Hypovitaminosis D in patients with type 2 diabetes: risk factors and association with glycemic control and established microvascular complications

Hipovitaminosis D en pacientes con diabetes tipo 2: factores de riesgo y asociación con control glucémico y complicaciones microvasculares establecidas

Hipovitaminose D em pacientes com diabetes tipo 2: fatores de risco e associaçãocom controle glicêmico e complicaçõesmicrovascularesestabelecidas

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La diabetes mellitus es una enfermedad caracterizada por niveles elevados de glucosa o azúcar en sangre. Se debe a la producción insuficiente de insulina o bien, a que esta no puede actuar debidamente. Si la diabetes no se trata adecuadamente pueden aparecer complicaciones en diferentes partes del cuerpo, como corazón, cerebro, riñones, ojos, etc. Por su parte, la vitamina D es una sustancia que actúa como una hormona y que regula, principalmente, la absorción intestinal de calcio. Por lo tanto, cuando existe una deficiencia de vitamina D las complicaciones son, preferentemente, esqueléticas. Asimismo, las personas con diabetes tipo 2 con mal control de su enfermedad o con complicaciones propias de la diabetes presentan menores niveles de esta vitamina D.

Conceptos clave:

Que se sabe del tema:

La hipovitaminosis D es una condición frecuente en los pacientes que padecen diabetes mellitus tipo 2.

Que se aporta con el trabajo:

Nuestro trabajo permite estratificar a los pacientes con diabetes tipo 2 y mayor riesgo de deficiencia de vitamina D.

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Abstract:

Introduction: Several studies reported than vitamin D deficiency increases the risk of macrovascular and microvascular disease in patients with type 2 diabetes (T2DM). We investigated the plasma levels of 25OHD in adult patients T2DM, risk factors for 25OHD deficiency and the relationship between 25OHD, glycemic control and chronic complications of T2DM. **Methods:** A cross-sectional study was carried out, in which 25OHD levels were evaluated in adult patients (over 18 years) with T2DM. Correlation analyses were performed to evaluate the interdependence of the 25OHD with other continuous variables. A receiver operating characteristic analysis was also performed to identify cutoff values for diagnosing vitamin D deficiency. Logistic regression was performed to identify the independent association between vitamin D deficiency and the variables associated with lower 25OHD. **Results:** 208 patients were analyzed. The mean age of the patients was 62 years. The 25OHD level was 19 ng/ml (IQR 13.28-24.43), 59.78% had vitamin D deficiency, and 10.33% had severe deficiency. Glycemia, HbA_{1c}, and BMI were negatively correlated with 25OHD. Cutoff point for vitamin D deficiency was 33.39 kg/m^2 for body mass index (BMI), 123 mg/dl for glycemia, and 6.65% for HbA_{1c}. In multivariate logistic regression, BMI>33.39 kg/m^2, glycemia>123.5 mg/dl, and albuminuria presented higher odds of vitamin D deficiency. **Major conclusion:** Vitamin D deficiency was highly prevalent among patients with T2DM. Low levels were related to higher fasting plasma glucose, higher BMI, and diabetic nephropathy.

Palabras clave: diabetes mellitus; vitamin D; albuminuria.

Resumen:

Introducción: Varios estudios reportaron que la deficiencia de vitamina D aumenta el riesgo de enfermedad macrovascular y microvascular en pacientes con diabetes tipo 2 (DM2). Investigamos los niveles de 25OHD en adultos con DM2, factores de riesgo de deficiencia de 25OHD y relación entre 25OHD, control glucémico y complicaciones crónicas de la DM2. **Métodos:** Se realizó un estudio transversal en el que se evaluaron los niveles de 25OHD en adultos (mayores de 18 años) con DM2. Se realizaron análisis de correlación para evaluar la interdependencia de la 25OHD con otras variables continuas. Se realizó un análisis de las características operativas del receptor para identificar valores de corte para diagnóstico de deficiencia de vitamina D. Se realizó una regresión logística para identificar asociación independiente entre deficiencia de 25OHD y variables asociadas con una menor 25OHD. **Resultados:** Se analizaron 208 pacientes. La edad media fue 62 años. El nivel de 25OHD fue 19 ng/ml (IQR 13.28-24.43), 59.78% tenía deficiencia de vitamina D y 10.33% tenía deficiencia severa. Glucemia, HbA_{1c} y IMC correlacionaron negativamente con 25OHD. El punto de corte para deficiencia de vitamina D fue 33,39 kg/m^2 para índice de masa corporal (IMC), 123 mg/dl para glucemia y 6,65% para HbA_{1c}. En la regresión logística multivariada, IMC >33,39 kg/m^2, glucemia >123,5 mg/dl y albuminuria presentaron mayores probabilidades de deficiencia de vitamina D. **Conclusión principal:** La deficiencia de vitamina D fue altamente prevalente en los pacientes con DM2. Niveles bajos de 25OHD se relacionaron con mayor glucemia, mayor IMC y nefropatía diabética.

