Association between vitamin D serum levels and inflammatory markers in patients on hemodialysis

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Abstract

Introduction: The relationship between 25-OH-vitamin D and the immune system in patients with chronic kidney disease is a subject of attention. **Objectives:** To assess the prevalence of vitamin D deficiency in patients on hemodialysis and to investigate the association between vitamin D, ultra-sensitive C-reactive protein (US-CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). **Method:** Cross-sectional study of 80 patients on hemodialysis, divided into two groups: a serum 25-OH-vitamin D level < 20 ng/mL was considered to be vitamin D deficiency and a serum level $\geq$ 20 ng/mL was regarded as normal. The relationship between the parameters was defined with Spearman's correlation analysis. **Results:** 40 % of the patients had vitamin D deficiency. There were significant differences between groups in US-CRP ($p = 0.047$), NLR ($p = 0.039$), PLR ($p = 0.042$) and treatment with vitamin D analogues ($p = 0.022$). Vitamin D had a significant negative correlation with US-CRP ($p = 0.026$), NLR ($p = 0.013$) and PLR ($p = 0.022$). **Conclusions:** The prevalence of vitamin D deficiency was 40 %. The values of US-CRP, NLR and PLR were significantly higher in the presence of vitamin D deficiency. A significant inverse correlation was found between vitamin D levels and US-CRP, NLR and PLR.

KEY WORDS: Vitamin D deficiency. Ultra-sensitive C-reactive protein. Neutrophil-to-lymphocyte ratio. Platelet-to-lymphocyte ratio.

Asociación entre los niveles séricos de vitamina D y marcadores inflamatorios en pacientes en hemodiálisis

Resumen

Introducción: La relación entre 25-OH-vitamina D y el sistema inmune en pacientes con enfermedad renal crónica es objeto de atención. **Objetivos:** Evaluar la prevalencia de la deficiencia de vitamina D en pacientes en hemodiálisis e investigar la asociación entre la vitamina D y proteína C reactiva ultrasensible (PCRus), índice neutrófilo-linfocito (INL) e índice plaqueta-linfocito (IPL). **Método:** Estudio transversal de 80 pacientes en hemodiálisis, divididos en dos grupos: un nivel sérico de 25-OH-vitamina D < 20 ng/mL se consideró como deficiencia de vitamina D y $\geq$ 20 ng/mL, como normal. Con el análisis de correlación de Spearman se definió la relación entre los parámetros. **Resultados:** 40 % de los pacientes presentó deficiencia de vitamina D. Hubo diferencias significativas entre los grupos en PCRus ($p = 0.047$), INL ($p = 0.039$), IPL ($p = 0.042$) y tratamiento con análogos de vitamina D ($p = 0.022$). La vitamina D tuvo una correlación negativa significativa con PCRus ($p = 0.026$), INL ($p = 0.013$) e IPL ($p = 0.022$). **Conclusiones:** La deficiencia de vitamina D fue de 40 %. Los niveles de PCRus, INL e IPL fueron significativamente más altos ante deficiencia de vitamina D. Se encontró correlación inversa significativa entre vitamina D y PCRus, INL e IPL.

PALABRAS CLAVE: Deficiencia de vitamina D. Proteína C reactiva ultrasensible. Índice neutrófilo-linfocito. Índice plaqueta-linfocito.

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Date of reception: 02-01-2020
Date of acceptance: 23-04-2020
DOI: 10.24875/GMM.M21000452

Gac Med Mex. 2020;156:509-515
Contents available at PubMed
www.gacetamedicademexico.com

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Introduction

Vitamin D deficiency is highly prevalent in the general population; particularly in the population with chronic kidney disease (CKD), evidence suggests that 76 to 92 % suffer from it.¹ Vitamin D deficiency is associated with high bone turnover, hyperparathyroidism and low bone mineral density in patients on hemodialysis (HD).^{2,3} 25-OH-vitamin D (25-OH-D) levels ≥ 30 ng/mL have been observed to improve muscle strength,² whereas 25-OH-D low levels have been associated with a decrease in muscle strength and mass,² as well as with risk of falls.⁴ On the other hand, low levels of vitamin D are associated with metabolic syndrome and central obesity,⁵ as well as with poorer cognitive function in patients on HD.⁶

