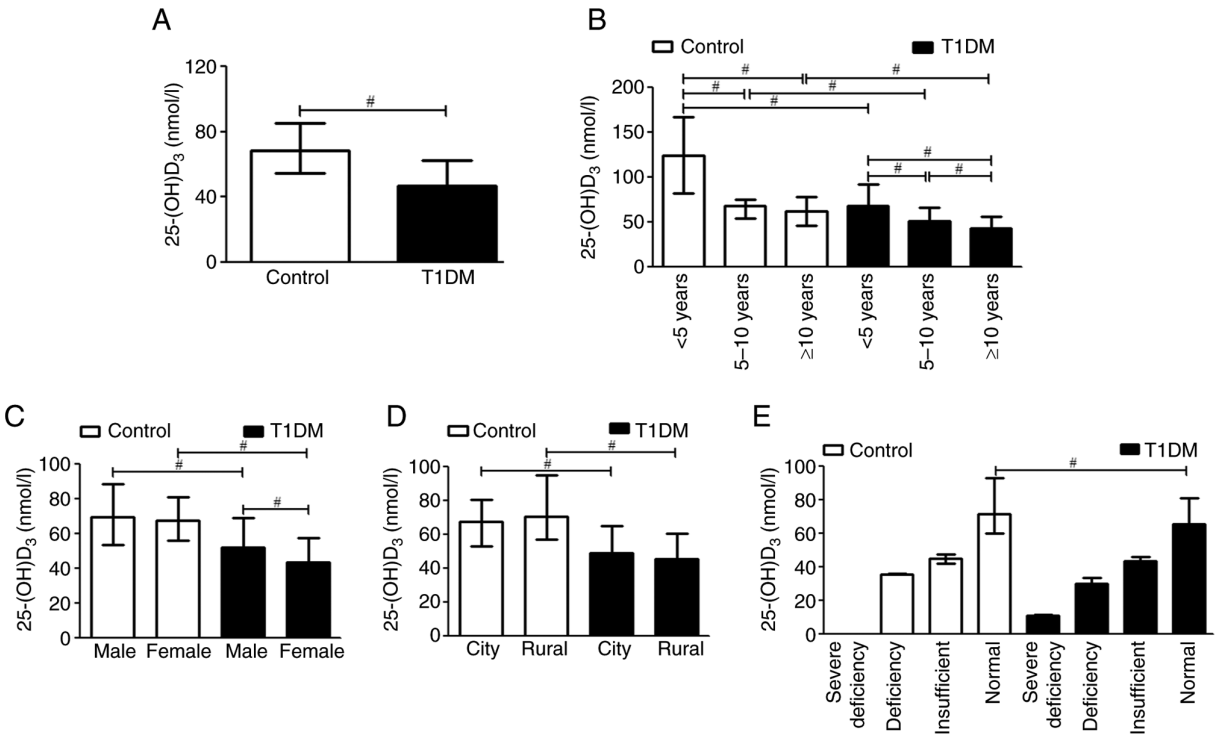

Figure 1. Between-group and within-group comparisons of 25-(OH)D_3 levels. (A) The comparison of 25-(OH)D_3 levels between the control group and T1DM group. (B-E) The between-group and within-group comparisons of 25-(OH)D_3 levels according to different grouping basis, including (B) age, (C) sex, (D) place of residence and (E) 25-(OH)D_3 level. #P<0.01.

Table III. Comparisons of 25-(OH)D_3 and related indices between or among T1DM subgroups.

