

## OPEN

# Suicide Risk in Rheumatoid Arthritis Patients is Associated With Suboptimal Vitamin D Levels

Ivette Calderón Espinoza, MD,\* Efrain Chavarria-Avila, PhD,\*†‡ Oscar Pizano-Martinez, PhD,\*†§//  
 Erika Aurora Martínez-García, PhD,†||¶ Juan Armendariz-Borunda, PhD,#\*\*  
 Ana Laura Marquez-Aguirre, PhD,†† Arcelia Llamas-García, MD,\*  
 Esther Guadalupe Corona-Sánchez, PhD,†||¶ Guillermo Toriz González, PhD,‡‡  
 and Monica Vazquez-Del Mercado, MD, PhD\*†||

(*J Clin Rheumatol* 2022;28: 137–142)

**Background/Objective:** Rheumatoid arthritis (RA) patients might experience anxiety and depressive symptoms. Deficient vitamin D levels may be a trigger for these conditions. The aim of this study was to determine the frequency of depression, anxiety symptoms, and suicidal risk or ideation in patients with RA associated with vitamin D serum levels.

**Methods:** In this cross-sectional study, we recruited RA patients older than 18 years, classified into 3 groups according to serum vitamin D levels: sufficient,  $\geq 30$  ng/mL; insufficient, 20–29 ng/mL; and deficient,  $< 20$  ng/mL. Based on the self-reported Plutchik and the Hospital Anxiety and Depression Scale, we evaluated the association of suicidal risk, depression, and anxiety with the vitamin D levels in RA and the Rheumatoid Arthritis Quality-of-Life Questionnaire.

**Results:** We studied 72 patients with RA between January and October 2019. We found an inverse correlation between Plutchik score and suicidal risk with inadequate vitamin D levels, but not with the Hospital Anxiety and Depression Scale. Suicidal ideation was associated with a higher score on the Rheumatoid Arthritis Quality-of-Life Questionnaire.

**Conclusions:** Despite the high prevalence of depressive and anxiety symptoms in RA patients, a Plutchik low correlation coefficient with inadequate serum levels of vitamin D was found. However, in the analysis of covariance, we were able to find that vitamin D levels remain associated with a reduction of suicide ideation. Further studies are needed to identify a risk profile for early psychological interventions to improve the quality of life in RA patients.

**Key Words:** rheumatoid arthritis, suicide ideation, suicide intention, suicide risk, vitamin D

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory autoimmune diseases that can cause disability if not diagnosed and treated on time.<sup>1</sup> Besides the rapid remission goal that establishes the treat-to-target strategy in RA, we are not able to evaluate in a holistic way in our patients the impact of constant pain suffering, the psychological impact of a chronic treatment, changes in the quality of life, or self-perception that might contribute to the susceptibility of RA patients to anxiety and depressive disorders.<sup>2,3</sup>

In a previous study by our group, the biopsychosocial aspects of RA were evaluated, showing significantly lower levels of quality of life in patients with RA than in the general population, associated with polypharmacy.<sup>4</sup> A shared pathophysiological pathway between depression and chronic diseases such as RA is chronic inflammation, where proinflammatory cytokines and neurotransmitters produce alterations in behavior. Altered levels of interleukin 6 and tumor necrosis factor  $\alpha$  have been detected in patients with major depression.<sup>5–7</sup> In addition, suicidal ideation has been reported in approximately 6% of patients with RA, up to 2-fold compared with non-RA subjects.<sup>8</sup> Vitamin D has a multitude of functions; the 2 main functions are classified based on the calcium relationship as calcemic and noncalcemic. The most important function of vitamin D is related to bone health, including mineralization, remodeling, and maintenance.<sup>9</sup> However, the function of vitamin D is not limited to bone metabolism, because the renal 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase enzyme (CYP27B1) has been identified in a large number of cells and tissues, such as the immune system and the central nervous system.<sup>10</sup> The association between vitamin D levels and depressive, anxiety, and suicidal ideation has been reported.<sup>11,12</sup> Recent studies reveal the importance of evaluating the suicide risk in vulnerable populations not related to RA, especially in Latin American countries such as Mexico, Peru, and Colombia with increased suicide cases reported.<sup>13–16</sup> In Mexico, the suicide mortality rate has grown from 1.13 in the 1970s to 5.31 in 2017.<sup>13</sup> Notwithstanding in RA, the information seems to be oriented to emphasize the existence of depressive symptoms associated with the disease itself,<sup>17–19</sup> but the association of altered vitamin D levels as a possible triggering or additive factor to conceive depressive and anxiety symptoms including suicidal ideation in RA patients is scarce.<sup>8,11,12</sup> The aim of our study was to determine whether there is an association between depression, anxiety symptoms, and suicidal risk associated with vitamin D serum levels in patients with RA.

