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ASSOCIATION BETWEEN VITAMIN D, GLYCEMIC CONTROL AND MICROVASCULAR COMPLICATIONS IN TYPE 1 DIABETES

*Associação entre vitamina d, controle glic*ê**mico e complicaçõ***es microvasculares no diabetes tipo 1***

Asociación entre la vitamina D, el control glicémico y las complicaciones microvasculares del Diabetes tipo I

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ABSTRACT

Objective: To assess the association between vitamin D levels, parameters of metabolic control and presence of microvascular complications in type 1 diabetes mellitus (T1DM) patients. **Methods:** Analytical and observational cross-sectional study of medical records of fifty patients carried out in 2016 in Fortaleza, Ceará, Brazil. Clinical and epidemiological data were analyzed: sex, age, BMI (body mass index), skin color, glycemic control, duration of diabetes, daily insulin dose, presence of microvascular complications, and vitamin D assay by chemiluminescence. Fisher's test, students's t test and Mann-Whitney U test were used with $p< 0.05$. **Results:** Vitamin D deficiency was seen in 34 (68%) patients, with a mean of 25(OH) vitamin D of 23.24±4.29 ng/mL in the Vitamin D deficiency group and 38.22±7.72 ng/mL in the normal Vitamin D group. In addition, 37 patients (78%) exhibited glycated hemoglobin above 7%, which was similar in booth groups. The daily insulin dose in the vitamin D deficiency group was higher than in the normal vitamin D group, 54.81±27.4 vs 55.55±19.2, but with no significant association with vitamin D levels. Vitamin D levels were not associated with clinical and epidemiological such as: sex, age, BMI, skin color, glycemic control, duration of diabetes, daily insulin dose and presence of microvascular complications or insulin daily dose. **Conclusion:** Vitamin D deficiency was present in most of the T1DM patients analyzed. However, such deficiency was not associated with the clinical and epidemiological variables analyzed.

Descriptors: Diabetes Mellitus; Vitamin D; Medical Records.

RESUMO

Objetivo: *Avaliar a associação entre os níveis de vitamina D, os parâmetros do controle metabólico e a presença de complicações microvasculares em pacientes portadores de diabetes mellitus tipo1 (T1DM).* ***Métodos****: Estudo transversal, analítico e observacional, realizado em 2016, em Fortaleza, Ceará, com prontuários de cinquenta pacientes. Investigaram-se os dados clínicos e epidemiológicos: sexo, idade, IMC (índice de massa corporal), cor da pele, controle glicêmico, duração do diabetes, dose diária de insulina, presença de complicações microvasculares e dosagem de vitamina D por quimiluminescência. Utilizaram-se os testes exato de Fisher, t-Student e Mann-Whitney com $p< 0,05$.* ***Resultados:*** *Observou-se deficiência de vitamina D em 34 (68%) pacientes, com média de 25(OH) de vitamina D, 23,24 ± 4,29 ng/mL no grupo vitamina D deficiente e 38,22± 7,72 ng/mL no grupo vitamina D suficiente. Além disso, 37 pacientes (78%) apresentaram hemoglobina glicada acima de 7% e semelhante nos dois grupos. A dose diária de insulina no grupo vitamina D deficiente foi maior que no grupo vitamina D suficiente, 54,81 ± 27,4 vs 55,55 ± 19,2, mas sem associação significativa com níveis de vitamina D. O nível sérico da vitamina D não se associou com parâmetros clínicos e epidemiológicos, como: sexo, idade, IMC, cor da pele, controle glicêmico, duração do diabetes, dose diária de insulina e presença de complicações microvasculares.* ***Conclusão:*** *A deficiência de vitamina D esteve presente na maioria dos pacientes com T1DM avaliados. No entanto, sem associação entre essa deficiência e as variáves clínicas e epidemiológicas analisadas.*