		RBG		HbA1c		25-(OH)D_3		25-(OH)D_3 <50 nmol/l	
Subgroups	n	Value, mmol/l	P-value	Value, %	P-value	Value, nmol/l	P-value	n (%)	P-value
Normal range		<11. 1		4-5.6		50-250			
T1DM group	757	14.04 (7.66-22.58)		10.70 (8.30-12.95)		47.13 (35.72-62.66)		412 (54.4)	
Disease									
Established	433	11.28 (6.59-18.07)	<0.0001	8.70 (7.20-10.50)	<0.0001	50.69 (40.43-64.30)	<0.0001	208 (48.0)	<0.0001
Newly-diagnosed	324	19.37 (10.96-26.44)		12.60 (11.50-13.90)		42.64 (30.91-60.49)		204 (63.0)	
DKA/DK									
Without	373	9.04 (6.04-13.65)	<0.0001	8.40 (7.10-10.20)	<0.0001	51.25 (40.78-65.73)	<0.0001	172 (46.1)	<0.0001
With	384	20.22 (12.65-27.19)		12.50 (10.95-13.80)		43.72 (32.09-60. 16)		240 (62.5)	
Infection									
Without	625	12.45 (7.01-20.64)	<0.0001	10.30 (8.10-12.80)	<0.0001	48.39 (36.76-64. 17)	<0.0001	325 (52.0)	0.0048
With	132	19.83 (13.57-27.09)		12.05 (9.85-13.70)		41.15 (32.47-58.03)		87 (65.9)	
Complication status									
Without DKA/DK and infection	346	9.00 (6.03-13.38)	<0.0001	8.50 (7.10-10.20)	<0.0001	51.25 (40.78-65.73)	<0.0001	162 (46.8)	0.0021
With DKA/DK or infection	411	19.65 (12.30-26.52)		12.40 (10.70-13.75)		43.72 (32.09-60.16)		250 (60.8)	
Admission quarter									
1st quarter	135	14.71 (7.89-23.56)	<0.0001	10.90 (8.00-13.38)	<0.0001	43.67 (30.63-57.21)	<0.0001	85 (63.0)	<0.0001
2nd quarter	147	15.88 (9.71-25.72)		11.30±3.03		40.75 (31.01-52.26)		103 (70.1)	
3rd quarter	316	10.55 (6.36-17.75)		9.05 (7.40-11.70)		54.93 (42.47-68.25)		130 (41.1)	
4th quarter	159	18.81 (11.04-24.39)		12.03±2.42		43.14 (33.09-61.35)		94 (59.1)	

T1DM, type 1 diabetes mellitus; DKA, diabetic ketoacidosis; DK, diabetic ketosis; RBG, random blood glucose; HbA1C, glycated hemoglobin A1C. Measurement data with normal or approximate normal distribution are expressed as the mean ± SD. Skewed data are presented as the median (IQR). The Mann-Whitney U test was used for comparisons between two subgroups. The Kruskal-Wallis test was used for comparisons among multiple subgroups. The χ^2 test was used for comparisons of proportions. P<0.05 was considered to indicate a statistically significant difference.

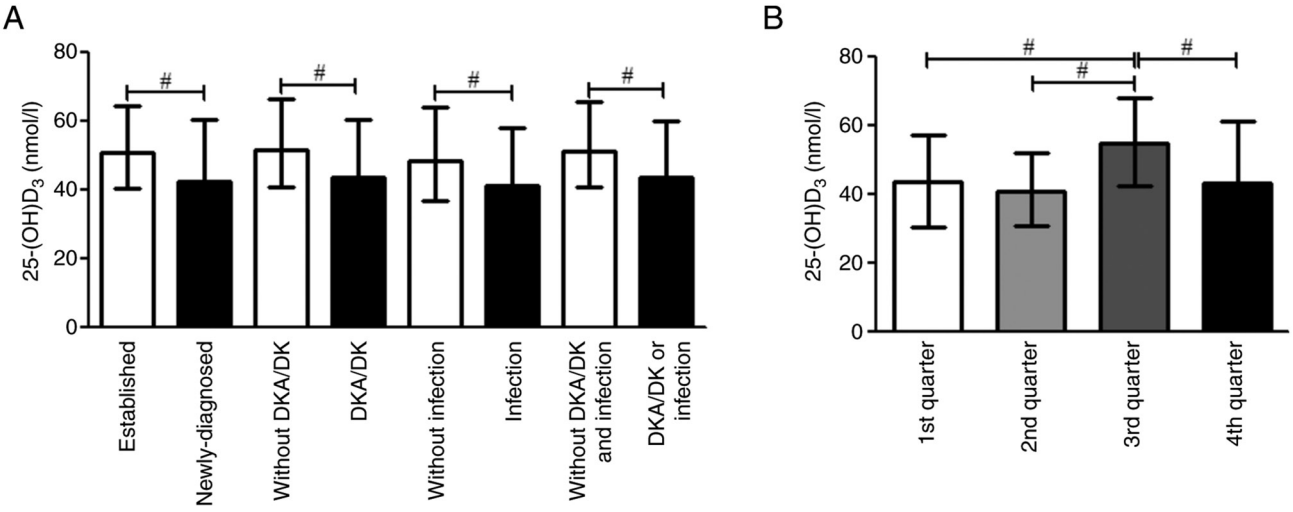

Figure 2. Comparisons of 25-(OH)D_3 between or among T1DM subgroups according to different grouping basis, including (A) whether newly diagnosed or complicated with DKA/DK or infection, and (B) the admission quarter. #P<0.01.

