

Vitamin D Levels in Patients With Type 2 Diabetes Mellitus

José María Calvo-Romero, MD and José Manuel Ramiro-Lozano, MD

Background: Vitamin D may influence many diseases, including type 2 diabetes mellitus.

Patients and Methods: We studied serum levels of 25-hydroxyvitamin D (25(OH)D) and associated characteristics in type 2 diabetic outpatients with pharmacologic treatment attended in internal medicine offices in a first-level hospital from Extremadura (Southern Spain).

Results: We included a total of 103 patients. Seventy-two patients (69.9%) had serum levels of 25(OH)D lower than 20 ng/mL. There was inverse correlation between serum levels of 25(OH)D and glycosylated hemoglobin ($r = -0.74, P = 0.01$). In 78 patients without insulin therapy, we found inverse correlation between serum levels of 25(OH)D and fasting serum insulin ($r = -0.82, P = 0.001$) and Homeostasis Model Assessment–Insulin Resistance ($r = -0.51, P < 0.001$).

Conclusions: Vitamin D deficiency is common in type 2 diabetic patients. There are inverse correlations between vitamin D and metabolic control and insulin resistance.

Key Words: type 2 diabetes mellitus, insulin resistance, vitamin D

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There is controversy about the extraskeletal effects of vitamin D.^{1–4} Epidemiological data together with the demonstration of the presence of vitamin D receptor in multiple organs suggest a link between vitamin D and multiple diseases, including type 2 diabetes mellitus (DM).^{1–4} Vitamin D deficiency is common in all populations and age groups.^{1–4} In a population-based study in a sunny country like Spain, 34.7% of a sample of 1226 individuals had vitamin D deficiency, defined as a level of serum 25-hydroxyvitamin D (25(OH)D) lower than 20 ng/mL.⁵ We carried out a study to determine the frequency of this deficiency in type 2 diabetic patients and its associated characteristics.

PATIENTS AND METHODS

We consecutively studied all outpatients with type 2 DM with drug treatment attended in internal medicine offices of a first-level hospital in Extremadura (Southern Spain) between January and December 2013. We excluded all patients treated with vitamin D. The study protocol was approved by the ethics committee in our hospital.

Charlson index was used to assess comorbidity.⁶ Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease 4 Isotope Dilution Mass Spectrometry formula. High-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay. The glycosylated hemoglobin (HbA1c) was determined by high-resolution liquid chromatography with National Glycohemoglobin Standardization Program standardization. Serum 25(OH)D and fasting insulin levels were determined by chemiluminescence. Homeostasis Model Assessment (HOMA)–

Insulin Resistance (IR) was used to determine insulin resistance and was calculated by HOMA-2 calculator (www.dtu.ox.ac.uk/homacalculator/).⁷ Statistical analysis was performed using the χ^2 test and Fisher exact test, when any of the expected values was less than 5, for comparison of proportions and Student *t* test for comparison of means. Statistical significance was defined as *P* value less than 0.05. The correlation between variables was assessed by the correlation coefficient (*r*).

RESULTS

We included a total of 103 patients. The characteristics of all patients and patients with and without insulin therapy are described in Table 1. Seventy-two patients (69.9%) had a serum level of 25(OH)D lower than 20 ng/mL and 25 (24.3%) lower than 10 ng/mL. In 37 patients (35.9%), 25(OH)D levels were determined in March–April–May period, in 10 (9.7%) in June–July–August period, in 24 (23.3%) in September–October–November period, and in 32 (31.1%) in December–January–February period. Serum levels of 25(OH)D in June–July–August period were significantly higher than in September–October–November, December–January–February, and March–April–May periods (20.1 ± 7.7 vs 15.5 ± 7.9 , 14.8 ± 9.1 , and 15.2 ± 8.2 ng/mL; $P < 0.05$). Serum levels of 25(OH)D were lower in women (13.7 ± 7.3 vs 17.8 ± 9.1 ng/mL; $P = 0.01$). Serum levels of 25(OH)D lower than 20 ng/mL were significantly more common among women than among men (82.7% vs 56.9%; $P = 0.002$). Serum levels of 25(OH)D were lower in patients with body mass index (BMI) greater than 30 (14.8 ± 6.5 vs 18.3 ± 8.4 ng/mL; $P = 0.06$). The characteristics of patients with serum 25(OH)D levels lower and higher than 20 ng/mL are compared in Table 2. There was inverse correlation between serum levels of 25(OH)D and HbA1c ($r = -0.74, P = 0.01$) and hs-CRP ($r = -0.77, P < 0.001$). In 77 patients without insulin therapy, we found inverse correlation between serum 25(OH)D and fasting insulin ($r = -0.82, P = 0.001$) and HOMA–IR ($r = -0.51, P < 0.001$).