Keywords: diabetes mellitus; vitamina D; albuminuria.

Resumo:

Introdução: Vários estudos relataram que a deficiência de vitamina D aumenta o risco de doença macrovascular e microvascular em pacientes com diabetes tipo 2 (DM2). Nós investigamos os níveis de 25OHD em adultos com DM2, fatores de risco para deficiência de 25OHD e a relação entre 25OHD, controle glicêmico e complicações crônicas do DM2. **Métodos:** Foi realizado um estudo transversal em que os níveis de 25OHD foram avaliados em adultos (maiores de 18 anos) com DM2. Análises de correlação foram realizadas para avaliar a interdependência de 25OHD como utrasvariáveis contínuas. Uma análise das características operatórias do receptor foi realizada para identificar valores de corte para o diagnóstico de deficiência de vitamina D. Uma regressão logística foi realizada para identificar uma associação independente entre a deficiência de 25OHD e variáveis associadas a uma menor 25OHD. **Resultados:** 208 pacientes foram analisados. A média de idade foi de 62 anos. O nível de 25OHD foi de 19 ng/ml (IQR 13,28-24,43), 59,78% eram deficientes em vitamina D e 10,33% eram severamente deficientes. Glicemia, HbA1c e IMC correlacionaram-se negativamente com 25OHD. O ponto de corte para deficiência de vitamina D foi de 33,39 kg/m^2 para índice de massa corporal (IMC), 123 mg/dl para glicose no sangue e 6,65% para HbA_{1c}. Na regressão logística multivariada, IMC> 33,39 kg/m^2, glicemia >123,5 mg/dl e albuminúria apresentaram maiores probabilidades de deficiência de vitamina D. **Conclusão principal:** A deficiência de vitamina D foi altamente prevalente em pacientes com DM2. Níveis baixos de 25OHD foram associados a maior glicose no sangue, maior IMC e nefropatia diabética.

Palavras-chave: diabetes mellitus; vitamina D; albuminúria.

INTRODUCTION

Vitamin D has been known for its role in the regulation of bone and calcium metabolism, and vitamin D deficiency as a cause of rickets and osteomalacia[1]. However, in recent years it has been shown that the effects of vitamin D are not limited to the regulation of calcium metabolism homeostasis and that vitamin D receptor (VDR) is present in most cells and tissues of the body[2,3].

Type 2 diabetes mellitus (T2DM) is characterized by impaired pancreatic β-cell function, insulin resistance, and systemic inflammation, and there is evidence that vitamin D modulates these mechanisms[4]. Numerous studies showed that vitamin D deficiency is associated with impaired secretion of insulin by pancreatic β-cells[5]. It has been found that vitamin D mediated increase in insulin sensitivity occurs via binding of calcitriol to VDR[6], induction of insulin receptors expression[7], and the activation of peroxisome proliferator-activated receptor delta[8].

Furthermore, although adequate glycemic control is associated with higher vitamin D status in people with T2DM, studies did not show any glycemic benefit from vitamin D supplementation[9]. Several studies reported than vitamin D deficiency increased the risk of macrovascular and microvascular disease[10-11]. However, other studies no found association[12].

The present study investigated the plasma levels of 25OHD in adult patients T2DM, determine risk factors for vitamin D deficiency and relate vitamin D levels to glycemic control and the presence of micro and macrovascular complications.