HbA1c and RBG, and positively associated with the duration of disease. As shown in Table V, using multiple linear regression analysis to screen the factors associated with 25-(OH)D_3 levels, age, month of admission, duration of disease, sex, place of residence and HbA_1C level were all significant factors associated with 25-(OH)D_3 levels (all P<0.05).

Discussion

In the present study, inpatients with T1DM, especially those who were newly diagnosed or whose cases were complicated with DKA/DK or infection, admitted in the third quarter had lower 25-(OH)D_3 levels, with a higher proportion of patients with vitamin D insufficiency or deficiency. Age, month of admission, duration of disease, sex, place of residence and HbA_1C were the factors significantly associated with 25-(OH)D_3 levels.

Vitamin D insufficiency or deficiency in childhood may be an important risk factor for the onset and progression of T1DM and development of its complications (2,5,7-9). The mechanism by which vitamin D affects the development of T1DM may be as follows: i) Polymorphisms of vitamin D metabolism genes: Genetic susceptibility to T1DM is affected by different polymorphisms of genes encoding the vitamin D receptor (VDR), vitamin D-dependent calcium-binding protein (VDBP) and vitamin D hydroxylase (10,11). Vitamin D regulates the amount of VDR and the level of VDBP in pancreatic islet β cells, acting as a transcription factor to regulate the expression of cell cycle, cell differentiation, apoptosis- and insulin-related genes, and promotes insulin synthesis and secretion (11,12). ii) Immunomodulatory effects: Vitamin D inhibits the expression of antigen-presenting cell surface costimulatory and MHC II molecules, inhibits the differentiation, maturation and antigen presentation ability of dendritic cells, and increases their apoptosis (3,11). Vitamin D inhibits the proliferation, differentiation and activation of T lymphocytes and promotes immune tolerance, as well as inhibiting the secretion of pro-inflammatory cytokines, and enhancing the production of anti-inflammatory cytokines (3,13). The vitamin reduces the proliferation of B lymphocytes and the production of autoantibodies, induces B cell apoptosis, prevents the overactivation of the immune system and reduces the destruction of normal islet β cells (3,11,13). iii) Antioxidant effect: Vitamin D can fight intracellular oxidative stress by reducing the myeloperoxidase content, protein carbonyl groups and glycation end products, and by upregulating the mRNA expression of superoxide dismutase and other anti-oxidative pathways (14,15). Vitamin D reduces the oxidative damage of chromosomal telomere sequences and mitochondria in pancreatic islet β cells, and reduces insulin resistance (11,14,15).

Although a high-quality ongoing prospective cohort study in Finland (16) showed that no significant differences were observed in the serum 25(OH)D_3 levels between 126 children who progressed to T1DM and 126 matched controls, and that the occurrence of T1DM was not associated with vitamin D status, the study had limited samples with vitamin D deficiency and left possible variables affecting vitamin D metabolism, such as dietary vitamin D intake, physical activity, and genetic polymorphisms of VDR and VDBP, unassessed. The present findings, derived from a larger case-control sample, contribute additional descriptive data on the association between T1DM and vitamin D status in a different geographic and clinical context, but do not resolve the causal question addressed by prospective designs (16). Serum 25(OH)D_3 levels in T1DM children were lower than those in controls (8,10,17), even when exposed to abundant sunlight. However, the reported differences in 25(OH)D_3 levels appeared after the diagnosis of T1DM and the associated complications may affect vitamin D metabolism. Therefore, changes in vitamin D levels during the development of T1DM need to be detected and analyzed in more ongoing prospective case-cohort studies.

