Nutrición Hospitalaria

Trabajo Original

Otros

Association of serum vitamin D levels with chronic disease and mortality
Asociación de los niveles séricos de vitamina D con la enfermedad crónica y la mortalidad

Hillary K. Osorio-Landa[1], Iván Pérez-Díaz[1,2], Sara Laguna-Bárcenas[1], Juan M. López-Navarro[1], María F. Abella-Roa[1], Mariel Corral-Orozco[1], Juan P. Mancilla-Ortega[1], Diana A. Martínez-Duarte[1], Susana I. Morales-Montalvo[1], Sebastián Múzquiz-Aguirre[1] and Elizabet Sánchez-Landa[1]

[1]Department of Internal Medicine. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Ciudad de México, México. [2]Tecnológico de Monterrey. Ciudad de México, México

Abstract

Introduction: whether hypovitaminosis D is an overarching cause of increased mortality or a prognostic marker of poor health has not been well elucidated.

Objectives: we sought to determine the association of serum 25-hydroxyvitamin D [25-(OH)-D3] levels with the clinical biochemical parameters and mortality risk in chronic diseases.

Methods: we reviewed the clinical charts and collected the clinical biochemical parameters of patients diagnosed with chronic conditions who had at least one 25-(OH)-D3 determination, with or without calcium and vitamin D supplementation, and who were selected using a cluster random sampling design (n = 1,705). The analysis was focused on metabolic disorders (type-2 diabetes mellitus [T2DM] and obesity), autoimmune disorders, and mortality. Multivariate logistic regression analyses were performed.

Results: low 25-(OH)-D3 levels were reported in 1,433 (84.0 %) patients, of which 774 (45.4 %) had insufficiency (20-29 ng/mL) and 659 (38.6 %) patients had deficiency (< 20 ng/mL). Lower 25-(OH)-D3 levels in T2DM patients were associated with higher glycosylated hemoglobin levels (p < 0.001). Patients with 25-(OH)-D3 levels < 12.5 ng/mL had a higher mortality risk than those with levels ≥ 12.5 ng/mL (HR: 3.339; 95 % CI: 1.342-8.308). We observed lower 25-(OH)-D3 levels in patients with grade-III obesity (p = 0.01). We found a higher risk of 25-(OH)-D3 deficiency in rheumatoid arthritis, type-1 diabetes, and systemic lupus erythematosus (p = 0.032, p = 0.002, p = 0.049, respectively).

Conclusions: we found a significant relationship between 25-(OH)-D3 levels and glycemic control, body mass index, autoimmune disease, and mortality risk. Nevertheless, whether hypovitaminosis D plays a causal role or is a consequence of chronic disease remains controversial.

Resumen

Introducción: si la hipovitaminosis D constituye una causa general de mayor mortalidad o un marcador de mal pronóstico para la salud no se ha dilucidado por completo.

Objetivos: determinar la asociación de los niveles séricos de 25-hidroxivitamina D [25-(OH)-D3] con los parámetros clínico-bioquímicos y el riesgo de mortalidad en la enfermedad crónica.

Métodos: se revisaron los expedientes clínicos y recopilamos los parámetros clínico-bioquímicos de pacientes diagnosticados de enfermedades crónicas que tenían al menos una determinación de 25-(OH)-D3, con o sin suplemento de calcio y vitamina D, y que se seleccionaron mediante muestreo aleatorio por grupos (n = 1705). El análisis se centró en los trastornos metabólicos (diabetes mellitus de tipo 2 [DM2] y obesidad), los trastornos autoinmunes y la mortalidad. Se realizaron análisis multivariados de regresión logística.

Resultados: se encontraron niveles bajos de 25-(OH)-D3 en 1433 (84,0 %) pacientes, de los cuales 774 (45,4 %) tenían insuficiencia (20-29 ng/mL) y 659 (38,6 %) tenían deficiencia (< 20 ng/mL) de esta vitamina. Los niveles más bajos de 25-(OH)-D3 en los pacientes con DM2 se asociaron a niveles más altos de hemoglobina glucosilada (p < 0,001). Los pacientes con niveles de 25-(OH)-D3 < 12,5 ng/mL tenían mayor riesgo de mortalidad que aquellos con niveles ≥ 12,5 ng/mL (HR: 3,339; IC del 95 %: 1,342-8,308). Apreciamos niveles más bajos de 25-(OH)-D3 en los pacientes con obesidad de grado III (p = 0,01). Se encontró un mayor riesgo de deficiencia de 25-(OH)-D3 en la artritis reumatoide, la diabetes de tipo 1 y el lupus eritematoso sistémico (p = 0,032, p = 0,002, p = 0,049, respectivamente).

Conclusiones: apreciamos una relación significativa entre los niveles de 25-(OH)-D3 y el control glucémico, el índice de masa corporal, la enfermedad autoinmune y el riesgo de mortalidad. Sin embargo, sigue siendo controvertido si la hipovitaminosis D desempeña un papel causal o constituye una consecuencia de las enfermedades crónicas.

Correspondence:

Iván Pérez-Díaz. Department of Internal Medicine. Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán". Vasco de Quiroga 15, Sección XVI, Tlalpan. CP. 14000 Ciudad de México. México
e-mail: ivan.endocrino@gmail.com

INTRODUCTION

Vitamin D is a lipid-soluble compound essential for calcium homeostasis and bone metabolism (1). Besides these well-known classic effects, numerous published articles in the last few decades have correlated vitamin D deficiency with nearly the entire spectrum of human illness (2), as it has been associated with diabetes, hypertension, metabolic syndrome, cancer, and autoimmune, cardiovascular, neuropsychiatric, and infectious disease, among others (3-5). These nonclassic roles of vitamin D have been attributed to the wide distribution of the vitamin D receptor (VDR) in many tissues and cells, including adipocytes, pancreas, kidney, skin, and immune cells (6,7).