Descritores: *Diabetes Mellitus; Vitamina D; Registros Médicos.*

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RESUMEN

Objetivos: *Evaluar la asociación entre los niveles de vitamina D, los parámetros del control metabólico y la presencia de complicaciones microvasculares de pacientes con Diabetes Mellitus Tipo I (DM1).* ***Métodos****: Estudio transversal, analítico y observacional realizado en 2016 en Fortaleza, Ceará, con historiales clínicos de cincuenta pacientes. Se investigaron los siguientes datos clínicos y epidemiológicos: el sexo, la edad, el IMC (Índice de Masa Corporal), el color de la piel, el control glicémico, la duración del diabetes, la dosis diaria de insulina, la presencia de complicaciones microvasculares y la dosificación de vitamina D por quimioluminiscencia. Se utilizaron las pruebas ecxato de Fisher, t-Student y Mann-Whitney con p< 0,05.* ***Resultados:*** *Se observó la deficiencia de vitamina D en 34 (68%) pacientes con media de 25(OH) de vitamina D, 23,24 ± 4,29 ng/mL en el grupo de vitamina D deficiente y 38,22± 7,72 ng/mL en el grupo de vitamina D suficiente. Además, 37 pacientes (78%) presentaron hemoglobina glicosilada por encima del 7% y semejante para los dos grupos. La dosis diaria de insulina en el grupo de vitamina D deficiente ha sido mayor que en el grupo de vitamina D suficiente, 54,81 + 27,4 vs 55,55 + 19,2, pero sin asociación significativa con los niveles de vitamina D. El nivel sérico de vitamina D no se ha asociado con los parámetros clínicos y epidemiológicos como el sexo, la edad, el IMC, el color de la piel, el control glicémico, la duración del diabetes, la dosis diaria de insulina y la presencia de complicaciones microvasculares.* ***Conclusión:*** *La deficiencia de vitamina D se dio en la mayoría de los pacientes con DM1 evaluados. Sin embargo, no hubo asociación entre la deficiencia y las variables clínicas y epidemiológicas analizadas.*

Descriptores: *Diabetes Mellitus; Vitamina D; Registros Médicos.*

INTRODUCTION

Diabetes mellitus (DM) represents a group of metabolic diseases with diverse etiologies characterized by hyperglycemia resulting from defects in insulin secretion and/or action[1]. Type 1 diabetes mellitus (T1DM) accounts for 5 to 10% of diabetes cases, primarily resulting from autoimmune cell destruction of pancreatic β cells associated with changes in cellular immunity and mood and genetic predisposition[2-4].

The incidence of T1DM has increased about 3% a year[5]. In Brazil, its incidence rate is around 7.6/100,000 individuals under 15 years of age[2]. Environmental factors seem to influence the epidemiology of T1DM. These factors include: diet in childhood and adolescence, vitamin D level, sun exposure, viral diseases, breastfeeding duration, early weaning, and immunization[6].

In vivo studies have shown that 1,25 hydroxy (OH) vitamin D inhibits the expression of inflammatory cytokines, such as interleukin-1β, interleukin-6, tumor necrosis factor α (TNF-α), interferon γ, interleukin-8 (IL 8) and interleukin 12, in normal individuals[7]. Diabetes has shown an association of supplementation of 2000 IU of vitamin D with reduction of the inflammatory process and delay in the progression of the disease, with preservation of beta cell function, but without impact on glycemic control[8].

Supplementation of 25(OH) vitamin D during childhood and maternal exposure during pregnancy were associated with a reduction in the risk of developing T1DM. Children who took 2000 IU of vitamin D regularly had a relative risk (RR) of 0.22 (0.05-0.89), while children with suspected rickets during the first year of life had a RR of 3.0 (1.0-9.0) for risk of T1DM[7].

Newly diagnosed children or young adults with T1DM exhibit lower levels of 25 (OH) vitamin D than healthy controls[4,9]. These low levels were correlated with increased biomarkers of inflammation, including C-reactive protein and toll-like receptor (TLR) expression[10].

Studies have demonstrated a causal relationship between vitamin D deficiency and the presence of retinopathy in T1DM and T2DM. Pathophysiology involves angiogenesis and inflammation, causing damage to retinal vessels[11-13].

Vitamin D insufficiency may influence the pathogenesis of albuminuria and vitamin D replacement reduces proteinuria. In the diabetes control and complications trial (DCCT), patients with low levels of vitamin D were associated with a higher risk of microalbuminuria, but there was no evidence on loss of kidney function and development of hypertension[14]. The association between vitamin D levels and presence of peripheral neuropathy in T1DM in addition to exacerbation of symptoms was also described in a previous study[15].

With regard to glycemic control, the replacement of vitamin D in patients with T2DM assisted in the reduction of glycated hemoglobina. However, the same did not occur in T1DM[16]. The association of BMI with vitamin D status is still uncertain and vitamin D is believed to regulate adipocyte apoptosis, leading to reduced fat mass. However, this relationship was observed only in children with T2DM[16].