Some prospective studies (18,19) have shown that vitamin D intake or 25(OH)D_3 levels during pregnancy and childhood are not significantly associated with the development of T1DM, as concluded in a review (1). Some observational studies have found that timely vitamin D supplementation in early childhood, especially infancy, reduces the risk of developing T1DM later in life. The effect of vitamin D on reducing

Table IV. Pearson's correlation analysis of 25-(OH)D_3 levels and quantitative variables in the type 1 diabetes mellitus group.

25-(OH)D_3	r	P-value
Age	-0.3589	<0.0001
HbA1C	-0.2275	<0.0001
RBG	-0.127	0.0021
Disease duration	0.1054	0.0037

Pearson correlation analysis was used to assess the relationships between 25-(OH)D_3 and age, HbA1c, RBG and disease duration. RBG, random blood glucose; HbA1C, glycated hemoglobin A1C.

Table V. Variable screening of 25-(OH)D_3 influencing factors by multiple linear regression analysis.

Parameter	b	P-value
(Intercept)	78.522	<0.001
Age	-2.818	<0.001
Admission month	-2.622	<0.001
Disease duration	1.13	0.002
Sex	5.565	0.002
Place of residence	4.399	0.016
HbA1C	-0.823	0.014

P<0.05 was considered to indicate a statistically significant difference.

the incidence of T1DM was dose-dependent, and the incidence of T1DM was the lowest in participants with a daily intake of vitamin D >2,000 IU (20,21). Therefore, the efficacy of vitamin D intake in preventing T1DM remains controversial and requires additional randomized controlled trials (RCTs) to provide evidence. However, for children at a high risk of developing T1DM, such as those with a T1DM family history, islet autoantibodies and high-risk HLA genotypes, vitamin D insufficiency and deficiency should be diagnosed and treated promptly in the first few years of life, given the greater benefits of vitamin D and the fact that prevention is better than a cure.

Many direct and indirect factors affect vitamin D in children, such as related gene polymorphisms, exposure time to sunlight, regular and appropriate vitamin D supplementation, diet, medications, underlying medical conditions, gestational age and maternal vitamin D status at birth (22). The present analysis was limited by the absence of data on several important confounders, including BMI, dietary vitamin D and calcium intake, daily outdoor activity time, sun protection habits, history of vitamin D supplementation, family history of diabetes and birth history (22-24). Failure to account for these factors means that the observed association between T1DM and low 25-(OH)D_3 levels may be subject to residual confounding. The present study found that age, month of admission, sex, place of residence, duration of disease and HbA_1C levels were the significant factors affecting 25-(OH)D_3 levels. With increasing age, 25-(OH)D_3 levels and the proportion of children with normal 25-(OH)D_3 levels decreased, and 25-(OH)D_3 levels were negatively correlated with age. Although the traditional peak incidence of T1DM is in children aged 10-14 years, recent studies indicate a shift toward younger age at onset, with the peak now occurring at 4-5.9 years and significant changes in age distribution observed more recently (12,14,25-27). The present study also found that the number of children aged 5-10 years was relatively high among newly-diagnosed children with T1DM. Studies have shown an overall downward trend in the proportion of children taking outdoor activities and regular/moderate and irregular/insufficient vitamin D supplementation with increasing age, which may lead to more severe vitamin D insufficiency and deficiency and a higher risk of T1DM (23,24,28). In addition, according to the admission quarter, in the present study, the 25-(OH)D_3 level and the proportion of children with normal 25-(OH)D_3 levels were highest in the third quarter, which may be related to the greater accumulation of vitamin D in the summer. Shanxi Province is located at a latitude between 35 and 40° north, and July and August are the hottest months of the third quarter, as well as being summer vacation time. During this period, the sunlight hours are long, ultraviolet rays are strong, children wear less and have more skin exposure, and outdoor activities are long, which can greatly increase the synthesis and storage of vitamin D in the body. In addition, the present study found that girls had lower 25-(OH)D_3 levels, and a lower proportion of girls had normal 25-(OH)D_3 levels, compared with boys, which may be related to the fact that girls usually spend less time outdoors (24). Although place of residence was also a significant factor affecting 25(OH)D_3 levels, no significant differences were observed in 25(OH)D_3 levels and the proportion of patients with 25(OH)D_3 levels <50 nmol/l between different place of residence subgroups within the control group. A significant difference was observed only in the proportion of patients with 25(OH)D_3 level <50 nmol/l between different place of residence subgroups in the T1DM group, which may require more sample data for analysis.