Furthermore, the active metabolite of vitamin D $(1,25[OH]_2D_3)$ regulates approximately 3 % of the human genome, there being at least 229 genes related to the growth and differentiation of cells as well as to an increased risk of various chronic diseases such as diabetes and arthritis (7,8).

Hypovitaminosis D is a major public health problem that affects not only bone health but also an extensive range of acute and chronic diseases (3,9). Nowadays it has become a pandemic, being observed worldwide in all ethnicities and age groups, independently of country latitude (3,4).

Whether vitamin D deficiency is an overarching cause of increased morbidity and mortality or a prognostic marker of poor health in chronic diseases has not been well elucidated (10,11). Moreover, controversy prevails regarding the standardization of vitamin D measurements, as it has been proposed that cutoff values for its deficiency might need to be established specific to region, sex, and season (12-14). The aim of this study was to determine the association of serum 25-hydroxyvitamin D [25-(OH)-D3] levels with clinical biochemical parameters and mortality risk in chronic diseases in a tertiary-care hospital.

MATERIAL AND METHODS

We conducted an observational and retrolective study from January 2010 to December 2013 in a tertiary-care hospital. During this period, we obtained a total of 2,935 25-(OH)-D3 measurements in outpatients; of these, 1,705 patients who met the following criteria were selected using a cluster random sampling design: patients ≥ 18 years old treated at the hospital during the study period, who had at least one 25-(OH)-D3 determination with or without calcium and vitamin D supplementation.

For the analysis we reviewed their clinical charts and collected their clinical and biochemical parameters. Among clinical parameters we obtained the following information: age, gender, diagnoses, medications, and anthropometry measurements (weight, height, and body mass index [BMI]). Among biochemical parameters, we recorded the levels of 25-(OH)-D3, albumin, creatinine, fasting glucose, and glycosylated hemoglobin (HbA1c).

The present study was focused on the analysis of chronic diseases. Specifically, patients with the following diagnoses reported in their clinical charts were included: metabolic conditions (type-2 diabetes mellitus [T2DM] and obesity) and autoimmune disorders (hypothyroidism, rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], Sjögren's syndrome, type-1 diabetes mellitus [T1DM], pernicious anemia, systemic sclerosis, ankylosing spondylitis, autoimmune liver disease, CREST syndrome [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia], autoimmune polyglandular syndrome, antiphospholipid syndrome, immune thrombocytopenic purpura, and myasthenia gravis). The study also collected mortality data.

According to the American Diabetes Association (ADA), T2DM was defined by the following criteria: fasting blood glucose ≥ 126 mg/dL or 2-hour plasma glucose ≥ 200 mg/dL during a 75-g oral glucose tolerance test, or HbA1c ≥ 6.5 %, or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, with a random plasma glucose measurement ≥ 200 mg/dL. Furthermore, prediabetes was defined by the following criteria: fasting blood glucose of 100-125 mg/dL, or 2-hour plasma glucose of 140-199 mg/dL during a 75-g oral glucose tolerance test, or HbA1c of 5.7-6.4 % (15).

From the clinical charts we recorded the number of deaths until 2016. The Institutional Ethical Committee approved the present study, and all protocols for reviewing clinical charts were fulfilled as required.

MEASUREMENT OF 25-(OH)-D3

We obtained the measurement of 25-(OH)-D3 using liquid chromatography in tandem with mass spectrophotometry (LC-MS/MS, QUEST DIAGNOSTICS, Nichols Institute, SJC, CA, USA). We classified patient vitamin D levels into three groups: deficiency (< 20 ng/mL), insufficiency (20-29 ng/mL), and sufficiency (≥ 30 ng/mL) (16). Also, we collected 25-(OH)-D3 measurements within 3 months before and after the outpatient follow-up visit. We documented all clinical and biochemical parameters within 6 months previous to 25-(OH)-D3 measurement.

MEASUREMENT OF HbA1c

We determined the degree of glycemic control by using HbA1c levels (HPLC, Bio-rad), which we collected from clinical charts within 6 months previous to 25-(OH)-D3 measurement. Then, we classified patients according to their level of glycemic control into the following groups: optimal (HbA1c ≤ 7 %), suboptimal (HbA1c = 7.1-8.0 %), and poor control (HbA1c > 8 %) (17).

STATISTICAL ANALYSIS

We expressed results as average ± SD (standard deviation) for variables with normal distribution, or as median and interquartile range (IQR) for those without normal distribution. We evaluated normal distribution with the Kolmorov-Smirnov test, and performed the statistical analysis with the IBM SPSS Statistics 23 (IBM, New York, USA) software. *P*-values < 0.05 were considered statistically significant.

We used the Mann-Whitney U-test to compare continuous variables without normal distribution between 2 groups, and the Kruskal-Wallis test to compare variables between more than 2 groups. In addition, we used the chi-square test to compare categorical variables. Then, we used Spearman's test to evaluate correlations between 25-(OH)-D3 levels and different continuous variables. We performed multivariate logistic regression analyses, expressed as odds ratio (OR), in order to determine the diseases that increase the risk of presenting low 25-(OH)-D3 levels. These analyses were adjusted for sex, age, BMI, different comorbidities, vitamin D supplementation, steroid or immunosuppressant treatment, and 25-(OH)-D3 measurement during winter.