From the \*Hospital Civil Dr. Juan I. Menchaca, División de Medicina Interna, Servicio de Reumatología 004086, PNPC CONACyT, †Instituto de Investigación en Reumatología y del Sistema Músculo-Esquelético (IIRSM), ‡Departamento de Disciplinas Filosóficas, Metodológicas e Instrumentales, §Departamento de Morfología, ||UDG-CA-703, Inmunología y Reumatología, ¶Departamento de Fisiología, #Instituto de Biología Molecular en Medicina, Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Guadalajara; \*\*Tecnológico de Monterrey Campus Guadalajara, Zapopan; and ††Unidad de Biotecnología Médica y Farmacéutica, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco (CIATEJ), A.C., Guadalajara; and ‡‡Instituto Transdisciplinar de Investigación y Servicios (ITRANS), Zapopan, Jalisco, México.

I.C.E. and E.C.-A. contributed equally to this work.

Funding was provided by PROINPEP 2019, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara.

All relevant data are within the article.

The authors declare no conflict of interest.

Correspondence: Monica Vazquez-Del Mercado, MD, PhD, Sierra Mojada 950, Puerta 7, Edificio P, planta baja. CP 44340, Colonia Independencia, Guadalajara, Jalisco, México. E-mail: dravme@hotmail.com.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site ([www.jclinrheum.com](http://www.jclinrheum.com)).

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 1076-1608

DOI: 10.1097/RHU.0000000000001823

## METHODS

### Patients

This cross-sectional study was conducted between January and October 2019. All patients were recruited from the outpatient

clinic of rheumatology at the Hospital Civil “Dr. Juan I. Menchaca,” Guadalajara, Mexico. All patients signed the informed written consent with the institutional review board of the Hospital Civil “Dr. Juan I. Menchaca” with the approval of the Secretaria de Salud Jalisco (Register 0332/19 HCJIM/2019). The research was conducted following the Helsinki criteria last updated in 2013, Fortaleza, Brazil.

The inclusion criteria were age >18 years and patients who fulfilled the 2010 classification criteria of the American College of Rheumatology/European League Against Rheumatism.<sup>20</sup> The exclusion criteria were as follows: psychiatric disorders previously diagnosed; use of antidepressive drugs; comorbidities such as renal damage, liver failure, parathyroid disease, pregnancy, and osteoporosis; use of antiresorptive bone remodeling therapy; and use of glucocorticoids (>7.5 mg/d), antifungals, antiretroviral drugs, thiazides, valproate, phenobarbital, diuretics, and phenytoin. Elimination criterion was as follows: patients who withdrew their informed consent.

The patients were classified into 3 groups according to their vitamin D levels as follows: sufficient,  $\geq 30$  ng/mL; insufficient, 20–29 ng/mL; and deficient, <20 ng/mL.<sup>21</sup>

## Disease Activity Indexes

The clinical activity of RA was evaluated using 2 scores: Simplified Disease Activity Index (SDAI)<sup>22</sup> and Clinical Disease Activity Index (CDAI).<sup>23</sup>

## Suicide, Depression, and Anxiety Evaluation

The suicide risk was assessed by the Spanish adaptation of the self-applied Plutchik scale. This scale consists of 15 items with a score maximum of 15 points. High risk of suicide is considered higher than 6 points. This instrument is able to differentiate between suicidal intention and ideation in the past or in the present, and the evaluation of these items uses dichotomy answers (yes or no). The frequency of suicide ideation spans items 13 and 14, and frequency of suicide intention is on the 15 items of the Plutchik scale.<sup>24–27</sup>

Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) score. This scale is made up of 2 subscales, one for anxiety and the other for depression; each subscale evaluates 7 items with scores from 0 to 3, and the standard cutoff point is  $\geq 8$  for both subscales.<sup>28,29</sup> The sensitivity and specificity are shown greater than 80% according to a meta-analysis.<sup>30</sup> The Mexican Spanish language of this instrument has already been validated in the Mexican population, showing consistency (Cronbach  $\alpha = 0.86$ ) and good sensitivity and specificity (0.80).<sup>31</sup>

## Functional Capacity and Quality-of-Life Measurement

Functional capacity was evaluated using the Health Assessment Questionnaire–Disability Index (HAQ-DI), which evaluates the quality of life. Using a Likert scale from 0 to 3, it evaluates 8 aspects of daily life of the patient. A greater score implies more impact on the quality of life.<sup>32–34</sup> Rheumatoid Arthritis Quality-of-Life Questionnaire (RAQoL) is composed of 30 elements, and its interpretation is that the higher score, the worse quality of life in RA.<sup>32,35</sup> On the other hand, RAQoL contains 30 questions with dichotomic answers (yes/no), and the qualification is the result of the sum of yes answers (range, 0–30). A greater score implies more impact on the quality of life.