In addition to the aforementioned factors, T1DM can affect 25-(OH)D_3 levels, which may be related to oxidative stress caused by blood glucose fluctuations (2). Oxidative stress can lead to decreased 25-hydroxylase levels and 25-(OH)D_3 synthesis (11). In addition, some pancreatic islets can produce vitamin D, which binds to VDR to promote insulin synthesis and secretion (28,29). Oxidative stress can also damage the pancreatic islet cells (2) and reduce vitamin D production. The present study found that the RBG and HbA1C levels of newly-diagnosed T1DM children were significantly higher than the normal ranges and the levels of those children with established T1DM, whereas the 25-(OH)D_3 levels and the proportion of children with normal 25-(OH)D_3 levels were lower. 25-(OH)D_3 levels were negatively correlated with RBG and HbA1C, indicating that lower 25-(OH)D_3 levels in newly-diagnosed children with T1DM may be due to larger blood glucose fluctuations and more serious oxidative stress damage, which is consistent with the results of some studies (15,17,30). In addition, Vitamin D levels are inversely correlated with oxidative stress in patients with T1DM (31). Therefore, 25-(OH)D_3 may serve as an indirect indicator of oxidative stress in patients with T1DM.

In addition, DKA may affect vitamin D metabolism, and low vitamin D levels may contribute to a higher risk of DKA presentation in patients with T1DM (13,32-34). DKA can inactivate 1-α-hydroxylase, increase renal excretion of VDBP and decrease vitamin D levels (32). The present study found that the RBG and HbA1C levels in children with DKA/DK were significantly higher than those in children without DKA/DK, and the 25-(OH)D_3 levels and the proportion of children with normal 25-(OH)D_3 levels were lower, which is also consistent with the aforementioned study (32). Although, whether the patient case was complicated with DKA/DK was not a variable affecting 25-(OH)D_3 levels in the multiple linear regression analysis, univariate analysis revealed significantly lower 25-(OH)D_3 levels in children with DKA/DK, a clinically meaningful difference. Thus, clinical attention to vitamin D status in T1DM children with DKA/DK remains warranted.

Children with vitamin D insufficiency or deficiency are more susceptible to infections (3,34). When cases in children are complicated by infection, glycemic control is affected, and acute complications such as DKA and DK are more likely to occur, thus affecting 25-(OH)D_3 levels. In the present study, 106 of 132 co-infected children also experienced complications with DKA/DK. The mean RBG level was as high as 23.12 mmol/l, while the median 25-(OH)D_3 level was only 39.66 nmol/l, and the proportion of patients with 25-(OH)D_3 <50 nmol/l was up to 78/106 (73.6%). Therefore, prompt vitamin D supplementation in children with T1DM may reduce the occurrence of infections and the risks of DKA and DK.

Vitamin D deficiency can affect blood glucose control and the development of metabolic diseases in patients with T1DM, while vitamin D or active vitamin D supplementation is effective in preventing the incident of T1DM and improving the prognosis, including improving the function of residual pancreatic β cells and insulin resistance, reducing blood glucose and HbA1c levels in diabetic patients, and preventing and improving acute and chronic complications (5,35-39). Owing to the shorter observation duration in most studies, most children with diabetes have not yet developed chronic complications at the time of the study; therefore, relevant studies, long-term observation and follow-up are lacking (25). However, as a relatively safe, reliable, effective and inexpensive drug, vitamin D as an additional therapy may open new perspectives for the control of T1DM and the improvement of patient health (7,28).