MATERIALS AND METHODS

A cross-sectional, and analytical study was carried out, in which 25OHD levels were evaluated in adult patients with T2DM. A total of 208 adult patients (over 18 years) with T2DM were evaluated consecutively during the period from January 1, 2016, to December 31, 2016, under conditions of usual clinical practice belonging to the Endocrinology Service of the Hospital Español from the city of Rosario, Argentine. This study was approved by the ethical review board of Hospital Español and in compliance with the Helsinki declaration. All subjects agreed to participate in the study and provided written informed consent.

Inclusion criteria were patients older than 18 years with T2DM. Exclusion criteria were neoplastic, granulomatous, or collagen disease, chronic liver disease, chronic kidney stage 5 (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2), diseases that affect the intestinal absorption of vitamin D and other diseases or conditions affecting bone metabolism. Treatment with antiepileptics, glucocorticoids, lithium, bone antiresorptive treatment, estrogen treatment, vitamin D, and bone anabolic agents was an exclusion criterion.

We collected information on age, sex, smoking status, alcohol consumption, duration of diabetes, and types of diabetic medication used from patient medical records. Height and weight were measured, and body mass index (BMI) was calculated by dividing the weight in kilograms by the height squared in meters. A history of arterial hypertension, dyslipidemia and metabolic syndrome was recorded. The level of physical activity was recorded, and the patients were classified according to low level and moderate-high level of physical activity[13].

The following laboratory data were analyzed: glycemia (mg/dl), HbA_{1c} (%), serum creatinine (mg/dl), serum calcium (mg/l), serum phosphate (mg/dl), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and creatinine levels. The urinary albumin-to-creatinine ratio (UACR) was assessed on a random spot urine sample and measured using radioimmunoassay. Albuminuria was defined when UACR it was greater than 30 mg/g. The eGFR was calculated using the following Modification of Diet in Renal Disease equation: $186\times(\text{serum creatinine})^{-1.154}\times(\text{age})^{-0.203}\times(0.742 \text{ if female})$[14].

25OHD levels were measured using a chemiluminescent immunoassay in a centralized laboratory (Centauro®, Siemens). Vitamin D status was defined as following: severely deficient for 25OHD <10 ng/ml, deficient for 10 ng/ml-20 ng/ml, insufficient for 20 ng/ml-30 ng/ml, and sufficient for 25OHD ≥30 ng/ml[15].

The presence diabetic complications were investigated through medical record reviews. Diabetic retinopathy was defined as either a non-proliferative or proliferative diabetic retinopathy or previous laser photocoagulation therapy. Diabetic nephropathy was defined as UACR≥30 mg/g and/or with eGFR ≤60 ml/min/1.73 m^2. Diabetic neuropathy was identified based on the presence of reported compatible symptoms (pain, burning, tingling, or numbness in the feet or hands) or complementary studies (electromyography). Cardiovascular disease (CVD) included myocardial infarction, unstable angina, stroke, or peripheral arterial disease.

Statistical analyses

The software R version 4.0.4 was used to perform the statistical analysis. Numerical variables were compared using non-parametric tests (Mann-Whitney for the comparison of two groups and Kruskal-Wallis, post hoc Holm, for the comparison of more than two groups) and the results were expressed as median and interquartile range. Comparisons of categorical variables were performed using the de $\chi 2$ test. Correlations analyses were performed to evaluate the interdependence of the 25OHD with other continuous variables. A receiver operating characteristic (ROC) analysis was also performed to identify cutoff values for diagnosing vitamin D deficiency. Bi and multivariate logistic regression was performed to identify the independent association between vitamin D deficiency and the variables associated with lower levels of 25OHD. The differences were considered significant if $p<0.05$.

RESULTS

208 patients were analyzed. The mean age of the patients was 62 years (IQR 56-67), 55.77% were women, and BMI was 32.53±6.03 kg/m^2. The HbA_{1c} was 7.1% (IQR 6.4-8.2) and 48.77% of the patients had HbA_{1c} less than 7%. The duration of diabetes was 7.5 years (IQR 3-15), and 46.15% used one oral antidiabetic drugs (90.6% used metformin), and 27.88% of patients used insulin.

