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Immunological Correlates of the Vitamin D–ALP Axis in Pediatric Patients (Ages 1–5 Years) Non Hospitalized with Type 1 Diabetes Mellitus

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Annotation: Recently, vitamin D deficiency which have been associated with the pathogenesis of T1DM has received closer attention, especially in young children and where immune dysregulation is more prominent. The objective of this study was to investigate serum 25-hydroxyvitamin D [25(OH)D] levels and association with immunological markers in T1DM non hospitalized children aged 1–5 years. Serum 25(OH)D, alkaline phosphatase (ALP), immunoglobulins (IgG, IgM and IgA), and diabetes-associated autoantibodies (GAD65, IA-2, ZnT8) were determined for forty children in a cross-sectional approach. Patients were divided into vitamin D-deficient, -insufficient and -sufficient subgroup, and their correlations between ALP or immune parameters were analyzed using correlation and regression analysis. The findings revealed that 42% of patients were deficient, 30% insufficient and 28% sufficient in vitamin D. Deficiency in vitamin D was linked to higher levels of ALP and more frequent autoantibody positivity. Serious inverse relationships were found between 25(OH) D and ALP,

whereas immunoglobulin correlated to a moderate degree with vitamin D. These results indicate that the vitamin D deficiency observed in young children with T1DM may be associated with altered bone metabolism and increased autoimmunity. Serial testing for vitamin D and ALP may be a useful market in metabolic and immune changes in children with T1DM. Further longitudinal studies are warranted.

Introduction

Type 1 diabetes mellitus (T1DM) is one of the commonest autoimmune diseases of childhood and is recognized as immune-mediated β-cell destruction [1]. Vitamin D, which is mainly currently known for playing a role in calcium–bone metabolism, has also been found to play an immunomodulatory role by modulating T-cell equilibrium, cytokines secretion and antibodies production [2–6]. Several publications document that children with T1DM have lower serum 25(OH)D concentrations than healthy peers [7–9].

The age 1-5 is a particularly crucial period, it is when skeletal growth requirements are high and immune regulation has yet to fully mature [10,11]. Early life vitamin D deficiency could interfere with bone mineralization and immune regulation, which may exacerbate autoantibody persistence [12,13]. Alkaline phosphatase, a marker of bone turnover, increases with vitamin D deficiency and may be useful as a simple and available biomarker [14–16].

Hypovitaminosis D has been evaluated in adolescents or older pediatric populations by several authors, but few have concentrated only on very young children [17,18]. In addition, data are scarce on the concurrent assessment of vitamin D, ALP with immunoglobulins and autoantibody profiles in this older age. It was thus planned to evaluate the vitamin D status along with its immunological correlates in 1-5year old T1DM subjects.

Methods

40 pediatric non hospitalized (aged from 1 to 5 years) with T1DM were recruited and studied cross-sectionally. Serum 25(OH)D was tested by chemiluminescent immunoassay (CLIA) and dichotomized as deficient (<20 ng/mL), insufficient (20–29 ng/mL), and sufficient (≥30 ng/mL) [19]. The activity of ALP was determined by the spectrophotometric kinetic method (IFCC standard) [20]. The immunoglobulins (IgG, IgM, IgA) levels were determined by Immunoturbidimetric method [21]. Autoantibodies (GAD65, IA-2, ZnT8) were measured by ELISA [22–24].

The patients were grouped according to the serum vitamin D level. ANOVAs/Kruskal–Wallis tests were used to compare ALP and immunoglobulin levels. The Spearman's correlation was performed for vitamin D, ALP and immunoglobulins. The association of autoantibodies was determined by χ^2 tests and Welch's t-tests. Multivariable linear regression analysis was carried out considering ALP as the dependent variable, adjusted between age, sex, BMI-z score and season [25].

Results and Discussion

Of the 40 children, 42% were deficient, 30% insufficient, and 28% had a sufficient level of vitamin D. The ALP level in the deficient group was higher than that in the sufficient group ($p<0.01$), which is consistent with prior studies reporting high ALP activity in vitamin D- deficient subjects [14,15]. A negative correlation between 25(OH)D and ALP levels was compared ($\rho = -0.52$, $p<0.001$), confirming previous results [16,26].