RESULTS

In the total group (n = 1,705) we found that 1,446 (84.81 %) patients were female, whereas 259 (15.19 %) were male. No statistically significant difference was found in 25-(OH)-D3 determinations between females and males (p = 0.513). Median patient age was 60 years (48-70), and median 25-(OH)-D3 level was 22 ng/mL (16-27). In the present study 1,433 (84.0 %) patients were reported with low 25-(OH)-D3 levels (< 30 ng/mL): of these, 774 (45.4 %) had 25-(OH)-D3 insufficiency (20-29 ng/mL) and 659 (38.6 %) patients had deficiency (< 20 ng/mL) (Table I). All the multivariate analyses were adjusted for sex, age, BMI, different comorbidities, vitamin D supplementation, steroid or immunosuppressant treatment, and 25-(OH)-D3 measurement during winter.

VITAMIN D LEVELS AND GLYCEMIC CONTROL

By comparing 25-(OH)-D3 levels in patients with and without T2DM we found that patients with T2DM had lower 25-(OH)-D3 levels (20 ng/mL [15-26] vs. 22 ng/mL [17-28], p < 0.001).

In the multivariate logistic regression analysis we observed that T2DM was associated with a higher risk of 25-(OH)-D3 deficiency (< 20 ng/mL) (OR, 1.508; 95 % CI: 1.044-2.178; p = 0.029), especially for levels lower than 12.5 ng/mL (OR, 2.243; 95 % CI: 1.393-3.610; p = 0.001).

By dividing patients with T2DM into 3 groups according to glycemic control (HbA1c levels) we confirmed that the patients with higher HbA1c levels had lower 25-(OH)-D3 levels (p < 0.001) (Table II).

By multivariate analysis, we found that patients diagnosed with T2DM with 25-(OH)-D3 levels < 30 ng/mL had a higher risk of suboptimal and poor glycemic control (HbA1c > 7 %) than those with 25-(OH)-D3 sufficiency (≥ 30 ng/mL) (OR, 2.069; 95 % CI: 1.215-3.524; p = 0.007) (Fig. 1). Besides, we observed a higher risk of suboptimal and poor control in patients with 25-(OH)-D3 levels < 12.5 ng/mL compared with patients with 25-(OH)-D3 sufficiency (OR, 5.042; 95 % CI: 2.395-10.615; p < 0.001) (Fig. 2).

Finally, by comparing fasting glucose and HbA1c levels between patients with 25-(OH)-D3 sufficiency and 25-(OH)-D3 levels < 12.5 ng/mL in the total sample, we observed higher fasting glucose and HbA1c levels in patients with 25-(OH)-D3 levels < 12.5 ng/mL (p = 0.008, p = 0.002, respectively).

VITAMIN D LEVELS AND ADIPOSITY

By dividing patients according to their BMI we found lower 25-(OH)-D3 levels in patients with grade-III obesity (BMI ≥ 40 kg/m^2) (p = 0.01) (Fig. 3).

VITAMIN D AND AUTOIMMUNE DISEASE

We did not find a significant relationship between 25-(OH)-D3 levels and hypothyroidism, which was the most common autoimmune disease reported in our study (503 patients, 29.5 %). Nevertheless, by multivariate analysis we found that RA was associated with a higher risk of 25-(OH)-D3 deficiency (OR, 2.916; 95 % CI: 1.095-7.769; p = 0.032), especially for levels lower than 12.5 ng/mL (OR, 4.762; 95 % CI: 1.400-16.197; p = 0.012). Similarly, we identified that patients with T1DM had a higher risk of presenting 25-(OH)-D3 levels < 12.5 ng/mL (OR, 5.028; 95 % CI: 1.798-14.062; p = 0.002), and this included patients with SLE (OR, 2.229; 95 % CI: 1.002-4.958; p = 0.049).

VITAMIN D LEVELS AND MORTALITY RISK

A total of 27 deaths (1.6 %) were reported. We found a higher incidence of mortality in patients with 25-(OH)-D3 levels < 20 ng/mL compared with those with levels ≥ 20 ng/mL (p = 0.009).

We executed and adjusted a survival multivariate analysis with hazard ratio (HR) for sex, age, BMI, different comorbidities, GFR, serum albumin, and 25-(OH)-D3 levels. We observed that patients with 25-(OH)-D3 levels < 12.5 ng/mL had a higher mortality risk than those with 25-(OH)-D3 levels ≥ 12.5 ng/mL (HR 3.339; 95 % CI: 1.342-8.308; p = 0.010).

DISCUSSION

In this study we reported an association between chronic disease and low 25-(OH)-D3 levels, specifically regarding metabolic and autoimmune disorders. Safarpour et al. conducted a double-blind, randomized clinical trial in which they reported that increased 25-(OH)-D3 levels significantly decreased serum HbA1c levels in patients with T2DM (18). Regarding glycemic control, we found that lower 25-(OH)-D3 levels were associated with higher HbA1c levels.

Several studies have proposed that sufficient vitamin D status could prevent prediabetes and T2DM, but this association remains unclarified due to inconsistent results among studies (19-21). Health et al. performed a case-cohort study within the Melbourne Collaborative Cohort study in which they found that vitamin D status was inversely associated with risk of T2DM (22).