CVD were present in 16.83%, whereas retinopathy, neuropathy, and nephropathy were present in 8.65%, 10.10%, and 21.15%, respectively. Among patients with diabetic nephropathy, 9.13% had albuminuria and 17.82% had eGFR ≤60 ml/min/1.73 m^2.

The 25OHD level was 19 ng/ml (IQR 13.28-24.43), 59.78% had vitamin D deficiency, and 10.33% had severe deficiency. Only 12.4% had optimal levels of vitamin D. 25OHD levels were lower in winter compared to summer [16.65 ng/ml (IQR 11.2-20.27) vs 20.10 ng/ml (IQR 17.08-27.1125), p=0.013]. The clinical and metabolic characteristics of the patients according to the vitamin D deficiency status are summarized in Table N° 1.

Table N°1: Baseline characteristics according to vitamin D status

	25OHD <20 ng/ml (n=124)	25OHD >20 ng/ml (n=84)	p
Age (years)	61 (56-67)	63 (55.25-67)	0.70
Female (%)	73 (58.87)	46 (54.76)	0.61
Duration of diabetes (years)	8 (3-15)	6 (2-14)	0.16
BMI (kg/m^2)	33.58±6.35	31.04±5.44	0.006
Glycemia (mg/dl)	141 (117-165)	123 (113-146)	0.01
HbA_{1c} (%)	7.3 (6.6-8.3)	6.7 (6.3-8.0)	0.01
Insulin therapy (%)	34 (30.9)	17 (23)	0.24
Total cholesterol (mg/dl)	195.35±41.44	192.61±33.40	0.64
HDL-c (mg/dl)	45.47±14.40	49.17±14.59	0.10
Triglyceride (mg/dl)	165.50±96.02	157.20±95.63	0.57
eGFR (ml/min/1.73 m^2)	79.04±21.81	82.48±21.91	0.33
Total calcium (mg/dl)	9.8 (9.35-10.15)	9.8 (9.38-10.36)	0.64
Phosphorus (mg/dl)	3.70 (3.2-4.0)	3.65 (3.2-3.8)	0.62
L-BMD (g/cm^2)	1.169±0.196	1.144±0.209	0.61
FN-BMD (g/cm^2)	0.902±0.098	0.834±0.149	0.07

Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; L-BMD, lumbar spine bone mineral density; FN-BMD, femoral neck bone mineral density.

Glycemia, HbA_{1c}, and BMI were negatively correlated with 25OHD (Table N° 2). There was no correlation between eGFR and 25OHD (rho 0.103, p=0.20).

Table N°2: Correlation analysis between 25OHD and clinical and biochemical variables

Item	Glycemia	HbA_{1c}	BMI
25OHD			
rho	-0.161	-0.184	-0.204
p-value	0.033	0.012	0.007

Spearman's correlation coefficient

Abbreviations: 25OHD, 25-hydroxyvitamin D; HbA_{1c}, glycated hemoglobin; BMI, body mass index

Results of ROC analysis showed that the cutoff point for vitamin D deficiency was 33.39 kg/m^2 for BMI (AUC=0.620), 123 mg/dl for glycemia (AUC=0.610), and 6.65% for HbA_{1c} (AUC=0.610). Results of sensitivity and specificity are shown in Table N° 3.

Table N°3: ROC analysis to diagnose vitamin D deficiency

	Cut-off point	Sensitivity	Specificity	AUC (95% CI)
BMI	33.39 kg/m^2	74%	51%	0.620 (0.530-0.700)
Glycemia	123.5 mg/dl	52%	71%	0.610 (0.530-0.700)
HbA_{1c}	6.65%	49%	72%	0.610 (0.520-0.690)

Receiver operating characteristic (ROC) analysis

Abbreviations: AUC, Area under the ROC Curve; BMI, body mass index; HbA_{1c}, glycated hemoglobin

The 25OHD levels were lower in patients with arterial hypertension [18.8 ng/ml (12.20-23.65) vs. 19.4 ng/ml (15.83-26.90), p=0.03], metabolic syndrome [18.85 ng/ml (13.02-23.22) vs. 20.40 ng/ml (15.22-27.37), p=0.04], and a low level of physical activity [18.45 ng/ml (12.55-23.93) vs. 20 ng/ml (14.95-26.25), p=0.04]. There were no significant differences according to the presence of dyslipidemia [18.05 ng/ml (12.75-23.93) vs. 19.40 ng/ml (14.7-26.83), p=0.08].