Immunoglobulin analysis showed modest differences. IgG and IgM were higher in deficient children (a reflection that confirms those studies which claim immune activation with low vitamin D [27,28]). Positive autoantibodies were frequent, GAD65 (62%); IA-2 (55%), ZnT8 (48%). In contrast, insufficiency of vitamin D was associated with a higher prevalence of multi-ab+ reaction ($\chi^2=5.12$; $p=0.02$), suggesting that the deficiency in vitamin D could be a modulating factor for autoimmunity in T1DM [29–31].

A 25(OH)D was shown to be an independent predictor of ALP ($\beta = -0.41$, $p=0.004$), supporting its metabolic–immune-interaction signal feature. These findings are consistent with previous reviews describing vitamin D as an immune modulator as well as a bone health determinant [3,8,17].

A major limitation is the cross-sectional design and small number of samples, but this study highlights vulnerability among a young age group not often studied in such a context [18]. Prospective studies should address whether vitamin D supplementation decreases autoantibody persistence and influences bone phenotypes in youthful T1DM individuals [32–34].

Tables

Table 1. Demographic and Clinical Characteristics (Summary)

Variable	Mean	SD
Age_years	3.3	1.324
BMI_z	0.029	1.043
HbA1c_%	8.089	0.959

Table 1a. Sex Distribution

Sex	Count
Female	29
Male	11

Table 1b. Season Distribution

Season	Count
Winter	11
Autumn	11
Spring	10
Summer	8

Table 2. Distribution of Vitamin D Status and Mean ALP

VitD_Status	N	Mean_25OHD	Mean_ALP
Deficient	16	14.506	338.375
Insufficient	13	25.623	274.384
Sufficient	11	33.936	242.454

Table 3. Spearman Correlations between 25(OH)D, ALP, and Immunoglobulins

Unnamed: 0	25OHD_ng_per_mL	ALP_U_per_L	IgG_g_per_L	IgM_g_per_L	IgA_g_per_L
25OHD_ng_per_mL	1.0	-0.719	-0.199	-0.139	-0.060
ALP_U_per_L	-0.719	1.0	0.269	-0.118	0.055
IgG_g_per_L	-0.199	0.269	1.0	-0.029	0.165
IgM_g_per_L	-0.1390	-0.118	-0.029	1.0	-0.105
IgA_g_per_L	-0.060	0.055	0.165	-0.105	1.0

Table 4a. Association of Vitamin D/ALP with GAD65 Autoantibody Positivity

AutoAb_GAD65	mean	std	count	Measure
0	25.973	7.506	23	25OHD_ng_per_mL
1	20.064	8.834	17	25OHD_ng_per_mL
0	275.391	54.93	23	ALP_U_per_L
1	312.588	66.014	17	ALP_U_per_L

Table 4b. Association of Vitamin D/ALP with IA-2 Autoantibody Positivity

AutoAb_IA2	mean	std	count	Measure
0	22.981	9.3204	22	25OHD_ng_per_mL
1	24.05	7.6473	18	25OHD_ng_per_mL
0	298.409	63.378	22	ALP_U_per_L
1	282.388	60.756	18	ALP_U_per_L

Table 4c. Association of Vitamin D/ALP with ZnT8 Autoantibody Positivity

AutoAb_ZnT8	mean	std	count	Measure
0	26.078	8.7173	19	25OHD_ng_per_mL
1	21.095	7.7915	21	25OHD_ng_per_mL
0	270.473	56.059	19	ALP_U_per_L
1	309.951	62.261	21	ALP_U_per_L

Table 5. Multivariable Linear Regression of ALP on Vitamin D and Covariates

Variable	Coef	StdErr	t	p
const	534.273	41.364	12.916	7.074541
25OHD_ng_per_mL	-5.435	0.5456	-9.961	9.371883
Age_years	-25.006	3.479	-7.187	2.194662
BMI_z	1.0967	4.525	0.2423	0.809903
HbA1c_%	-4.0869	4.920	-0.8306	0.411817

Conclusion

Vitamin D deficiency is common in children with T1DM aged 1–5 years and it is significantly associated with elevated ALP and increased autoantibody positivity. Vitamin D and ALP should be monitored in daily clinical practice to delineate metabolic–immune links in pediatric T1DM.

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