Numerous studies published in recent years have demonstrated that there is a close association between reduced levels of 25-OH-D and all-cause mortality, as well as with cardiovascular mortality in subjects with CKD, including incident and prevalent patients on HD and peritoneal dialysis, in whom inflammation is one of the main mechanisms underlying the condition.⁷⁻⁹ Inflammation in patients on HD can be measured using C-reactive protein (CRP), ultrasensitive CRP (US-CRP), interleukin-6, tumor necrosis factor alpha, procalcitonin, albumin, ferritin and cholesterol. Of these markers, US-CRP quantification is the gold standard owing to its low cost and availability.¹⁰ Recently, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as inflammation markers in patients with different disorders, including those on HD.^{11,12}

The direction of the relationship between vitamin D levels and inflammatory biomarkers remains controversial. Some studies have stated that inflammation reduces vitamin D levels, while others indicate that an increase in vitamin D can suppress inflammation.^{13,14} Characteristically, patients on HD tend to have low levels of 25-OH-D; however, few studies have looked into the relationship between vitamin D and inflammation in patients on HD. Therefore, the purposes of this study were to evaluate the prevalence of vitamin D deficiency in patients on HD and to analyze the association between 25-OH-D levels and inflammatory markers.

Method

Cross-sectional study conducted in 102 patients from the Hemodialysis Unit of the San Juan de Dios

Hospital of Zaragoza, Spain, who were evaluated in August 2019. The inclusion criteria were being ≥ 18 years of age and having been on chronic HD for at least three months. Exclusion criteria included absence of data on vitamin D levels, active infection, history of malignancy, active inflammatory disease, and use of immunosuppressive therapy. Overall, four patients had no 25-OH-D levels available, one patient was excluded due to an active infection, 13 due to malignancy, two to the use of immunosuppressive drugs, and other two due to an active inflammatory disease. Of the 102 patients, 80 met the study criteria, which was approved by the local ethics committee.

Patient clinical and demographic characteristics (age, gender, type of vascular access, time on HD, presence of diabetes mellitus, Charlson comorbidity index, body mass index and medication) were recorded.

Laboratory data such as 25-OH-D, hemoglobin, leukocytes, albumin, US-CRP, ferritin, parathyroid hormone (PTH), calcium, phosphorus, HDL cholesterol, LDL cholesterol and triglycerides were obtained from the electronic medical record database.

Kt/v was estimated using the Daugirdas second-generation equation:¹⁵

$$Kt/v = -\ln[(C2/C1) - (0.008 \times T)] + (4 - 3.5 \times (C2/C1)) \times UF/weight$$

Where:

C1, C2 = initial and final urea.

T = time in hours.

UF = pre-post-dialysis weight change in kg.

Although there is no consensus on serum 25-OH-D optimal levels, most experts define vitamin D deficiency as a serum 25-OH-D level < 20 ng/mL.¹⁶ Therefore, a serum 25-OH-D level < 20 ng/mL was identified as vitamin D deficiency and ≥ 20 ng/mL was regarded as normal in our study; however, the Kidney Disease Outcomes and Quality Initiative (KDOQI) guidelines were used to define vitamin D status in patients on HD according to serum 25-OH-D level:

- Deficiency, < 20 ng/mL.
- Insufficiency, from 21 to 30 ng/mL.
- Sufficiency > 30 ng/mL.

We subcategorized patients with severe vitamin D deficiency if serum level was < 10 ng/mL.¹⁷

NLR was obtained by dividing absolute neutrophil count by peripheral blood absolute lymphocyte count, and PLR, by dividing absolute platelet count by absolute lymphocyte count in peripheral blood.

To measure erythropoietin requirements, the erythropoietin resistance index was used (weekly erythropoietin units/weight in kg/hemoglobin in g in 100 mL).

For statistical analysis, the SPSS program, version 21.0 for Windows, was used. Descriptive statistical analysis was carried out for each variable. Median and interquartile range were used to describe quantitative variables with asymmetric distribution. Statistically significant difference between groups was determined using Pearson's chi-square test (for categorical variables) and Mann-Whitney's U-test (for continuous variables without normal distribution). Associations between variables were explored using Spearman's rho (for abnormally distributed data). A p-value < 0.05 was considered to be significant. A subgroup analysis was carried out by dividing the patients according to 25-OH-D levels (< 20 and $\geq$ 20 ng/mL).

Results

A total of 80 patients were included in the study. Median age was 73.35 years, 62.5 % of the patients were males, and median 25-OH-D level was 25.2 ng/mL, as observed in baseline characteristics of the study population (Table 1). The patients were divided in two groups: group 1, with 25-OH-D < 20 ng/mL, and group 2, with 25-OH-D $\geq$ 20 ng/mL. Median 25-OH-D was 11.9 (9.8-14.5) ng/mL in the group with deficiency and 38.6 (26.4-56.1) ng/mL in the group with normal levels. US-CRP, NLR and PLR showed statistically significant differences between both groups ($p = 0.047$, 0.039 and 0.042 , respectively).