Table I. General characteristics of the study population (n = 1705)

	Total 1705 (100 %)	Deficiency 25-(OH)-D3 < 20 ng/mL 659 (38.6 %)	Insufficiency 25-(OH)-D3 20-29 ng/mL 774 (45.4 %)	Sufficiency 25-(OH)-D3 ≥ 30 ng/mL 272 (16.0 %)	p-value (< 0.05)
Gender, n (% female)	1446 (84.8)	557 (84.5)	660 (85.3)	229 (84.2)	
Age, years, median (IQR)	60 (48-70)	60 (47-72)	60 (50-70)	60 (47-69)	
BMI, kg/m² , median (IQR)	25.7 (22.8-28.9)	25.7 (22.5-29.2)	25.7 (23-28.8)	25.4 (22.8-28.4)	[b] 0.045
HbA1c, %, median (IQR)	6.5 (5.9-8.0)	6.8 (6.0-8.7)	6.4 (5.8-8.0)	6.2 (5.7-7.1)	[a] 0.001 [b] 0.002 [c] 0.002 [d] < 0.001 [e] 0.044 [f] 0.031
Fasting blood glucose mg/dL, median (IQR)	93 (84.5-105)	93 (85-110)	93 (84 - 103)	92 (85 -103)	
Cancer, n (%)	44 (2.6)	17 (2.6)	21 (2.7)	6 (2.2)	
Autoimmune disease, n (%)	826 (48.4)	311 (47.2)	389 (50.3)	126 (46.3)	
Hypothyroidism, n (%)	503 (29.5)	185 (28.1)	243 (31.4)	75 (27.6)	
Rheumatoid arthritis, n (%)	92 (5.4)	40 (6.1)	45 (5.8)	7 (2.6)	[c] 0.025 [d] 0.027 [e] 0.034
SLE, n (%)	70 (4.1)	32 (4.9)	27 (3.5)	11 (4.0)	
Sjögren's syndrome, n (%)	195 (11.4)	72 (10.9)	81 (10.5)	42 (11.4)	[c] 0.024 [e] 0.028
T1DM, n (%)	25 (1.5)	12 (1.8)	12 (1.6)	1 (0.4)	
Ischemic heart disease, n (%)	21 (1.2)	9 (1.4)	6 (0.8)	6 (2.2)	
Systemic hypertension, n (%)	643 (37.7)	265 (40.2)	274 (35.4)	104 (38.2)	
T2DM, n (%)	432 (25.3)	199 (30.2)	174 (22.5)	59 (21.7)	[a] 0.001 [b] < 0.001 [f] 0.001 [d] 0.008
Prediabetes, n (%)	141 (8.3)	39 (5.9)	81 (10.5)	21 (7.7)	[a] 0.007 [b] 0.005 [f] 0.002
Dyslipidemia, n (%)	457 (26.8)	174 (26.4)	208 (26.9)	75 (27.6)	
CKD, n (%)	81 (4.8)	34 (5.2)	31 (4.0)	16 (5.9)	
Psychiatric disorder, n (%)	65 (3.8)	29 (4.4)	28 (3.6)	8 (2.9)	
Deaths, n (%)	27 (1.6)	17 (2.6)	6 (0.8)	4 (1.5)	[a] 0.024 [b] 0.009 [f] 0.007
Vitamin D supplementation, n (%)	1029 (60.4)	445 (67.5)	431 (55.7)	153 (56.3)	[a] < 0.001 [b] < 0.001 [f] < 0.001 [d] 0.001

[a]*p-value indicates comparison between all groups;* [b]*p-value indicates comparison between 25-(OH)-D3 deficiency vs. insufficiency and sufficiency;* [c]*p-value indicates comparison between 25-(OH)-D3 deficiency and insufficiency vs. sufficiency;* [d]*p-value indicates comparison between 25-(OH)-D3 deficiency vs. sufficiency;*
[e]*p-value indicates comparison between 25-(OH)-D3 insufficiency vs. sufficiency;* [f]*p value indicates comparison between 25-(OH)-D3 deficiency vs. insufficiency.*
IQR: inter-quartile range; 25-(OH)-D3: 25-hydroxyvitamin D; BMI: body mass index; HbA1c: glycosylated hemoglobin; SLE: systemic lupus erythematosus;
T1DM: type-1 diabetes mellitus; T2DM: type-2 diabetes mellitus; CKD: chronic kidney disease. Significant differences between groups (p < 0.05) are shown.

Table II. Biochemical and clinical parameters by glycemic control group

Total HbA1c n = 344	Optimal control (1) ≤ 7 % n = 139	Suboptimal control (2) 7.1-7.9 % n = 79	Poor control (3) ≥ 8 % n = 126	p-value	Comparison group	Post-hoc p-value
25-(OH)-D3 ng/mL, median (IQR)	22 (17-28)	20 (16-26)	19 (13-24)	0.001	1 vs. 2 1 vs. 3 2 vs. 3	0.126 < 0.001* 0.110
BMI kg/m², median (IQR)	26.4 (24.0-30.0)	27.3 (23.8-31.6)	26.3 (23.4-28.8)	0.196	1 vs. 2 1 vs. 3 2 vs. 3	0.601 0.186 0.088
Fasting blood glucose mg/dL, median (IQR)	105 (95-117)	124 (104-140)	160.5 (131-200.5)	< 0.001	1 vs. 2 1 vs. 3 2 vs. 3	< 0.001* < 0.001* < 0.001*
Age, years, median (IQR)	66 (57-75)	67 (61-73)	66 (56-76)	0.856	1 vs. 2 1 vs. 3 2 vs. 3	0.572 0.945 0.675
Gender, n (% female)	113 (81.3)	70 (88.6)	106 (84.1)	0.367	1 vs. 2 1 vs. 3 2 vs. 3	0.157 0.543 0.370
Vitamin D supplementation, n (%)	102 (73.4)	58 (73.4)	92 (73)	0.997	1 vs. 2 1 vs. 3 2 vs. 3	0.995 0.947 0.950

