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

Associação entre vitamina D, controle glicêmico e complicações microvasculares no diabetes tipo I

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 both 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 tipo 1 (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 variáveis clínicas e epidemiológicas analisadas.

Descritores: Diabetes Mellitus; Vitamina D; Registros Médicos.
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 exacto 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 (74%) 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.

INTRODUCCIÓN

Diabetes mellitus (DM) representa un grupo de enfermedades metabólicas caracterizado por un aumento de la glucosa en sangre resultante de defectos en la secreción de insulina y/o acción de la misma. Tipo 1 diabetes mellitus (T1DM) representa entre 5 y 10% de todos los casos de diabetes, con mayor prevalencia en niños y jóvenes. Se ha descrito que la deficiencia de vitamina D puede influir en la génesis de la microalbuminuria y el tratamiento con vitamina D puede reducir la proteinuria. En estudios de células humanas, se ha descrito que la vitamina D reduce el expresión de citocinas inflamatorias, como interleukina-1β, interleukina-6, factor de necrosis tumoral α (TNF-α), interferón γ, interleukina-8 (IL 8) y interleukina 12, en células normales..

En vida, los estudios han mostrado que el déficit de vitamina D se da en más de la mitad de los pacientes diagnosticados con T1DM, con niveles de vitamina D 25(OH) de aproximadamente 23,24 ± 4,29 ng/mL en el grupo de pacientes con vitamina D deficiente y 55,55 ± 19,2 ng/mL en el grupo de pacientes con vitamina D suficiente. Sin embargo, no se observó una asociación significativa 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. La deficiencia de vitamina D se dio en la mayoría de los pacientes con T1DM evaluados, pero no se observó una asociación con los parámetros clínicos y epidemiológicos analizados.

La deficiencia de vitamina D se dio en 34 (68%) pacientes con media de 25(OH) de vitamina D de 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 (74%) 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. 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. 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.

INTRODUCCIÓN

Diabetes mellitus (DM) representa un grupo de enfermedades metabólicas caracterizado por un aumento de la glucosa en sangre resultante de defectos en la secreción de insulina y/o acción de la misma. Tipo 1 diabetes mellitus (T1DM) representa entre 5 y 10% de todos los casos de diabetes, con mayor prevalencia en niños y jóvenes. Se ha descrito que la deficiencia de vitamina D puede influir en la génesis de la microalbuminuria y el tratamiento con vitamina D puede reducir la proteinuria. En estudios de células humanas, se ha descrito que la vitamina D reduce el expresión de citocinas inflamatorias, como interleukina-1β, interleukina-6, factor de necrosis tumoral α (TNF-α), interferón γ, interleukina-8 (IL 8) y interleukina 12, en células normales.

En vida, los estudios han mostrado que el déficit de vitamina D se da en más de la mitad de los pacientes diagnosticados con T1DM, con niveles de vitamina D 25(OH) de aproximadamente 23,24 ± 4,29 ng/mL, en el grupo de pacientes con vitamina D deficiente y 38,22± 7,72 ng/mL en el grupo de pacientes con vitamina D suficiente. Además, 37 pacientes (74%) 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. 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. 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.
Regarding the role of vitamin D and its role in health promotion, research\textsuperscript{(13)} 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\textsuperscript{(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 Cantídio da Universidade Federal do Ceará – HUWC/UFC) from January 1\textsuperscript{st} to 30\textsuperscript{th}, 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)\textsuperscript{(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 ≥ 30ng/ml and vitamin D deficiency group if levels < 30ng/ml\textsuperscript{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 Cantídio – 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 1).

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 1). Regarding treatment, different insulin regimens were used by the patients. Mean total daily insulin dose was 55.31 ± 21.8 IU/day (Table 1).

As for data on glycated hemoglobin, 39 (78%) patients exhibited values >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 1).

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 1).
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.

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<td>&lt; 7%</td>
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<td>78%</td>
<td>28</td>
<td>82.4%</td>
<td>11</td>
<td>68.80%</td>
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</table>

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\(^{(7,8,12,19)}\). 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\(^{(20)}\).
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 age25.

The present study did not find an association of vitamin D levels with age or sex. Another study24 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-analyses26,27 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 research16,28,29.

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 Paulo29.

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 hemoglobin11. 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 consistent with the Danish study conducted at the Steno Diabetes Center12.

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 study13.

Positive anti-TPO (anti-thyroid 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 thyroiditis13,19,30.

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 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 metabolism10.

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Sufficient (16)</th>
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<tbody>
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<td>Mean</td>
<td>SD</td>
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<td>Age at diagnosis (years)</td>
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<td>Disease duration (years)</td>
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<td>BMI (Kg/m²)</td>
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<td>Glycated hemoglobin</td>
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<td>Daily insulin dose</td>
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Table II - Association of clinical and laboratory variables according to serum vitamin D levels of patients with type 1 diabetes. Fortaleza, Ceará, Brazil, 2016.

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

REFERENCES