There were no significant differences in 25OHD levels according to CVD [16.7 ng/ml (11.4-22.7) vs. 19.4 ng/ml (14.2-25.05), p=0.11], neuropathy [15.1 ng/ml (11.6-20) vs. 19.2 ng/ml (14.3-25.3), p=0.08], and diabetic retinopathy [17.3 ng/ml (12.9-24.75) vs. 19.2 ng/ml (14.03-24.28), p=0.81]. Lower levels of 25OHD were found in those patients with diabetic nephropathy [17.9 ng/ml (12-20) vs. 19.4 ng/ml (14.35-25.5), p=0.02]. However, this difference persisted only in those with albuminuria [12.6 ng/ml (10-18.9) vs. 19.4 ng/ml (14.65-25.4), p=0.0008] and did not vary according to eGFR lower or higher than 60 ml/min/1.73 m^2 [19 ng/ml (12.4-21.1) vs. 18.9 ng/ml (13.25-25.35), p=0.37].

Using the vitamin D insufficiency and sufficiency groups as a reference, bivariate and multivariate logistic regression analyzes were applied to evaluate the determinants associated with vitamin D deficiency using the variables associated with lower levels of 25OHD. Results of bivariate logistic regression analysis indicated that BMI>33.39 kg/m^2, glycemia>123.5 mg/dl, HbA_{1c}>6.65%, and albuminuria had higher odds of vitamin D deficiency. In multivariate logistic regression, considering all these predictor variables simultaneously, BMI>33.39 kg/m^2, glycemia>123.5 mg/dl, and albuminuria presented higher odds of vitamin D deficiency (Table N° 4).

Table N° 4: Multivariate regression logistic analysis for vitamin D deficiency

	OR (95% CI)	p value
BMI>33.39 kg/m^2	3.06 (1.51-6.23)	0.002
Glycemia >123.5 mg/dl	2.42 (1.13-5.19)	0.02
HbA_{1c} >6.65%	1.42 (0.66-3.05)	0.37
Albuminuria (Yes)	12.7 (1.56-104)	0.01

Multivariate regression logistic analysis

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HbA_{1c}, glycated hemoglobin

DISCUSSION

In the present study, we demonstrated a high prevalence of hypovitaminosis D in patients with T2DM and corroborated a relationship between 25OHD levels and clinical and biochemical variables associated with glycemic and metabolic control, such as BMI, fasting plasma glucose, and HbA_{1c}. A variation in the levels of 25OHD was observed during the different seasons of the year. As expected, the levels were higher in summer compared to winter[16].

Vitamin D deficiency is a global health problem that affects not only musculoskeletal health but also a wide range of acute and chronic diseases. It has been estimated that 20% to 80% of people are deficient in vitamin D[17], while in Argentina it is 30 to 45%[18].In our study, the median 25OHD level was 19 ng/ml, 59.78% presented vitamin D deficiency while 10.33% presented severe deficiency. Only 12.4% had optimal levels of vitamin D. While some studies reported a higher prevalence of vitamin D deficiency[19], other studies showed results like those reported in our cohort[20].

Observational studies have reported an inverse relationship between obesity and serum 25OHD levels[21]. In multivariate analyzes, body weight was one of the most significant predictors of 25OHD levels, explaining 34.5% of the variation[22].However, there is no evidence of a BMI reduction effect with higher levels of vitamin D. In our study, 25OHD levels were negatively correlated with BMI with a cutoff value of 33.39 kg/m^2 to identify patients with vitamin D deficiency.

In addition, we demonstrated lower levels of 25OHD in patients with arterial hypertension, low level of physical activity, and metabolic syndrome. These findings are consistent with previous reports showing that hypovitaminosis D is associated with unfavorable CVD risk factors[23].