Significant differences between groups (p < 0.05). IQR: inter-quartile range; HbA1c: glycosylated hemoglobin; 25-(OH)-D3: 25-hydroxyvitamin D; BMI: body mass index.
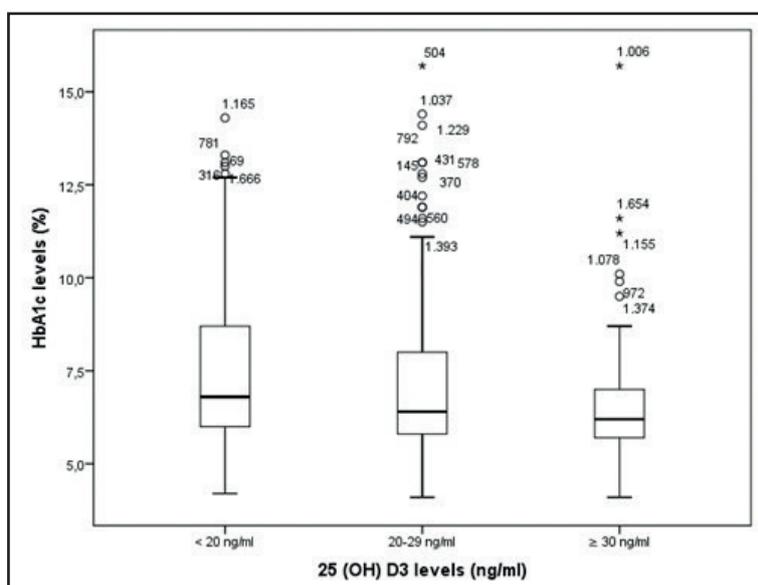
Figure 1.
Glycemic control (HbA1c levels) compared to 25-(OH)-D3 levels. (HbA1c: glycosylated hemoglobin; 25-(OH)-D3: 25-hydroxyvitamin D).
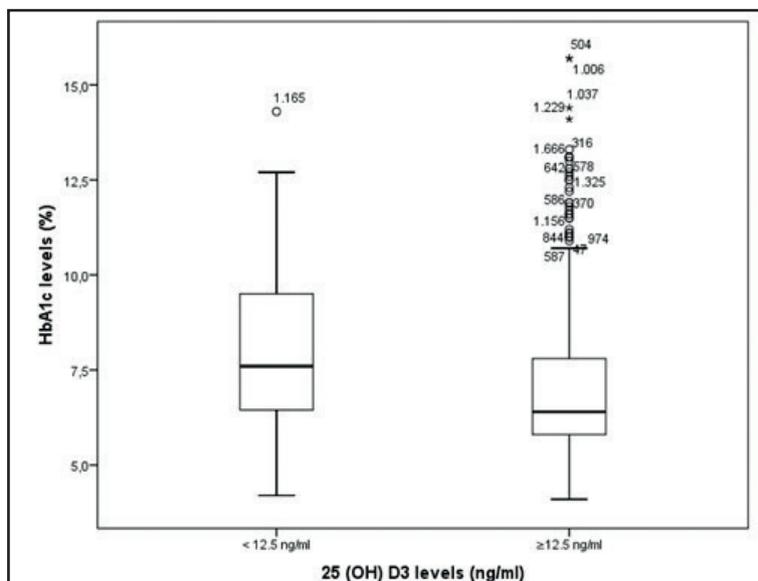
Figure 2.

Glycemic control (HbA1c levels) compared to 25-(OH)-D3 levels < 12.5 ng/mL. (HbA1c: glycosylated hemoglobin; 25-(OH)-D3: 25-hydroxyvitamin D).
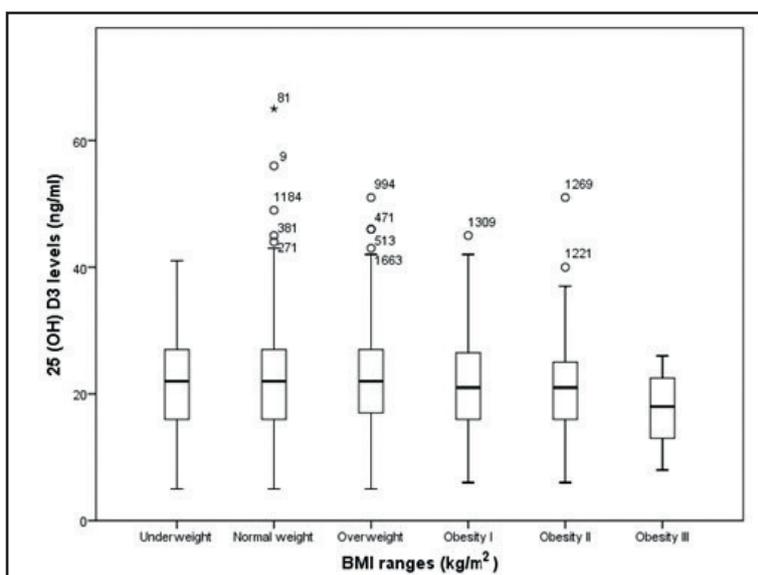
Figure 3.