Hashimoto's thyroiditis (HT) occurs in 17% to 30% of patients with T1DM and approximately 25% of T1DM patients have thyroid antibodies, suggesting the presence of autoimmunity at the time of diagnosis[1]. Activation of T and B lymphocytes in T1DM may inhibit the expression of thyroid antigens leading to HT, and vitamin D would play a protective role in this process[17].

Regarding the role of vitamin D and its role in health promotion, research[18] emphasized that it is a nutrient of interest because of its importance not only in bone health but also in the prevention of cancer and diabetes, in the full functioning of the immune and neuropsychological systems, as well as in other conditions, such as in inflammatory processes and in cardiovascular disease[18].

Based on the evidence of the interrelations between the control of diabetes mellitus, the appearance of chronic complications and vitamin D levels, this study aimed to assess the association between vitamin D levels, parameters of metabolic control and presence of microvascular complications in patients with type 1 diabetes mellitus (T1DM).

METHODS

This is an analytical and observational cross-sectional study that used information from medical records of patients with T1DM receiving follow-up care at the Type 1 Diabetes Outpatient Clinic of the Walter Cantídio University Hospital of the Federal University of Ceará (*Hospital Universitário Walter Cant*ídio *da Universidade Federal do Ceará – HUWC/UFC*) from January 1st to 30th, 2016. The convenience sample included the medical records of the first 50 patients treated during the study period.

The demographic variables assessed were: sex, age, education (according to the guidelines of the Brazilian Ministry of Education and Culture), household income (in minimum wages) and self-reported skin color. Clinical variables were: age at diagnosis, disease duration, body mass index (BMI) assessed according to the values established by World Health Organization (WHO)[17], presence of microvascular complications, and total daily insulin dose. Laboratory variables were: vitamin D levels, glycated hemoglobin levels and anti-thyroid peroxidase (TPO) antibodies.

Vitamin D level was measured using chemiluminescent microparticle immunoassay (Automated Abbott Architect i2000SR). Patients were divided into 2 subgroups according to Vitamin D levels: 1) Sufficient vitamin D group if levels $\geq$ 30ng/ml and vitamin D deficiency group if levels < 30ng/ml[7]. Given the relevance of vitamin D for diabetic patients, its measurement became part of routine care in the service and its results are informed in the medical records.

Glycated hemoglobin was measured using high-performance liquid chromatography (HPLC) with a 7% cut-off value to discriminate good and poor control. Presence or absence of anti-TPO antibody was assessed. The search for association between autoimmune thyroid disease and type 1 diabetes mellitus is part of routine care in the service and the results are informed in the medical record.

The data were tabulated in 2007 Microsoft Excel and analyzed using SPSS version 20.0, Texas, USA. Descriptive statistics was expressed using frequency and percentage for qualitative variables and mean and standard deviation for continuous variables. The Shapiro-Wilk test was used to check the normal distribution of the quantitative variables; Levene's test was used to test the equality of variances; and Fisher's Exact test was used for the analysis of categorical variables. In the analysis of the groups according to vitamin D level, we used the Student's t-test for the variables with normal distribution and the Mann-Whitney test for the variables whose distribution was not normal. Maximum level of statistical significance for the tests was 5% ($p<0.05$). The variation used in all the variables was the standard error of the mean.

The study was approved by the Research Ethics Committee of the Walter Cantídio University Hospital (*Hospital Universitário Walter Cant*ídio – *HUWC*) of the Federal University of Ceará with Approval No. 1.383.656.

RESULTS

Data from 50 medical records of T1DM patients seen at the HUWC diabetes outpatient clinic were analyzed. Of the total sample, 15 (30%) were men. Mean age was 26.9 ± 11.13 years, with a minimum age of 10 and a maximum of 50 years, and a median of 26 years. As for the level of education, 22 (44%) had secondary education and 15 (30%) had primary education. Regarding skin color, 24 (48%) patients were white and 26 (52%) were non-white. The most frequent household income was less than 2 minimum wages, which was found in 22 (44%) patients (Table I).

Mean age at diagnosis and disease duration were 13.90 ± 9.4 years and 12.83 ± 7.8 years, respectively. Mean BMI was 24.05 ± 3.9, with a median of 24.0. The assessment of microvascular complications revealed nephropathy and neuropathy in 10 (20%) patients, followed by retinopathy in 8 (16%) patients (Table I). Regarding treatment, different insulin regimens were used by the patients. Mean total daily insulin dose was 55.31 ± 21.8 IU/day (Table I).