## Laboratory Measurements

Anti-cyclic citrullinated peptide antibodies and rheumatoid factor were determined by enzyme-linked immunosorbent assay (Axis-Shield Diagnostics Ltd., Dundee, Scotland). Erythrocyte sedimentation rate was measured using Wintrobe's method and C-reactive protein by nephelometry.<sup>36</sup> Vitamin D quantification was determined using the chemiluminescence immunoassay technique (Liaison 25-OH Vitamin D Total Assay, Stillwater, MN).

## Statistical Analysis

We used descriptive statistics including measures of central tendency and dispersion, categorical variables expressed as measures of absolute and relative frequency, and linear variables such as mean and SD or median and interquartile ranges, corresponding to the frequency distribution. The normality of the included variables was analyzed using the Kolmogorov-Smirnov test.

**TABLE 1.** Clinical and Demographic Data of RA Patients

Variable	
Female/male, n	68/4
Age, mean $\pm$ SD, y	50.6 $\pm$ 12.76
Weight, mean $\pm$ SD, kg	66.0 $\pm$ 13.36
Height, mean $\pm$ SD, m	1.6 $\pm$ 0.07
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	25.9 $\pm$ 4.81
Smoke, n (%)	8 (11.1)
CRP, mean $\pm$ SD, mg/L	10.4 $\pm$ 17.20
Anti-CCP, n (%)	41/72 (56.9%)
Anti-CCP, mean $\pm$ SD, IU/mL	86.3 $\pm$ 118.4
RF, n (%)	65/72 (90.3%)
RF, mean $\pm$ SD, IU/L	145.8 $\pm$ 192.0
SDAI, n (%)	
$\leq 3.3$ : remission	13 (18.1)
$\leq 11$ : low activity	23 (31.9)
$> 11$ and $< 26$ : moderate activity	23 (31.9)
$> 26$ : high activity	12 (16.7)
CDAI n (%):	
$\leq 2.8$ : remission	10 (13.9)
$\leq 10$ : low activity	26 (36.1)
$> 10$ and $< 22$ : moderate activity	25 (34.7)
$> 22$ : high activity	11 (15.3)
HAQ-DI, mean $\pm$ SD	0.9 $\pm$ 0.74
Vitamin D levels, n (%)	
Sufficient: $\geq 30$ ng/mL	10 (13.9)
Insufficient: 20–29 ng/mL	25 (34.7)
Deficient: $< 20$ ng/mL	37 (51.4)
DMARDs	
Methotrexate	57 (79.2)
Sulfasalazine	16 (22.2)
Leflunomide	2 (2.8)
Chloroquine	39 (54.2)
Prednisone ( $< 5$ mg/d)	25 (34.7)
Rituximab	4 (5.6)

Anti-CCP, anti-cyclic citrullinated peptide antibodies; BMI, body mass index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; RF, rheumatoid factor.

