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

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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, ≥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

METHODS

Patients

This cross-sectional study was conducted between January and October 2019. All patients were recruited from the outpatient...
The 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 HJCIM/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.20 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, ≥30 ng/mL; insufficient, 20–29 ng/mL; and deficient, <20 ng/mL.21

Disease Activity Indexes

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

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/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.24–27

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 ≥8 for both subscales.28,29 The sensitivity and specificity are shown greater than 80% according to a meta-analysis.30 The Mexican Spanish language of this instrument has already been validated in the Mexican population, showing consistency (Cronbach α = 0.86) and good sensitivity and specificity (0.80).31

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.32–34 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.32,35 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.36 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                      | Value       |
|-------------------------------|-------------|
| Female/male, n                | 68/4        |
| Age, mean ± SD, y             | 50.6 ± 12.76|
| Weight, mean ± SD, kg         | 66.0 ± 13.36|
| Height, mean ± SD, m          | 1.6 ± 0.07  |
| BMI, mean ± SD, kg/m²         | 25.9 ± 4.81 |
| Smoke, n (%)                  | 8 (11.1)    |
| CRP, mean ± SD, mg/L          | 10.4 ± 17.20|
| Anti-CCP, n (%)               | 41/72 (56.9%)|
| Anti-CCP, mean ± SD, IU/mL    | 86.3±118.4  |
| RF, n (%)                     | 65/72 (90.3%)|
| RF, mean ± SD, IU/L           | 145.8±192.0 |
| SDAI, n (%)                   | 2.8: remission 10 (13.9) |
| CDAI n (%)                    | 10: low activity 26 (36.1) |
| >11 and <26: moderate activity 23 (31.9) |
| >26: high activity 12 (16.7)  |
| HAQ-DI, mean ± SD             | 0.9 ± 0.74  |
| Vitamin D levels, n (%)       | 10 (13.9)   |
| Sufficient, ≥30 ng/mL         | 25 (34.7)   |
| Insufficient, 20–29 ng/mL     | 37 (51.4)   |
| Deficient, <20 ng/mL          | 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.
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 χ² test or Fisher exact test. Correlation analysis was carried out using the Pearson (r) or Spearman (ρ) 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 α 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, ≥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 ± 0.8) versus insufficient (0.6 ± 0.6) and sufficient (0.6 ± 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.14 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 disorders15,38,39 and in agreement with other authors.38

Notwithstanding the high prevalence of depressive and anxiety symptoms, we were able to demonstrate an association and a low correlation coefficient with Plutchik scale 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 ≥50,000 IU seem to improve the quality of life and diminish the clinical disease activity index.40 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 ≥8 were referred to the psychology service. When the Plutchik scale score was ≥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 inadequately 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.

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