The present study has certain limitations. First, the main limitation was the lack of dynamic and long-term monitoring of 25-(OH)D_3 levels in the patients. Second, the retrospective, observational design means that the findings only support associations, not causality. Reverse causation (i.e., disease state affecting vitamin D levels rather than the converse) and confounding by disease severity, acute metabolic stress (such as DKA) and hospitalization status are important limitations that must be considered when interpreting the observed associations (17,29,30). Specifically, it is plausible that the metabolic disturbances associated with T1DM, particularly during acute presentation with DKA, directly contribute to lower measured 25-(OH)D_3 levels, rather than vitamin D deficiency predisposing to T1DM onset. Third, the control group was not matched to the case group for age, and significant age differences existed between groups. Although adjustments were made for age in the logistic regression models, residual confounding may persist. Additionally, the control group (n=136) was substantially smaller than the case group (n=757). Consequently, subgroup comparisons between T1DM subgroups and their corresponding control subgroups (for example, stratifying by age or sex) may be too underpowered to detect small-to-moderate effects. Therefore, findings from underpowered subgroup analyses should be interpreted cautiously and considered hypothesis-generating rather than conclusive. Fourth, Due to the retrospective design, several key covariates, including dietary vitamin D/calcium intake, daily outdoor activity time, sun protection habits and history of vitamin D supplementation, were not routinely documented in the electronic medical records of Shanxi Children's Hospital (Taiyuan, China). Covariates such as BMI, family history of diabetes and birth history (for example, prematurity) should have been recorded in standard clinical practice; however, due to incomplete documentation, high missing rates or unstructured text formats, they could not be reliably extracted for analysis. An additional complexity was that BMI in children must be interpreted via age- and sex-specific percentiles or z-scores, requiring precise age, sex, height and weight data fields that were often incomplete or inconsistently recorded in this retrospective cohort. While such standardization is feasible in well-curated prospective datasets, applying it here would risk imputation errors, misclassification (especially at age extremes where BMI changes rapidly) and further sample size reduction. Forcing their inclusion would have led to a substantial reduction in sample size and introduced selection bias. Notably, any residual confounding from these unmeasured factors would likely bias the effect estimate toward the null, as lower vitamin D levels tend to cluster with unfavorable profiles of these variables (for example, higher BMI, less outdoor activity and no supplementation), all of which are independently associated with increased T1DM risk. Thus, the observed association is likely conservative. Moreover, all participants were recruited from the same geographic region during a similar calendar period, and lifestyle factors are relatively homogeneous across this pediatric population. Consequently, differential confounding between groups is unlikely. Prospective studies with standardized covariate collection are required to counter this limitation.. Fifth, this was a single-center, hospital-based study in a specific region of Shanxi Province. Vitamin D status is strongly influenced by geographic, climatic and local practice factors, which limits the generalizability of the findings to other populations or outpatient settings. Finally, the effects of vitamin D supplementation on patients with T1DM were not investigated.

In conclusion, in the present single-center retrospective case-control study, children with T1DM had significantly lower serum 25-(OH)D_3 levels and a higher prevalence of vitamin D insufficiency or deficiency compared with healthy controls, even after adjusting for age, sex and admission quarter. These associations were particularly pronounced in children with newly-diagnosed T1DM, those with DKA/DK and those with concurrent infections. Age, admission quarter, disease duration, sex, place of residence and HbA1c levels were significantly associated with 25-(OH)D3

levels. However, due to the observational design, the absence of matching for key confounders, and the lack of data on important covariates such as BMI, dietary intake and sun exposure, the findings support only associations and cannot establish causality. The possibility of reverse causation, whereby T1DM or its acute complications lead to reduced vitamin D levels, remains a major alternative explanation. Given the various benefits of vitamin D, the timely diagnosis and treatment of vitamin D insufficiency and deficiency are necessary, especially in infants and adolescents at the peak of growth and at high risk of diabetes. Future high-quality, large-scale prospective interventional RCTs and well-designed prospective cohort studies with comprehensive covariate assessment are needed to fully elucidate the role of vitamin D in T1DM, to clarify the direction of the association and to guide clinical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JJW and XJC were responsible for the study conceptualization and methodology. Collection of clinical data was performed by JSW and XTF. Data analysis was performed by GQF, JNX and XYY. JJW and JSW wrote the original manuscript. JJW and XJC reviewed and edited the manuscript. The study was supervised by JJW and XJC. All authors have read and approved the final manuscript. JJW and XJC confirm the authenticity of all the raw data.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Shanxi Medical University (Taiyuan, China; approval no. 2020sll003-3) and the Ethics Committee of Shanxi Children's Hospital/Shanxi Maternal and Child Health Hospital (Taiyuan, China; approval no. IRB-WZ-2024-032). The requirement for written informed patient consent was waived by the Ethics Committee of Shanxi Medical University, since this study was a retrospective investigation without any interventions, and no personal information was involved.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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