As for data on glycated hemoglobin, 39 (78%) patients exhibited values $\geq$7%, which indicates poor glycemic control. Regarding presence of thyroid dysfunction, 10 (20%) patients had hypothyroidism; of these, 30 (60%) had positive anti-TPO antibodies. In all, 16 (32%) patients of the study sample had sufficient vitamin D levels and 34 (68%) had poor vitamin D levels (Table I).

Vitamin D levels were not associated with demographic variables (BMI, sex and skin color) or with microvascular complications (retinopathy and neuropathy). Nephropathy was present in 8 (23.5%) patients in the vitamin D deficiency group and in 2 (12.5%) patients in the sufficient vitamin D group. Therefore, there was no statistically significant difference ($p=0.498$). (Table I).

Table I - Descriptive characteristics of the sample of patients with type 1 diabetes mellitus and association with serum vitamin D level. Fortaleza, Ceará, Brazil, 2016.

	Vitamin D Level						
	Total		Deficient		Sufficient		p
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	
Sex							
Men	15	30	8	23.5%	7	43.80%	0.191
Women	35	70	26	76.5%	9	56.30%	
Education							
Higher	12	24	9	26.5%	3	18.80%	0.925
Secondary	22	44	14	41.2%	8	50.00%	
Illiterate/primary	16	32	11	32.4%	5	31.30%	
Household income							
≤ 1 mw	24	48	16	47.1%	8	50.00%	1
≥ 2 mw	26	52	18	52.9%	8	50.00%	
Skin color							
White	24	48	18	52.9%	6	37.50%	0.372
Non-white	26	52	16	47.1%	10	62.50%	
Comorbidities							
Thyroidopathy	10	20	9	26.5%	1	6.30%	0.138
Retinopathy	8	16	5	14.7%	3	18.80%	0.699
Nephropathy	10	20	8	23.5%	2	12.50%	0.498
Neuropathy	10	20	7	20.6%	3	18.80%	1
Anti-TPO antibody	10	20	8	34.8%	2	22.20%	0.681
Treatment							
Insulin	40	80	27	79.4%	13	81.30%	1
Insulin + OA	10	20	5	14.7%	4	25.00%	0.442
HbA1C							
< 7%	11	22	6	17.6%	5	31.30%	0.297
≥7%	39	78	28	82.4%	11	68.80%	

Fisher's Exact Test; OA: oral antidiabetics; HbA1C: glycated hemoglobin.

The sufficient vitamin D group exhibited mean vitamin D levels of 38.22 ± 7.7, and the vitamin D deficiency group exhibited mean levels of 23.24 ± 4.2 (Table II).

The analysis of the association of demographic variables between the groups according to serum vitamin D levels revealed no differences in mean age. The age at diagnosis of diabetes was also similar between the groups, with a mean duration of diagnosis of 13.9 years (14.9 vs 13.4, p=0.60). However, thyroid disease was more frequent in patients in the vitamin D deficiency group, that is, 9 (26.5%) patients, thus increasing the power to 10% of the prevalence of thyroid disease in the vitamin D deficiency group. Such prevalence was significantly higher than in the sufficient vitamin D group (p=0.01) (Table II).

There was no evidence of an association between glycated hemoglobin levels and vitamin D levels in the T1DM patients analyzed. The total daily insulin dose used in the vitamin D deficiency group was higher than that in the sufficient vitamin D group (55.55 ± 19.2 vs. 54.81 ± 27.4); however, it was not significantly associated with vitamin D levels (Table II).

DISCUSSION

Studies have shown the association between vitamin D deficiency and T1DM[7-9,12,19]. A Finnish study showed that after starting vitamin D supplementation in 220 Finnish children from 2003 on, the incidence of type 1 diabetes reduced and reached a plateau[20].

Table II - Association of clinical and laboratory variables according to serum vitamin D levels of patients with type 1 diabetes. Fortaleza, Ceará, Brazil, 2016.

	Vitamin D Classification						
	Deficient (34)			Sufficient (16)			
Variables	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**p**
Age (years)	26.2	11.07	24.5	28.4	11.48	28.0	0.52
Age at diagnosis (years)	13.4	8.87	11	14.9	10.71	14.5	0.739
Disease duration (years)	12.6	8.36	11	13.4	6.83	12.5	0.479
BMI (Kg/m²)	24.4	3.47	24	23.4	4.97	22.6	0.453
Glycated hemoglobin	9.1	2.33	8.5	8.0	1.63	8.0	0.102
Daily insulin dose	55.6	19.22	52.5	54.8	27.44	53.5	0.913

Student's t-test, Mann-Whitney U test. SD: standard deviation; BMI (Kg/m²): body mass index (kilogram per square meter)

The prevalence of low levels of vitamin D is common in both the young and adult population, either because of low intake, low sun exposure or absorption disorders. Furthermore, it has become a public health problem[7,21,22]. High prevalence of lower levels of vitamin D in patients with T1DM is also described by other authors[7,21-23].