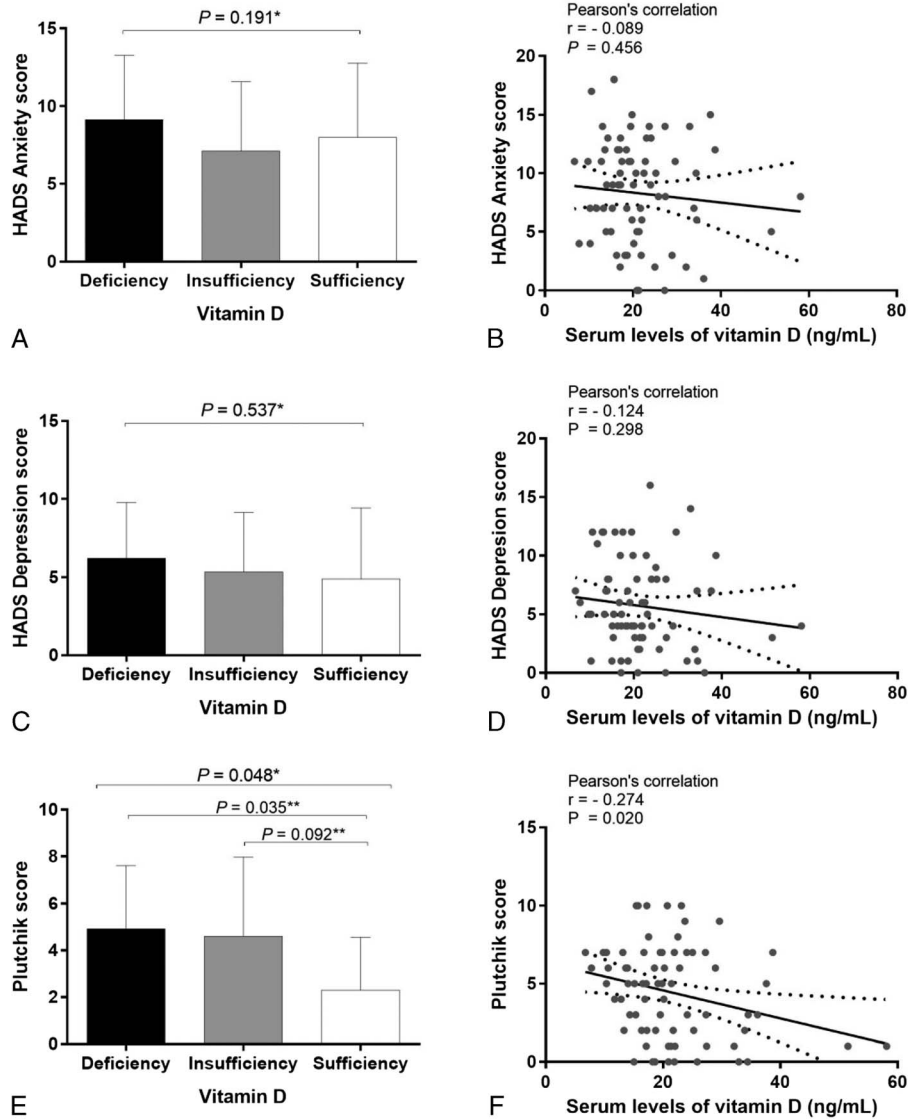


FIGURE 1. Association and correlation between serum levels of vitamin D and HADS and Plutchik scores.

### Inferential Statistics

Groups were made according to the levels of vitamin D, depression, anxiety, suicidal ideation, and suicidal intention, which were compared among these groups.

The hypothesis tests to evaluate linear variables were the Student *t* test or the Mann–Whitney *U* test for independent samples or 1-way analysis of variance or the Kruskal–Wallis test. Categorical variables were analyzed using the  $\chi^2$  test or Fisher exact test. Correlation analysis was carried out using the Pearson (*r*) or Spearman ( $\rho$ ) coefficients according to the distribution and type of variables. Variables with significant correlations were included in the construction of linear multivariate logistic regression models to predict depression and anxiety scores using clinical variables, disease activity, and vitamin D levels as predictive variables. In addition, the variables were dichotomized for the presence of depression, anxiety, and suicidal ideation and were included in the construction of multivariate binary logistic regression models to identify variables with predictive capacity for the presence of these conditions. The measure of association strength was the odds ratio and

95% confidence interval. An adjusted  $\alpha$  error of less than 5% ( $p < 0.05$ ) at the 2 tails was considered significant. The statistical package STATA SE version 11.1 (StataCorp LLC, College Station, TX) was used.

### RESULTS

The study included 72 patients with RA. Most patients were women with clinically low to moderate active disease. The majority of RA patients were vitamin D deficient. The clinical and demographic variables evaluated are shown in the Table 1. When an additional analysis was made according to vitamin D levels classified as sufficient,  $\geq 30$  ng/mL; insufficient, 20–29 ng/mL; and deficient,  $< 20$  ng/mL, for all the variables assessed in the Table 1, only HAQ-DI showed a difference ( $p = 0.008$ ) between deficient ( $1.2 \pm 0.8$ ) versus insufficient ( $0.6 \pm 0.6$ ) and sufficient ( $0.6 \pm 0.7$ ). Frequency of depressive or anxiety symptoms was found in 88.9% by HADS. At the same time, the frequency of suicidal risk was 40.3%, as reported through the self-applied Plutchik scale. Based on the same scale, frequency of suicide ideation was