25-(OH)-D3 levels by BMI range. Body mass index (BMI) range as established by the World Health Organization (WHO). P-value: 0.011 (between groups), 0.043 (underweight vs. obesity III), 0.010 (normal weight vs. obesity III), and 0.007 (overweight vs. obesity III). (25-(OH)-D3: 25-hydroxyvitamin D; BMI: body mass index).

Furthermore, Mirhosseini et al. conducted a meta-analysis in which they found that improved vitamin D status by supplementation reduced glycemic parameters and insulin sensitivity (23). In contrast, He et al. reported in their pooled meta-analysis that vitamin D supplementation had no significant effect neither on improving fasting glucose levels or insulin resistance, nor on preventing T2DM in nondiabetics (24).

Bener et al. carried out a case-control study in which they found that patients with T2DM had increased risk of vitamin D deficiency when compared with the control group (25). By multivariate analysis, we found that T2DM was associated with a higher risk of vitamin D deficiency (< 20 ng/mL) as compared with non-T2DM patients. Moreover, we observed that T2DM patients with low 25-(OH)-D3 levels had a higher risk of suboptimal and poor glycemic control.

Similarly, Zoppini et al. determined that high HbA1c levels were associated with low serum concentrations of 25-(OH)-D3 in T2DM patients (26).

In particular, we observed a higher risk of suboptimal and poor control in patients with 25-(OH)-D3 levels < 12.5 ng/mL when compared to patients with 25-(OH)-D3 sufficiency. Likewise, 25-(OH)-D3 levels < 12.5 ng/mL were associated with a higher mortality risk when compared to 25-(OH)-D3 levels ≥ 12.5 ng/mL.

Regarding adiposity, Rafiq et al. showed through a meta-analysis an overall inverse relationship between vitamin D status and BMI in both diabetic and nondiabetic patients (27). In our results, we found lower 25-(OH)-D3 levels in patients with greater BMI, although this difference was statistically significant only for grade-III obesity (BMI ≥ 40 kg/m^2). Also, Camozzi et al. evaluated the response to oral loading with a single high dose of cholecalciferol and reported that lower 25-(OH)-D3 levels were seen in obese and overweight patients, probably due to a larger body volume and slower release of vitamin D into the circulation (28). Various retrolective studies reported similar findings, as they found that BMI is inversely associated with an increase in serum 25-(OH)-D3 levels in response to vitamin D supplementation, this being most significant in obese patients (class II and above group) (29).

Among autoimmune diseases, Broder et al. performed a logistic regression model in which they reported a higher risk of vitamin D deficiency in autoimmune diseases such as SLE and RA. However, this association was not statistically significant (30). Additionally, Serra-Planas et al. conducted a case-control study in which they found a two-fold higher prevalence of vitamin D deficiency in patients with T1DM when compared with the control group (31). Similarly, our results suggest that RA, T1DM, and SLE were associated with a higher risk of 25-(OH)-D3 deficiency, specifically at levels lower than 12.5 ng/mL.

Manson et al. proposed that the misinterpretation and misapplication of the recommended dietary allowance for vitamin D has created the appearance of a deficiency pandemic; however, by applying an adequate cutoff to the National Health and Nutrition Examination Survey (NHANES) 2007-2010, they reported that less than 6 % of cases were deficient (25-(OH)-D3 levels < 12.5 ng/mL) (32,33). Nevertheless, further randomized clinical trials should be performed in order to clarify whether < 12.5 ng/mL could be an appropriate cutoff value for vitamin D deficiency.

In recent years several studies have correlated low 25-(OH)-D3 levels with chronic disease; nevertheless, whether vitamin D deficiency increases morbidity and mortality or is just a marker of poor health remains unclear due to contradictory results. For instance, Pludowski et al. conducted a review of randomized controlled trials and meta-analyses, from which they concluded that vitamin D deficiency/insufficiency is associated will all-cause mortality (34). Similarly, Sempos et al. described a reverse J-shaped association between serum 25-(OH)-D3 levels and all-cause mortality, but they clarified it was uncertain whether this association was causal or not (35). In contrast, Autier et al. performed a systemic review in which they concluded that a low 25-(OH)-D3 determination could be a marker rather than a cause of poor health (36). Also, Angelotti et al. supported in their study that vitamin D status is an excellent marker of good overall health (37). Meanwhile, Holick et al. proposed that 25-(OH)-D3 levels were an independent predictor of risk for chronic diseases, contrary to Schöttker et al., who suggested that vitamin D deficiency may not be a risk factor for the development of disease but may instead be a marker of resilience to fatality in potentially fatal diseases (38,39). In consequence, vitamin D deficiency and the possible benefit of its supplementation in chronic diseases remain controversial.

There are several limitations to the present study, including its nature (i.e., retrospective, single-center, observational design [only associations can be found, never causality]) and the lack of information about sun exposure, sunscreen use, diet, lifestyle, dose and adherence to vitamin D supplementation, medication compliance, other supplements taken, reason why vitamin D measurements were requested by the physician, and smoking history, all of which may have an impact on 25-(OH)-D3 levels. Moreover, we had no information related to antibody titers and severity of disease in the case of autoimmune disorders; subsequently, it would be interesting to find out if higher disease activity is correlated with 25-(OH)-D3 levels as implied by previous studies (40). In addition, only including patients already diagnosed with a chronic disease constitutes a relevant bias, as vitamin D levels could be lower due to the fact that the subjects have a health condition but not conversely. Further larger, population-based, prospective studies are required to validate the findings suggested by our current study.