Only 32 patients (40 %) had vitamin D sufficient levels, and 16 (20 %), insufficient. The remaining 32 patients (40 %) had vitamin D deficiency; out of them, eight (10 %) had severe deficiency (< 10 ng/mL) (Table 2).

The correlation between 25-OH-D and other parameters was assessed using a bivariate correlation analysis (Table 3). 25-OH-D had a significant positive correlation with Kt/v ($r = 0.245$, $p = 0.034$) and a negative correlation with US-CRP, NLR and PLR ($r = -0.334$, $p = 0.026$; $r = -0.523$, $p = 0.013$; and $r = -0.451$, $p = 0.022$, respectively). There was no significant association between albumin and vitamin D levels ($r = 0.003$, $p = 0.98$). No significant association was found between 25-OH-D, calcium, phosphorus and PTH ($r = 0.197$, $p = 0.08$; $r = -0.063$, $p = 0.579$; and $r = -0.093$, $p = 0.411$, respectively). No significant association was also observed between erythropoietin requirements and vitamin D levels ($r = -0.045$, $p = 0.694$).

Discussion

Patients with CKD on HD have elevated levels of serum inflammatory mediators, particularly US-CRP, since they have been shown to play a central role in the vicious circle of malnutrition, inflammation, atherosclerosis, increased risk of cardiovascular events, and overall mortality.¹⁸ In our study, patients were also observed to have an increase in the levels of inflammatory markers. In recent years, NLR and PLR have been identified as relatively inexpensive and universally available markers that can be used to estimate survival and adverse outcomes in various diseases, including end-stage CKD.^{13,18}

Vitamin D deficiency (serum 25-OH-D levels < 20 ng/mL) and insufficiency (serum 25-OH-D levels of 21 to 30 ng/mL) are common in patients with CKD, including those on HD. In this study, vitamin D deficiency and insufficiency were observed in 40 and 20 %, respectively. Severe deficiency was also common: 10 % of patients showed serum 25-OH-D values < 10 ng/mL. Our findings are consistent with previous data published by Marinelli, who reported 73 % of vitamin D deficiency and 23 % of insufficiency in patients on HD.¹⁹

An association between vitamin D and inflammation has been described, although there is no clear consensus on the subject. For example, Amer et al., in a cross-sectional study in 15,167 patients, observed a statistically significant inverse relationship between 25-OH-D levels < 21 ng/mL and CRP. A retrospective study in 4,120 patients reported a significant association of NLR and PLR with 25-OH-D levels.²⁰ Conversely, in a study of patients with chronic urticaria, no significant relationship was found between vitamin D levels and CRP.²¹ In addition, Yildirim et al. studied the association of 25-OH-D with CRP, erythrocyte sedimentation rate and leukocytes in a population with and without CKD, and did not identify any association between inflammatory markers and 25-OH-D.²²

There are only limited data on the relationship between vitamin D and inflammatory markers in the population undergoing HD. Mirchi et al. analyzed the relationship of 25-OH-D levels with NLR and CRP, which were significantly higher in the group with 25-OH-D < 10 ng/mL; they also found a weak inverse correlation between 25-OH-D and CRP.²³ Kara et al. studied the association between vitamin D levels and inflammatory markers, and reported a statistically significant inverse relationship between vitamin D and CRP and NLR values.²⁴

Table 1. Demographic, clinical and analytical characteristics of patients on hemodialysis with 25-OH-vitamin D deficiency or normal values

