Associated Risk Factors and Prevalence of Sleep Disorders in Patients With Rheumatoid Arthritis.

Pedro Santos-Moreno (✉ pedrivansamo@hotmail.com)

BIOMAB IPS <https://orcid.org/0000-0001-7802-0317>

Carlos Alberto Castro

SIIES Consultores SAS, Fundación Universitaria de Ciencias de la Salud - FUCS

Laura Villarreal

BIOMAB IPS

Guillermo Sánchez-Vanegas

SIIES Consultores SAS, Fundación Universitaria de Ciencias de la Salud - FUCS

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune chronic pathology, present in between 0.5% and 1% of adults. This disease is accompanied by comorbidities such as sleep disorders (SD) that occur in between 54% and 70% of the population with RA. The objective of this study was to identify the associated risk factors and the prevalence of sleep disorders in a group of patients with rheumatoid arthritis in a referral center for the management of autoimmune diseases in Bogotá, Colombia.

Methods: An analytical cross-sectional study was carried out on a population of patients with Rheumatoid Arthritis (RA) evaluated with the DSM-V. The factors related to sleep disorders and disease activity of were explored. The prevalence of sleep disorders was determined, and a multivariate logistic regression analysis was conducted.

Results: the study analyzed a total of 1436 patients, with a median age of 56 years. The prevalence of sleep disorders was 31.1%. There was an association between the presence of sleep disorders and Disease Activity Score 28 (DAS28) (OR: 3.8 CI 95%: 3-5), Health Assessment Questionnaire (HAQ) (OR: 3.2 CI 95%: 2.5-4.1), self-care activities (OR: 0.6 CI 95%: 0.4-0.9), and somatic symptom disorder (OR: 1.8, CI 95%: 1.3-2.6).

Conclusions: An association (p-value <0.05) was found between SDs and disease activity (DAS28), functional capacity (HAQ), scholarship level, smoking, sedentary lifestyle, metabolic diseases, and leisure and self-care activities. In one third of patients SD were prevalent. It is suggested that patients be approached comprehensively carrying out behavioral and cognitive activities.

Introduction

Rheumatoid arthritis (RA) is a chronic pathology of autoimmune origin, which affects the musculoskeletal system and the patient's psychosocial well-being (1). It is estimated that its worldwide prevalence ranges from 0.5 to 1.5%, figures that are like those reported for Latin America (1.5%) and Colombia (0.9%). This condition most often affects women with a female/male ratio of 2–4/1 respectively and most cases (60%) occur between the ages of 35 and 65 (2–4). In 65% of cases, RA is accompanied by comorbidities such as sleep disorders (SDs) (54–70%) (5, 6), which have an impact on sleep conciliation, sleep quality, and restless sleep (7). Multiple theories have been suggested, which have not yet been clearly determined; however, the relevance of the immunological mechanisms where cytokines play an important role in the pathophysiology of pain, in turn, is involved with sleep deprivation (8). These disorders affect physical aspects, which are reflected in the patients' disability on their daily performance, becoming a predisposing factor for the incidence of psychological and psychiatric pathologies (7). Studies have shown that the lack of control of these comorbidities can increase the negative aspects of RA, such as adherence to treatment, clinical response, and the prognosis of the disease. All this requires a comprehensive clinical approach, recommended by the "European League Against Rheumatism - EULAR" and which is a complementary tool to medical treatment, showing better

effectiveness when compared to conventional clinical treatment (9). Additionally, medical treatment for RA should be complemented with psychosocial or pharmacological interventions that control comorbidities, aiming to the management of pain and the perception of chronic disease, thus improving the psychosomatic aspects and therefore the patient's quality of life (10). According to the above and in the Colombian context, it is necessary to identify the presence of SDs and to investigate other associated factors that may contribute to the change in disease activity and its possible consequences. The above in order to advance a comprehensive treatment model and contribute to the global improvement of the patient, both of their underlying disease, and in the different pathologies that usually accompany RA.

Consequently, the objective of this research was to identify the associated risk factors and prevalence of sleep disorders in a group of patients with rheumatoid arthritis in a referral center for the management of autoimmune diseases in Bogotá, Colombia.