CONCLUSIONS

We found a significant relationship between 25-(OH)-D3 levels and glycemic control, BMI, autoimmune disease, and mortality risk. Nevertheless, whether vitamin D deficiency plays a causal role or is a consequence of chronic disease remains controversial; hence, the possible clinical implications and the potential benefits of optimizing vitamin D status in chronic diseases have not been well clarified. Further prospective, randomized, controlled studies are needed to clearly characterize this possible association, and to determine appropriate disease-specific cutoff values for vitamin D deficiency.

REFERENCES

1. Parva NR, Tadepalli S, Singh P, Qian A, Joshi R, Kandala H, et al. Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). Cureus 2018;10(6):e2741. DOI: 10.7759/cureus.2741
2. Plotnikoff G. Vitamin D Deficiency Time for Inaction? Glob Adv Health Med 2013;2(1):5-6. DOI: 10.7453/gahmj.2013.2.1.001
3. Palacios C, González L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014;144(Pt A):138-45. DOI: 10.1016/j.jsbmb.2013.11.003
4. Caccamo D, Ricca S, Currò M, Ientile R. Health Risks of Hypovitaminosis D: A Review of New Molecular Insights. Int J Mol Sci 2018;19(3):E892. DOI: 10.3390/ijms19030892
5. Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, et al. Vitamin D and Chronic Diseases. Aging Dis 2017;8(3):346-53. DOI: 10.14336/AD.2016.1021
6. Felicidade I, Sartori D, Coort SLM, Semprebon SC, Niwa AM, D'Epiro GFR, et al. Role of 1α,25-Dihydroxyvitamin D3 in Adipogenesis of SGBS Cells: New Insights into Human Preadipocyte Proliferation. Cell Physiol Biochem 2018;48(1):397-408. DOI: 10.1159/000491770

7. Jablonski NG, Chaplin G. The roles of vitamin D and cutaneous vitamin D production in human evolution and health. Int J Paleopathol 2018;23:54-9. DOI: 10.1016/j.ijpp.2018.01.005

8. Kutner A, Brown G. Vitamins D: Relationship between Structure and Biological Activity. Int J Mol Sci 2018;19(7):E2119. DOI: 10.3390/ijms19072119

9. Rosas-Peralta M, Holick MF, Borrayo-Sánchez G, Madrid-Miller A, Ramírez-Arias E, Arizmendi-Uribe E. Dysfunctional immunometabolic effects of vitamin D deficiency, increased cardiometabolic risk. Potential epidemiological alert in America? Endocrinol Diabetes Nutr 2017;64(3):162-73.

10. Schiller A, Gadalean F, Schiller O, Timar R, Bob F, Munteanu M, et al. Vitamin D deficiency-prognostic marker or mortality risk factor in end stage renal disease patients with diabetes mellitus treated with hemodialysis--a prospective multicenter study. PLoS One 2015;10(5):e0126586. DOI: 10.1371/journal.pone.0126586

11. Schöttker B, Saum K, Perna L, Ordóñez-Mena JM, Holleczek B, Brenner H. Is vitamin D deficiency a cause of increased morbidity and mortality at older age or simply an indicator of poor health? Eur J Epidemiol 2014;29(3):199-210. DOI: 10.1007/s10654-014-9894-3

12. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, Thamm M, Tian L, Merkel JM, et al. Vitamin D measurement standardization: The way out of the chaos. J Steroid Biochem Mol Biol 2017;173:117-21. DOI: 10.1016/j.jsbmb.2016.12.002

13. Sempos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. Br J Clin Pharmacol 2018;84(10):2194-207. DOI: 10.1111/bcp.13652

14. Schöttker B, Jorde R, Peasey A, Thorand B, Jansen EH, Groot Ld, et al. Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. BMJ 2014;348:g3656. DOI: 10.1136/bmj.g3656

15. American Diabetes Association (ADA). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S13-S28. DOI: 10.2337/dc19-S002

16. Okazaki R, Ozono K, Fukumoto S, Inoue D, Yamauchi M, Minagawa M, et al. Assessment criteria for vitamin D deficiency/insufficiency in Japan - proposal by an expert panel supported by Research Program of Intractable Diseases, Ministry of Health, Labour and Welfare, Japan, The Japanese Society for Bone and Mineral Research and The Japan Endocrine Society. Endocr J 2017;64(1):1-6. DOI: 10.1507/endocrj.EJ16-0548

17. Mathew CS, Dominic M, Isaac R, Jacob JJ. Prevalence of depression in consecutive patients with type 2 diabetes mellitus of 5-year duration and its impact on glycemic control. Indian J Endocrinol Metab 2012;16(5):764-8. DOI: 10.4103/2230-8210.100671

18. Safarpour P, Vafa MR, Amiri F, Janani L, Noorbakhsh M, Rajabpour Nikoo E, et al. A double blind randomized clinical trial to investigate the effect of vitamin D supplementation on metabolic and hepato-renal markers in type 2 diabetes and obesity. Med J Islam Repub Iran 2018;32:34. DOI: 10.14196/mjiri.32.34

19. Li D, Wei H, Xue H, Zhang J, Chen M, Gong Y, et al. Higher serum 25(OH)D level is associated with decreased risk of impairment of glucose homeostasis: data from Southwest China. BMC Endocr Disord 2018;18(1):25. DOI: 10.1186/s12902-018-0252-4