	Total (N = 80)	25-OH-D deficiency (n = 32)	No 25-OH-D deficiency (n = 48)	p
	Median (IQR)	Median (IQR)	Median (IQR)	
Age (years)	73.35 (57.8-80.1)	73.5 (56.7-79.9)	73.2 (59-80.4)	0.746
Gender				0.637
Males	50 (62.5 %)	19 (59.4 %)	31 (64.6 %)	
Females	30 (37.5%)	13 (40.6 %)	17 (35.4 %)	
Vascular access				0.486
Atrioventricular fistula	27 (33.8%)	12 (37.5 %)	15 (31.3 %)	
Jugular catheter	50 (62.5%)	18 (56.3 %)	32 (66.7%)	
Femoral catheter	3 (3.7%)	2 (6.2 %)	1 (2%)	
Time on HD (months)	21.75 (8-42.4)	18.5 (7.5-39.3)	25 (8.5-45.5)	0.207
Diabetes	34 (42.5%)	15 (46.9 %)	19 (39.6 %)	0.518
Charlson index	6 (4-8)	6 (4-7)	7 (4-8)	0.426
BMI (kg/m ²)	25.9 (23.6-29.95)	28 (24.9-30.7)	23.8 (22.3-29.2)	0.067
Kt/v	1.43 (1.2-1.61)	1.37 (1.13-1.56)	1.49 (1.27-1.65)	0.16
Hemoglobin (g/dL)	11.9 (11-12.6)	11.7 (11-12.5)	12 (10.9-12.7)	0.516
Leukocytes (× 10 ³ /mm ³)	6.5 (5.2-7.6)	6.7 (5.2-7.6)	6.3 (5.2-7.5)	0.848
Albumin (g/dL)	3.5 (3.2-3.7)	3.4 (3.2-3.6)	3.5 (3.2-3.7)	0.984
US-CRP (mg/dL)	0.75 (0.3-1.2)	0.9 (0.4-1.3)	0.6 (0.3-1)	0.047
NLR	2.7 (1.7-3.6)	3.3 (2-4.4)	2 (1.3-3.1)	0.039
PLR	130.3 (94.1-173.6)	149.1 (101.1-197.2)	111.5 (87.1-150)	0.042
25-OH-D (ng/mL)	25.2 (18.1-35.3)	11.9 (9.8-14.5)	38.6 (26.4-56.1)	< 0.01
Ferritin (ng/mL)	595.1 (385.5-880.7)	620.3 (401.9-932.1)	569.9 (369.1-829.3)	0.382
iPTH (pg/mL)	357.6 (212.1-591.2)	388.2 (208.8-668.9)	326.9 (215.3-513.5)	0.984
Calcium (mg/dL)	8.4 (8-8.9)	8.3 (8-8.8)	8.5 (8.1-9.1)	0.13
Phosphorus (mg/dL)	4.7 (4.2-5.9)	4.6 (4.1-5.7)	4.8 (4.3-6.2)	0.669
LDL-C (mg/dL)	78.3 (54.2-100.2)	83.5 (60.8-102.5)	73 (47.5-98)	0.252
HDL-C (mg/dL)	37 (32.7-43.9)	38 (32.3-45.3)	36 (33-42.5)	0.552
Triglycerides (mg/dL)	116.5 (84.2-158.8)	115 (83.5-147)	118 (85-170.5)	0.869
Treatments				
Erythropoietin	79 (98.8%)	31 (96.9 %)	48 (100 %)	0.218
Anti-hypertensives	57 (71.2%)	20 (62.5%)	37 (77.1 %)	0.158
Vitamin D analogues	59 (73.8%)	28 (87.5 %)	31 (64.6 %)	0.022
EPO dose (U/week)	8250 (4000-15000)	7500 (4500-15000)	9000 (3500-15000)	0.722
Iron dose (mg/week)	33.3 (25-81.25)	33.3 (25-87.5)	33.3 (12.5-75)	0.501
ERI	9.6 (5-19.25)	10.5 (4.7-18.8)	8.7 (5.3-19.7)	0.798

Mann-Whitney's U-test. IQR = interquartile range, 25-OH-D = 25-OH-vitamin D, BMI = body mass index, US-CRP = ultrasensitive C-reactive protein, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, EPO = erythropoietin, ERI = erythropoietin resistance index.

Our research supports the findings of the aforementioned studies and revealed an inverse association between 25-OH-D levels and the new inflammatory markers NLR and PLR. In addition, a positive correlation with Kt/v was also found, where K is urea clearance in the dialyzer, t is the dialysis time and

Table 2. Vitamin D status in patients on hemodialysis (N = 80)

	n	%
Vitamin D deficiency (25-OH- D < 20 ng/mL)	32	40
Vitamin D severe deficiency (25-OH- D < 10 ng/mL)	8	10
Vitamin D insufficiency (25-OH- D 21- 30 ng/mL)	16	20
Vitamin D sufficiency (25-OH- D > 30 ng/mL)	32	40

25-OH-D = 25-OH-vitamin D

Table 3. Bivariate correlation between 25-OH-vitamin D levels and other associated parameters (N = 80)