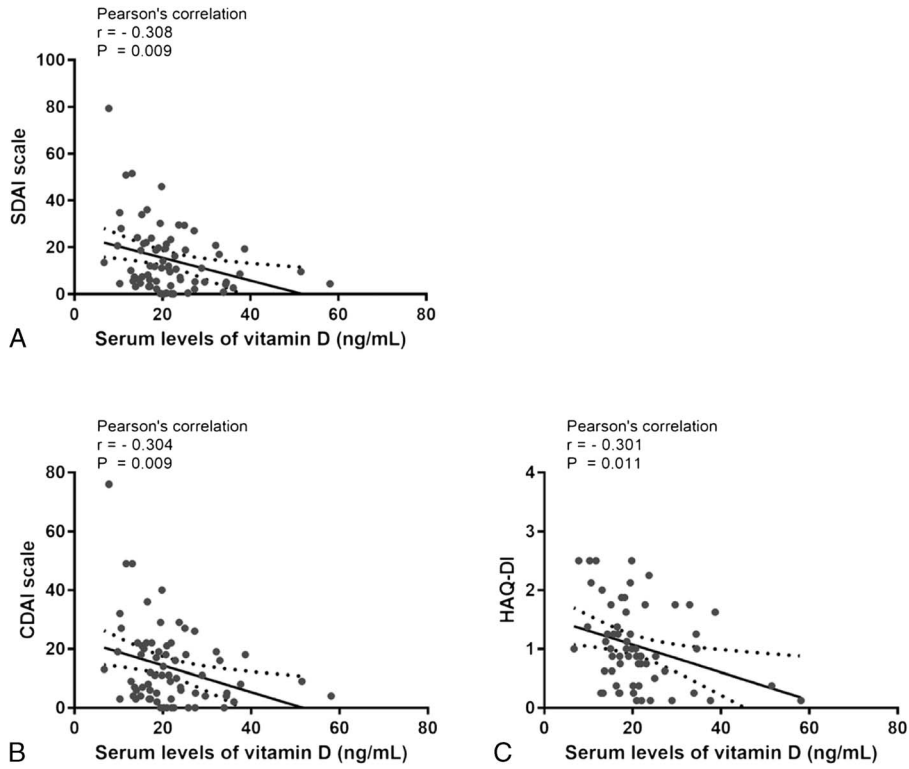


FIGURE 2. Correlation of RA clinical activity, functional capacity, and vitamin D.

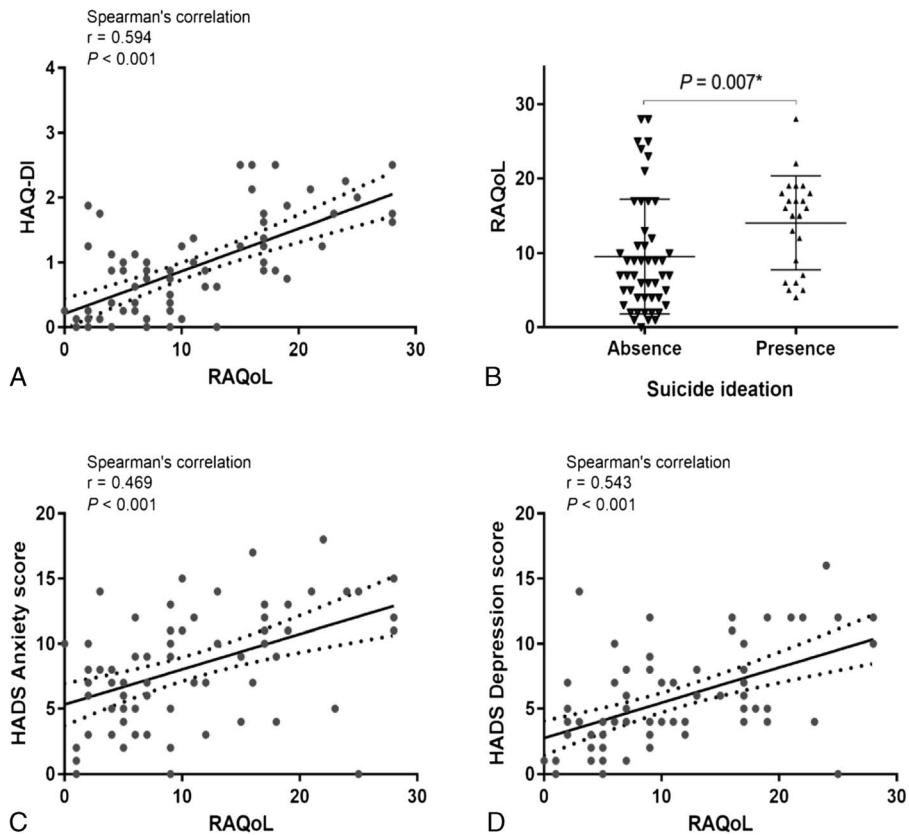


FIGURE 3. Correlation between RAQoL, HAQ-DI, and HADS scores and RAQoL with suicide ideation in RA patients.

identified in 23 subjects (31.9%), and frequency of suicide intention in 6 patients (8.3%).