20. Gao Y, Zheng T, Ran X, Ren Y, Chen T, Zhong L, et al. Vitamin D and Incidence of Prediabetes or Type 2 Diabetes: A Four-Year Follow-Up Community-Based Study. Dis Markers 2018;2018:1926308. DOI: 10.1155/2018/1926308

21. Moreira-Lucas TS, Duncan AM, Rabasa-Lhoret R, Vieth R, Gibbs AL, Badawi A, et al. Effect of vitamin D supplementation on oral glucose tolerance in individuals with low vitamin D status and increased risk for developing type 2 diabetes (EVIDENCE): A double-blind, randomized, placebo-controlled clinical trial. Diabetes Obes Metab 2017;19(1):133-41. DOI: 10.1111/dom.12794

22. Heath AK, Williamson EJ, Hodge AM, Ebeling PR, Eyles DW, Kvaskoff D, et al. Vitamin D status and the risk of type 2 diabetes: the Melbourne Collaborative Cohort Study. Diabetes Res Clin Pract 2018;149:179-87. DOI: 10.1016/j.diabres.2018.05.007

23. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM. Vitamin D Supplementation, Glycemic Control, and Insulin Resistance in Prediabetics: A Meta-Analysis. J Endocr Soc 2018;2(7):687-709. DOI: 10.1210/js.2017-00472

24. He S, Yu S, Zhou Z, Wang C, Wu Y, Li W. Effect of vitamin D supplementation on fasting plasma glucose, insulin resistance and prevention of type 2 diabetes mellitus in non-diabetics: A systematic review and meta-analysis. Biomed Rep 2018;8(5):475-84. DOI: 10.3892/br.2018.1074

25. Bener A, Al-Hamaq AO, Kurtulus EM, Abdullatef WK, Zirie M. The role of vitamin D, obesity and physical exercise in regulation of glycemia in Type 2 Diabetes Mellitus patients. Diabetes Metab Syndr 2016;10(4):198-204. DOI: 10.1016/j.dsx.2016.06.007

26. Zoppini G, Galletti A, Targher G, Brangani C, Pichiri I, Negri C, et al. Glycated haemoglobin is inversely related to serum vitamin D levels in type 2 diabetic patients. PLoS One 2013;8(12):e82733. DOI: 10.1371/journal.pone.0082733

27. Rafiq S, Jeppesen PB. Body Mass Index, Vitamin D, and Type 2 Diabetes: A Systematic Review and Meta-Analysis. Nutrients 2018;10(9):E1182. DOI: 10.3390/nu10091182

28. Camozzi V, Frigo AC, Zaninotto M, Sanguin F, Plebani M, Boscaro M, et al. 25-Hydroxycholecalciferol response to single oral cholecalciferol loading in the normal weight, overweight, and obese. Osteoporos Int 2016;27(8):2593-602. DOI: 10.1007/s00198-016-3574-y

29. King RJ, Chandrajay D, Abbas A, Orme SM, Barth JH. High-dose oral cholecalciferol loading in obesity: impact of body mass index and its utility prior to bariatric surgery to treat vitamin D deficiency. Clin Obes 2017;7(2):92-7. DOI: 10.1111/cob.12176

30. Broder AR, Tobin JN, Putterman C. Disease-specific definitions of vitamin D deficiency need to be established in autoimmune and non-autoimmune chronic diseases: a retrospective comparison of three chronic diseases. Arthritis Res Ther 2010;12(5):R191. DOI: 10.1186/ar3161

31. Serra-Planas E, Aguilera E, Granada ML, Soldevila B, Salinas I, Reverter JL, et al. High prevalence of vitamin D deficiency and lack of association with subclinical atherosclerosis in asymptomatic patients with Type 1 Diabetes Mellitus from a Mediterranean area. Acta Diabetol 2015;52(4):773-9. DOI: 10.1007/s00592-014-0699-3

32. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D Deficiency - Is There Really a Pandemic? N Engl J Med 2016;375(19):1817-20. DOI: 10.1056/NEJMp1608005

33. Yetley EA, Pfeiffer cm, Schleicher RL, Phinney KW, Lacher DA, Christakos S, et al. NHANES monitoring of serum 25-hydroxyvitamin D: a roundtable summary. J Nutr 2010;140(11):2030S-45S. DOI: 10.3945/jn.110.121483

34. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev 2013;12(10):976-89. DOI: 10.1016/j.autrev.2013.02.004

35. Sempos CT, Durazo-Arvizu RA, Dawson-Hughes B, Yetley EA, Looker AC, Schleicher RL, et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. J Clin Endocrinol Metab 2013;98(7):3001-9. DOI: 10.1210/jc.2013-1333

36. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014:2(1):76-89. DOI: 10.1016/S2213-8587(13)70165-7

37. Angellotti E, Pittas AG. The Role of Vitamin D in the Prevention of Type 2 Diabetes: To D or Not to D? Endocrinology 2017;158(7):2013-21. DOI: 10.1210/en.2017-00265

38. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266-81. DOI: 10.1056/NEJMra070553

39. Schöttker B, Brenner H. Vitamin D as a Resilience Factor, Helpful for Survival of Potentially Fatal Conditions: A Hypothesis Emerging from Recent Findings of the ESTHER Cohort Study and the CHANCES Consortium. Nutrients 2015;7(5):3264-78. DOI: 10.3390/nu7053264

40. Mak A. The Impact of Vitamin D on the Immunopathophysiology, Disease Activity, and Extra-Musculoskeletal Manifestations of Systemic Lupus Erythematosus. Int J Mol Sci 2018;19(8):E2355. DOI: 10.3390/ijms19082355