Parameter	Spearman's correlation coefficient (rho)	p
Age (years)	0.067	0.552
Time on HD (months)	0.177	0.117
Charlson index	0.059	0.6
BMI (kg/m ²)	-0.153	0.175
Kt/v	0.245	0.034
Hemoglobin (g/dL)	0.071	0.529
Leukocytes (× 10 ³ /mm ³)	0.08	0.481
Albumin (g/dL)	0.003	0.98
US-CRP (mg/dL)	-0.334	0.026
NLR	-0.523	0.013
PLR	-0.451	0.022
Ferritin (ng/mL)	0.052	0.644
iPTH (pg/mL)	-0.093	0.411
Calcium (mg/dL)	0.197	0.08
Phosphorus (mg/dL)	-0.063	0.579
LDL-C (mg/dL)	-0.052	0.662
HDL-C (mg/dL)	-0.073	0.525
Triglycerides (mg/dL)	0.097	0.395
EPO dose (U/week)	-0.045	0.694
Iron dose (mg/week)	-0.072	0.526
ERI	-0.005	0.966

25-OH-D = 25-OH-vitamin D, BMI = body mass index, US-CRP = ultrasensitive C-reactive protein, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, EPO = erythropoietin, ERI = erythropoietin resistance index

increase in HD and its metabolic effects on vitamin D synthesis. Experimental evidence indicates that uremic toxins can interfere with vitamin D cutaneous synthesis, similarly as accumulated melanin in the Malpighian layer, where vitamin D synthesis occurs.²⁶

A Kt/v < 1.2 is associated with a chronic inflammatory state that results in high levels of CRP.²⁷ Borazán et al. reported a negative correlation between serum CRP levels and Kt/v in patients on HD ($r = -0.436$, $p < 0.05$).²⁸ On the other hand, Herzig et al. described this correlation in patients on peritoneal dialysis ($r = -0.30$, $p < 0.05$).²⁹

Vitamin D deficiency can lead to secondary hyperparathyroidism in individuals with normal kidney function. However, the relationship between PTH and 25-OH-D has been less clear in clinical trials evaluating patients on dialysis. In our study, no significant association was found between 25-OH-D, phosphorus, calcium and PTH levels. Furthermore, in other investigations, no correlation was found either between vitamin D levels and bone metabolism parameters.^{19,30} Conversely, the observational study by Ojeda et al., carried out in patients on HD with 25-OH-D deficit, showed a decrease in CRP and PTH levels after three months of treatment with calcifediol.³¹

In the study by Ahmadi et al.,⁵ vitamin D deficiency was significantly associated with central obesity; in our analysis, patients with vitamin D deficiency had a higher body mass index, but the differences were not significant. We found that patients with a 25-OH-D level < 20 ng/mL had a lower albumin level in comparison with patients with vitamin D levels ≥ 20 ng/mL, although the difference was not significant. In the study by Bansal et al.,³² a weak negative correlation was found between 25-OH-D levels and body mass index, gender and albumin in patients on HD.

Our patients with vitamin D deficiency had lower hemoglobin levels and a higher erythropoietin resistance index; however, the differences were not statistically significant. One reason for this could be that the therapeutic goals regarding anemia in patients on HD have been achieved in our unit. In turn, one of the factors that most influences on erythropoietin resistance has been described to be the inflammatory state,³³ which in our study was higher in the group with vitamin D deficiency.

Our work has limitations. The study was cross-sectional in nature and, therefore, we cannot establish a causal relationship between inflammatory markers and serum vitamin D levels. The obtained data have limitations due to the fact that biochemical

v is urea distribution volume. Nessim et al. also demonstrated a correlation between vitamin D levels and Kt/v.²⁵ These results suggest a link between uremic clearance

measurements were only performed once, which does not take time-dependent changes into account. The sample size was relatively small, although the number of patients was adequate to show correlations' statistical significance. Another limitation was the reduced number of inflammatory markers that were studied, although those that were selected are widely used, inexpensive and have been shown to be effective.

Conclusions

We found that 40 % of patients had vitamin D deficiency. In addition, the study showed that the US-CRP, NLR and PLR values were significantly higher in the vitamin D-deficiency group, while Kt/v was significantly lower in this group. We showed a significant inverse correlation between serum vitamin D levels and US-CRP, NLR and PLR values, which are all inexpensive and universally available inflammatory markers. The results may suggest that there is an unknown underlying mechanism responsible for the inverse relationship observed in patients on HD. Our study provides a significant contribution to the literature, where controversial results have been generally reported on the subject; we believe that it can lead to other, more complete investigations that will better explore the relationship between vitamin D levels and inflammatory markers in the population on HD.

Conflicts of interest

None.

Funding

This research has not received any specific grant from agencies of the public, commercial, or non-profit sectors.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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