### Association and Correlation of Suicide Risk According to the Vitamin D Levels

The HADS scores according to anxiety and depression domains were neither associated nor correlated with vitamin D levels (Figs. 1A–D). Notwithstanding, the Plutchik scale score was associated and correlated with vitamin D levels ( $p = 0.020$ ) (Figs. 1E, F).

### RA Clinical Activity, Functional Capacity, and Vitamin D

The composite indices of disease activity SDAI and CDAI, as well as with the HAQ-DI self-questionnaire scores used in this study, showed a low correlation with serum levels of vitamin D (Figs. 2A–C).

### Quality-of-Life Evaluation, Disability, and Depressive and Anxiety Symptoms

The HAQ-DI and HADS scores showed a correlation with RAQoL used in this study (Figs. 3A–D). An association between RAQoL and suicide ideation was established in our patients (Fig. 3B).

### Multivariate Logistic Regression Analysis

When performing a multivariate logistic regression analysis, a valid model for ideation was not obtained (Supplementary Data, <http://links.lww.com/RHU/A420>). In a linear regression analysis, vitamin D was the only variable that remained significantly associated with ideation, explaining 27.8% of the total variance, and also indicates that each nanogram of vitamin D reduces the value of the suicide ideation constant 2.24% (Supplementary Data, <http://links.lww.com/RHU/A420>).

## DISCUSSION

To describe the associations between depressive and anxiety disorders, suicidal ideation, suicidal risk with vitamin D levels, and development of clinical trials related to vitamin D supplementation might help to develop a holistic approach in RA management.<sup>37</sup> In other words, supplementation with vitamin D could be used as another therapeutic step in the treat-to-target strategy for RA. An adequate and multidisciplinary management of depressive and anxious symptoms can improve a patient's health status and quality of life.

Our patients recruited for this study were low to moderately active according to SDAI and CDAI in approximately 60% associated with mild to moderate functional disability (Table 1). This study also showed a high prevalence of depressive and anxious symptoms (approximately 90%), as evaluated by the HADS score. In addition, the suicide risk in RA patients assessed by the self-reported Plutchik scale was found in 6 of 10 patients included. These results are remarkably high compared with those in the literature using this instrument in different disorders<sup>29,38,39</sup> and in agreement with other authors.<sup>38</sup>

Notwithstanding the high prevalence of depressive and anxiety symptoms, we were able to demonstrate an association and a low correlation coefficient with Plutchik score and inadequate serum levels of vitamin D (Figs. 1E, F). Our study showed that vitamin D levels were inversely related to the SDAI, CDAI, and HAQ-DI scores (Fig. 2). The importance of vitamin D supplementation has been debated in RA, and a recent meta-analysis showed that doses of vitamin D  $\geq 50,000$  IU seem to improve the quality of life and diminish the clinical disease activity index.<sup>40</sup> Finally, higher scores

of RAQoL correlated with a greater functional disability, anxiety, and depression (Figs. 3A, C, D), and suicide ideation was associated with the RAQoL score (Fig. 3B). Based on our results, patients with a HADS score  $\geq 8$  were referred to the psychology service. When the Plutchik scale score was  $\geq 6$ , a referral to the psychiatric service was performed. Vitamin D supplementation was started in all patients with insufficient or deficient levels, and disease-modifying antirheumatic drug treatment with moderate or severe RA activity was adjusted when needed. This study described suicidal ideation and suicidal risk in patients with RA associated with inadequate vitamin D serum levels. If vitamin D is identified as an additional risk factor for maintaining the quality of life in RA, adequate levels of vitamin D could reduce the suicidal and ideation risk in this group of patients. Our results suggest that further studies need to be carried out with a greater number of patients using other validated instruments that allow adequate and reliable screening of suicide, depression, and anxiety symptoms in RA patients in daily clinical practice.

Finally, we must be aware of the limitations of our study. First are the limitations inherent in cross-sectional studies like ours, such as: provide data from a single moment in time and it is impossible to make inferences of causality, mainly. Second is the fact that the RA itself could trigger depression, anxiety, and even suicide ideation related to the complexity of the RA patient's life. Third is the subclinical presence of these symptoms not registered through the instruments applied in this study. Fourth is the impact of comorbidities such as diabetes mellitus or vascular disease that might influence the anxiety or depressive symptomatology or the existence of fibromyalgia not evaluated in this study.