Several observational studies demonstrated an inverse association between HbA_{1c} and vitamin D status in T2DM patients, leading to the hypothesis that vitamin D could play a role in glycemic control[9] We observed a negative correlation with fasting plasma glucose and HbA_{1c} and we determined a cutoff value of HbA_{1c} 6.65% to detect vitamin D deficiency. A recent meta-analysis showed that vitamin D supplementation in patients with T2DM and vitamin D deficiency is associated with a reduction in HbA_{1c} and fasting blood glucose[24]. Another meta-analysis of 24 clinical trials demonstrated that supplementation with 4000 IU/day of vitamin D reduces fasting blood glucose, HbA_{1c} and HOMA in patients with T2DM. However, two recent randomized controlled trials have shown no beneficial role of vitamin D supplementation on glycemic outcomes, including prevention of T2DM[25]Therefore, although better glycemic control is associated with higher levels of 25OHD in people with T2DM, the studies reviewed would not support a clear benefit of vitamin D supplementation on glycemic control.

Epidemiological studies have shown an inverse association between vitamin D status and the prevalence and prognosis of acute myocardial infarction[26], risk of stroke[27], and risk of hospitalization for heart failure[28]. Several studies in patients with T2DM have shown an inverse association between vitamin D concentrations and CVD.29 Despite this evidence, we did not demonstrate an inverse association between 25OHD concentrations and established CVD.

Several clinical studies have recognized vitamin D deficiency as a risk factor for microvascular complications[10-11]. We did not demonstrate lower levels of 25OHD in patients with diabetic retinopathy or peripheral neuropathy. Only patients with diabetic nephropathy had lower levels of 25OHD. Vitamin D deficiency has been implicated as a possible risk factor for the appearance and progression of diabetic nephropathy[30].Recently, 25OHD level was negatively associated with UACR, and vitamin D deficiency was significantly associated with diabetic nephropathy after adjusting for multidirectional variable parameters[11].In our study, we demonstrated that 25OHD levels are lower according to the presence of albuminuria, but we did not demonstrate a correlation between 25OHD and eGFR. However, the interaction between decreased 25OHD levels and kidney damage would be expected and established, but it is intriguing to determine whether 25OHD deficiency is caused by kidney damage or is a promoter of it.

Finally, when including in the multivariate analysis the variables involved with lower levels of 25OHD and/or deficiency of 25OHD, we observed that only a BMI≥33.39 kg/m^2, fasting plasma glucose ≥123.5 mg/dl and the presence of albuminuria are associated independently with vitamin D deficiency.

The strength of our study was the inclusion in the multivariate analysis of different factors associated with vitamin deficiency, such as biochemical and anthropometric parameters, seasonal variations, CVD risk factors, antidiabetic medication and insulin treatment, level of physical activity, CVD, and microvascular complications. The limitations were that we did not determine parathyroid hormone levels or consider medications status other than for T2MD, such as aspirin, lipid-lowering or antihypertensive drugs. Furthermore, we did not analyze the UACR as a continuous variable. This limitation is important because it limited us to establishing a cutoff value that stratifies patients with a higher risk of vitamin D deficiency. Finally, the cross-sectional design of the study makes it difficult to establish causality in the relationships.

CONCLUSION

Vitamin D deficiency was highly prevalent among patients with T2DM, and low levels were related to higher fasting plasma glucose, higher BMI, and diabetic nephropathy.

Limitaciones de responsabilidad:
La responsabilidad del trabajo es exclusivamente de quienes colaboraron en la elaboración del mismo.

Conflicto de interés:
Ninguno.

Fuentes de apoyo:
La presente investigación no contó con fuentes de financiación.

Originalidad:
Este artículo es original y no ha sido enviado para su publicación a otro medio de difusión científica en forma completa ni parcialmente.

Cesión de derechos:
Quienes participaron en la elaboración de este artículo, ceden los derechos de autor a la Universidad Nacional de Córdoba para publicar en la Revista de la Facultad de Ciencias Médicas y realizar las traducciones necesarias al idioma inglés.

Contribución de los autores:
Quienes participaron en la elaboración de este artículo, han trabajado en la concepción del diseño, recolección de la información y elaboración del manuscrito, haciéndose públicamente responsables de su contenido y aprobando su versión final.

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