The present study found a prevalence of 68% of type 1 diabetic patients with vitamin D deficiency. In a similar study, the prevalence of vitamin D deficient patients among T1DM patients was 15%. Insufficient and sufficient vitamin D prevalence rates were 61% and 24%, respectively[20]. There were no differences in sex, skin color and BMI according to the data from the present research. A study of 30 children with T1DM also showed a high prevalence of vitamin D deficiency: 50% of the children had vitamin D deficiency and 45% had vitamin D insufficiency[22]. Another study of 60 adults with T1DM in Saudi Arabia found that 100% of the participants were vitamin D deficient[23]. Previous research detected vitamin D deficiency in 94.4% of 72 patients with diabetes and 58.5% of 41 healthy controls. In addition, severe vitamin D deficiency was more common in T1DM patients (60%) compared with controls (8.3%)[24].

A meta-analysis of observational studies suggests that the risk of developing T1DM is low in children who receive vitamin D supplementation compared with those who do not receive supplementation (odds ratio 0.71, 95%CI 0.60 to 0.84); in addition, supplementation between 7 and 12 months of age is more beneficial than between birth and 6 months of age[25].

The present study did not find an association of vitamin D levels with age or sex. Another study[24] found no difference in vitamin D levels among diabetic male and female children, although there was a higher prevalence of vitamin D deficiency among women in the non-diabetic population (65% vs 52.4%)[24].

Although meta-analyses[26,27] have shown that vitamin D deficiency is associated with an increased risk of developing T1DM, there is controversy over the effect of vitamin D action and glycemic control on T1DM. Studies have shown that patients who receive supplementation and achieve sufficient levels of vitamin D have a reduction in glycated hemoglobin, which is associated with an improvement in glycemic control. On the other hand, other studies have not found this association and are consistent with the findings of the present research[16,28,29].

In addition, there was no association between the total daily insulin dose used by patients and levels of vitamin D in the present study. This finding is similar to that of a previous study carried out with a T1DM population in São Paulo[8].

The severity of diabetic retinopathy was inversely related to vitamin D level in T2DM patients, but few data on microvascular complications in T1DM exist. There is an association between vitamin D deficiency and diabetic retinopathy, independent of the duration of diabetes and glycated hemoglobin[11]. Vitamin D receptors are present in the retina, and polymorphisms in these receptors may be responsible for the degree of severity of retinopathy, probably due to the angiogenic effect of vitamin D. This study did not show a significant association between vitamin D deficiency and presence of retinopathy, which is conistent with the Danish study conducted at the Steno Diabetes Center[12].

Two major classical T1DM studies, such as the DCCT (Diabetes Control and Complication Trial) and the EDIC (Epidemiology of Diabetes Interventions and Complications Study Research), did not demonstrate an association between low levels of vitamin D and the risk of developing nephropathy in patients with T1DM, which is consistent with our study[13].

Positive anti-TPO (anti-thyroyd peroxidase antibody), which was more prevalent in the vitamin D deficiency group (34.8%) in the present study, suggests a lack of protective action of vitamin D in the immune process of thyroiditis[19,30].

From a global health perspective, it is generally accepted that vitamin D deficiency is a global health problem that affects not only musculoskeletal health, but that is also related to a large number of chronic and degenerative diseases, such as diabetes. However, there remains a lack of studies and randomized clinical trials to support evidence of these health benefits, which are not related solely to skeleton and calcium metabolism[31].

The limitations of the present study relate to sample size, lack of data on dietary pattern, and information on previous vitamin D supplementation. Further studies should be carried out to suggest vitamin D dosing in all patients with T1DM to improve glycemic control and metabolic parameters and to delay microvascular complications, thus improving the health of these patients.

CONCLUSION

Vitamin D deficiency was present in the majority of the patients with T1DM analyzed. However, there was no association of this deficiency with gender, age, BMI, glycemic control, diabetes duration, total daily insulin dose, and presence of microvascular complications.

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