In conclusion, despite the high prevalence of depressive and anxiety symptoms in RA patients, a Plutchik low correlation coefficient with inadequate serum levels of vitamin D was found. However, in the analysis of covariance, we were able to find that vitamin D levels remain associated with a reduction of suicide ideation. Further studies are needed to identify a risk profile for early psychological interventions to improve the quality of life of RA patients.

## REFERENCES

- Petrovska N, Prajzlerova K, Vencovsky J, et al. The pre-clinical phase of rheumatoid arthritis: from risk factors to prevention of arthritis. *Autoimmun Rev*. 2021;20:102797. doi:10.1016/j.autrev.2021.102797.
- Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol*. 2016;12:532–542. doi:10.1038/nrrheum.2016.112.
- Besirli A, Alptekin JO, Kaymak D, et al. The relationship between anxiety, depression, suicidal ideation and quality of life in patients with rheumatoid arthritis. *Psychiatr Q*. 2020;91:53–64. doi:10.1007/s11126-019-09680-x.
- Gonzalez-Gamboa LM, Barocio-Ramirez AK, Rocha-Munoz AD, et al. Disease activity score on 28 joints and polypharmacy are independent predictors for health-related quality of life evaluated by INCAVISA in patients with rheumatoid arthritis. *J Clin Rheumatol*. 2016;22:399–404. doi:10.1097/RHU.0000000000000463.
- Lanquillon S, Krieg JC, Bening-Abu-Shach U, et al. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000;22:370–379. doi:10.1016/S0893-133X(99)00134-7.
- Alesci S, Martinez PE, Kelkar S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab*. 2005;90:2522–2530. doi:10.1210/jc.2004-1667.
- Tuglu C, Kara SH, Caliyurt O, et al. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder.