DISCUSSION

The best method to determine vitamin D status is serum 25(OH)D level.^{1–4} A consensus has defined vitamin D deficiency as a serum 25(OH)D level lower than 20 ng/mL,⁸ although there is controversy.⁹ Vitamin D deficiency, closely related with low sun exposure, is prevalent in all populations,^{1–4} including type 2 diabetic patients. In Scotland, 49% of 87 patients with type 2 DM had serum 25(OH)D levels lower than 20 ng/mL during winter.¹⁰ In Northern Italy, 39% of 390 type 2 diabetic patients had serum 25(OH)D levels lower than 15 ng/mL during the months of November to March.¹¹ In a series of 120 type 2 diabetic patients in a sunny Mediterranean country like Greece, 63% had serum 25(OH)D levels lower than 20 ng/mL,¹² similar to high frequency found in our study. Even in a Caribbean region as the French Guyana, 42% of 277 type 2 diabetic patients had serum 25(OH)D levels lower than 20 ng/mL.¹³ We found a slight seasonal variation in serum 25(OH)D levels. In June–July–August period levels were slightly higher. Diabetic women in our study had lower serum 25(OH)D levels than males, and vitamin D deficiency was significantly more frequent among women. In a large Canadian study in general population older than 35 years, vitamin D

From Internal Medicine Service, Hospital Ciudad de Coria, Coria, Cáceres, Spain. Received April 16, 2015, and in revised form July 19, 2015.

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Reprints: José María Calvo-Romero, MD, Internal Medicine Service, Hospital Ciudad de Coria, C/ Cervantes 75, 10800 Coria, Cáceres, Spain. E-mail: jm.calvo@orangemail.es.

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TABLE 1. Characteristics of Patients

	All Patients (n = 103)	Without Insulin Therapy (n = 77)	With Insulin Therapy (n = 26)
Age, y	72.9 ± 10.2	72.3 ± 9.8	74.4 ± 11.1
Age >70 y	67 (65)	51 (66)	16 (62)
Female sex	52 (50.5)	35 (45)*	17 (65)*
Charlson index	1.9 ± 0.8	1.8 ± 0.8	2.1 ± 0.7
BMI >30 kg/m ²	51 (49.5)	36 (47)	15 (58)
GF <60 mL/min	21 (20.4)	14 (18)	7 (27)

Values in brackets are percentages.
 *Statistical significant difference.
 GF indicates glomerular filtrate (MDRD-4 IDMS).

deficiency was only slightly more common in women than in men (20.6% vs 18.3%).¹⁴ Vitamin D is fat soluble and can be stored in the adipose tissue. It has shown inverse correlation between BMI and serum 25(OH)D.^{2,15} This observation is consistent with our result of serum 25(OH)D levels lower in patients with BMI higher than 30 kg/m², although without reaching statistical significance. One observational study showed inverse correlation between serum 25(OH)D and HbA1c.¹² In our study, we also observed this correlation. Patients with vitamin D deficiency had higher HbA1c, although without reaching statistical significance. These data suggest an association between vitamin D deficiency and poor metabolic control but do not allow to establish a causal relationship because they are observational studies. In a study of 152 type 2 diabetic patients, there was inverse correlation between serum 25(OH)D levels and insulin and HOMA-IR.¹⁶ These results agree with those obtained in our study. HOMA-IR is a method for evaluating the degree of insulin resistance. Again, we must say that studies are observational and causality cannot be established, but there was inverse association between serum 25(OH)D levels and insulin resistance. In our study, we excluded from the HOMA-IR calculation patients treated with insulin, due to the questionable reliability of this method in these patients. As

in our study, it has been described an inverse correlation between serum 25(OH)D levels and hs-CRP levels,¹⁶ a marker of subclinical systemic inflammation.

Different pathophysiological mechanisms may explain the negative effect of vitamin D deficiency in type 2 diabetes, through increased insulin resistance and pancreatic β -cell dysfunction.¹⁷ However, some authors suggest that vitamin D may be a marker of general health.^{17,18} Thus, a low serum 25(OH)D level might be the result of poorer health or even worse metabolic control of diabetes. In this regard, our patients with vitamin D deficiency had greater comorbidity, assessed using Charlson index, although without reaching statistical significance. Finally, it is noteworthy that there is a selection bias in our study because patients attending in internal medicine offices typically have higher age and comorbidity than type 2 diabetic patients from general population. Our results suggest the hypothesis that vitamin D status may influence metabolic control and insulin resistance in type 2 diabetic patients. Intervention studies must confirm or refute this hypothesis.

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TABLE 2. Comparison Between Patients With and Without Vitamin D Deficiency

	25(OH)D <20 ng/mL (n = 72)	25(OH)D ≥20 ng/mL (n = 31)	P
Age	73.3 ± 9.9	72 ± 10.8	0.56
Age >70 y	48 (66.7)	19 (61.3)	0.31
Female sex	43 (59.7)	9 (29)	0.002
Charlson index	2 ± 0.8	1.7 ± 0.8	0.13
Insulin therapy	20 (27.8)	6 (19.3)	0.25
BMI >30 kg/m ²	39 (54.2)	12 (38.7)	0.18
GF <60 mL/min	13 (18.1)	8 (25.8)	0.22
25(OH)D, ng/mL	11.3 ± 3.9	26.1 ± 6.7	<0.001
hs-CRP, mg/dL	0.49 ± 0.8	0.35 ± 0.7	0.51
HbA1c, %	7.8 ± 5.8	6.8 ± 1.3	0.18
Fasting insulin, mU/L*	9.3 ± 6.8	6.7 ± 4.1	0.18
HOMA-IR*	1.34 ± 1	0.97 ± 0.6	0.09

Values in brackets are percentages.

*Only in patients without insulin therapy (n = 77).

GF indicates glomerular filtrate (MDRD-4 IDMS); HbA1c, glycosylated hemoglobin.

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