- Psychopharmacology (Berl)*. 2003;170:429–433. doi:10.1007/s00213-003-1566-z.
8. Tektonidou MG, Dasgupta A, Ward MM. Suicidal ideation among adults with arthritis: prevalence and subgroups at highest risk. Data from the 2007–2008 National Health and Nutrition Examination Survey. *Arthritis Care Res (Hoboken)*. 2011;63:1322–1333. doi:10.1002/acr.20516.
  9. Bikle DD. Vitamin D and bone. *Curr Osteoporos Rep*. 2012;10:151–159. doi:10.1007/s11914-012-0098-z.
  10. Anderson PH, May BK, Morris HA. Vitamin D metabolism: new concepts and clinical implications. *Clin Biochem Rev*. 2003;24:13–26.
  11. Kim SY, Jeon SW, Lim WJ, et al. Vitamin D deficiency and suicidal ideation: a cross-sectional study of 157,211 healthy adults. *J Psychosom Res*. 2020;134:110125. doi:10.1016/j.jpsychores.2020.110125.
  12. Gokalp G. The association between low vitamin D levels and suicide attempts in adolescents. *Ann Clin Psychiatry*. 2020;32:106–113.
  13. Cervantes CAD, Montano AMP. Study of suicide burden of mortality in Mexico 1990–2017. *Rev Bras Epidemiol*. 2020;23:e200069. doi:10.1590/1980-549720200069.
  14. Cardona Arango D, Medina-Perez OA, Cardona Duque DV. Characterisation of suicide in Colombia, 2000–2010 [in Spanish]. *Rev Colomb Psiquiatr*. 2016;45:170–177. doi:10.1016/j.rp.2015.10.002.
  15. Roman-Lazarte V, Moncada-Mapelli E, Huarcaya-Victoria J. Evolution and differences of suicide rates in Peru by gender and department, 2017–2019. *Rev Colomb Psiquiatr (Engl Ed)*. 2021. doi:10.1016/j.rp.2021.03.005.
  16. Chaparro-Narvaez P, Diaz-Jimenez D, Castaneda-Orjuela C. The trend in mortality due to suicide in urban and rural areas of Colombia, 1979–2014. *Biomedica*. 2019; 39 : 339–353. 10.7705/biomedica.v39i3.4427
  17. Pu D, Luo J, Wang Y, et al. Prevalence of depression and anxiety in rheumatoid arthritis patients and their associations with serum vitamin D level. *Clin Rheumatol*. 2018;37:179–184. doi:10.1007/s10067-017-3874-4.
  18. Kim SY, Chanyang M, Oh DJ, et al. Association between depression and rheumatoid arthritis: two longitudinal follow-up studies using a national sample cohort. *Rheumatology (Oxford)*. 2020;59:1889–1897. doi:10.1093/rheumatology/kez559.
  19. Chimenti MS, Fonti GL, Conigliaro P, et al. The burden of depressive disorders in musculoskeletal diseases: is there an association between mood and inflammation? *Ann Gen Psychiatry*. 2021;20:1. doi:10.1186/s12991-020-00322-2.
  20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569–2581. doi:10.1002/art.27584.
  21. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–1930. doi:10.1210/jc.2011-0385.
  22. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)*. 2003;42:244–257. doi:10.1093/rheumatology/keg072.
  23. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7:R796–R806. doi:10.1186/ar1740.
  24. Plutchik R, Van Praag H. The measurement of suicidality, aggressivity and impulsivity. *Prog Neuropsychopharmacol Biol Psychiatry*. 1989;13 (Suppl):S23–S34. doi:10.1016/0278-5846(89)90107-3.
  25. Ordóñez-Carrasco JL, Cuadrado Guirado I, Rojas Tejada A. Scale of psychological pain: Spanish adaptation of the Psychache Scale in young adults. *Rev Psiquiatr Salud Ment (Engl Ed)*. 2019;S1888-9891: 30051–30055. doi:10.1016/j.rpsm.2019.04.003.
  26. Rangel-Garzón CXS-BM, Escobar-Córdoba F. Escalas de evaluación de riesgo suicida en atención primaria. *Rev Fac Med*. 2015;63:707–716. doi:10.15446/revfacmed.v63.n4.50849.
  27. Rubio GMI, Jáuregui J, Salvador M, et al. Validación de la escala de riesgo suicida de Plutchik en población española. *Arch Neurobiol (Madr)*. 1998; 61:143–152.
  28. Hitchon CA, Zhang L, Peshken CA, et al. Validity and reliability of screening measures for depression and anxiety disorders in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2020;72:1130–1139. doi:10.1002/acr.24011.
  29. Suarez-Mendoza A, Petersen-Aranguren F, Almeida-Velasco A, et al. Psychometric evaluation of the Hospital Anxiety and Depression Scale in Mexican adults with ischemic and hypertensive cardiomyopathy. *Arch Cardiol Mex*. 2019;89:221–226. doi:10.24875/ACME.M19000060.
  30. Terol-Cantero C, Cabrera-Perona V, Martín-Aragón M. Revisión de estudios de la escala de ansiedad y depresión hospitalaria (AD) en muestras españolas. *An Psicol*. 2015;31:494–503.
  31. Galindo-Vázquez O, Benjet C, Juárez-García F, et al. Propiedades psicométricas de la escala Hospitalaria de Ansiedad y Depresión (HADS) en una población de pacientes oncológicos mexicanos. *Salud Ment*. 2015; 38:253–258.
  32. Pacheco-Tena C, Reyes-Cordero G, McKenna SP, et al. Adaptation and validation of the Rheumatoid Arthritis Quality of Life Scale (RAQoL) to Mexican Spanish. *Reumatol Clin*. 2011;7:98–103. doi:10.1016/j.reuma.2010.02.002.
  33. Esteve-Vives J, Batlle-Gualda E, Reig A. Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptación del HAQ a la Población Española. *J Rheumatol*. 1993;20:2116–2122.
  34. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol*. 2005;23(5 Suppl 39):S14–S18.
  35. de Jong Z, van der Heijde D, McKenna SP, et al. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. *Br J Rheumatol*. 1997;36:878–883. doi:10.1093/rheumatology/36.8.878.
  36. Perez-Vázquez F, Back M, Chavarria-Avila E, et al. Enalapril influence on arterial stiffness in rheumatoid arthritis women: a randomized clinical trial. *Front Med (Lausanne)*. 2019;6:341. doi:10.3389/fmed.2019.00341.
  37. Nguyen Y, Sigaux J, Letarouilly JG, et al. Efficacy of oral vitamin supplementation in inflammatory rheumatic disorders: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2020;13:107. doi:10.3390/nu13010107.
  38. Igwesi-Chidobe CN, Muomah RC, Sorinola IO, et al. Detecting anxiety and depression among people with limited literacy living with chronic low back pain in Nigeria: adaptation and validation of the Hospital Anxiety and Depression Scale. *Arch Public Health*. 2021;79:72. doi:10.1186/s13690-021-00586-4.
  39. Tasnim R, Sujjan MSH, Islam MS, et al. Prevalence and correlates of anxiety and depression in frontline healthcare workers treating people with COVID-19 in Bangladesh. *BMC Psychiatry*. 2021;21:271. doi:10.1186/s12888-021-03243-w.
  40. Guan Y, Hao Y, Guan Y, et al. The effect of vitamin D supplementation on rheumatoid arthritis patients: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2020;7:596007. doi:10.3389/fmed.2020.596007.