Methods

Design and study population. An analytical cross-sectional study was carried out in a reference center for autoimmune diseases in the city of Bogotá, Colombia. This institution has an information registry of all patients admitted for the care of RA. Taking into account the criteria of the American College of Rheumatology - EULAR (11) all patients with a diagnosis of RA were attended by a rheumatologist who carried out a clinical (tender and swollen joint count) and whole-blood test with: creatinine, ESR, alkaline phosphatase, anticitrullinated antibodies, aminotraferase, and rheumatoid factor, who were treated at BIOMAB, and were evaluated in the psychology consultation as part of the comprehensive approach. The patients whose records did not have a Disease Activity Score 28 (DAS28) or a Health Assessment Questionnaire (HAQ) report were excluded.

Information Collection. The data originated from the reference center medical records management system, and it was extracted without identifiers guaranteeing the confidentiality of the patients. This information was the result of 5 years of care for patients with RA, within the comprehensive care plan of the RA center BIOMAB.

Origin of database

To improve results of health care, the Colombian Ministry of Health created a national health policy (12), and Rheumatoid Arthritis Registry (13), to monitor patients with RA. A retrospective real-world data (RWD) analysis was undertaken from clinical records of patients diagnosed with RA who had attended a center specialized in RA in Bogotá, Colombia between 2011 and 2015. A total of 89 variables including demographics, diagnosis, treatment, and clinical outcomes information were extracted and structured in a database to serve as the report, which is mandatory by law (13). The study was approved by the internal research committee of the center.

Variables of interest. The presence of sleep disorders was defined as the outcome variable. The remaining variables were considered as independent variables or related factors. Among these are: the

clinimetry behavior of RA, using DAS28 (Disease Activity Score) for disease activity which was categorized as *non-activity*: remission and mild DAS28 activity < 3.2 , and *activity*: moderate and severe activity DAS28 > 3.21 (14); functional capacity with the HAQ scale (Health Assessment Questionnaire), categorized into: without disability or mild disability (< 1) and with moderate or severe disability (> 1.1) (15, 16); sociodemographic variables (age, sex, schooling, marital status, companions); and psychological alterations (mood, sexual function and sleep disorders). Regarding treatment, it was classified as conventional treatment with and without biological drugs. To determine the clinical diagnosis, the patients were evaluated by interdisciplinary group specialized in RA made up of a rheumatologist, a physiatrist, a physical therapist, a nurse and a pharmaceutical chemist. Similarly, they were evaluated by a psychologist with experience in chronic diseases and RA. The diagnosis of DS was considered by the medical history, at the time of the initial evaluation, considering the medical history and by symptoms reported by the patient. For the diagnosis, the Diagnostic and Statistical Manual of Mental Illness (DSM-V) was taken into account (17). These patients were referred for a specialized evaluation for the treatment of DS.

Statistical analysis

A descriptive analysis of the data was performed using absolute and relative frequencies for the qualitative variables, and for the quantitative variables, measures of central tendency and dispersion. The Shapiro-Wilk test was applied for the evaluation of normality in the numerical variable distribution. For the calculation of prevalence, the cases of patients with a confirmed sleep disorder diagnosis were considered in the numerator, and the denominator included all patients with a confirmed RA diagnosis at the time of the evaluation. A p-value of less than 0.05 was considered for the hypothesis test. An exploration of possible factors associated with the presence of sleep disorders was carried out using parametric and non-parametric tests, according to the variable's characteristics. In order to estimate possible epidemiological associations, the indirect relative risk (Odds Ratio - OR) with its respective confidence intervals was calculated. A logistic regression model will be built, and it will include a set of possible predictors capable of explaining the occurrence of sleep disorders. This model will be validated with the Hosmer-Lemeshow goodness of fit test. This information was analyzed in STATA 12.

According to Resolution 1393 of 2015 from the Ministry of Health of Colombia, for whole private/public health care providers and insurances/payers companies is mandatory to report the data of patients with rheumatoid arthritis (RA) diagnosis to National Registry of RA (NARRA), which includes 89 clinical and administrative variables; additionally, according to Resolution 8430 of 1993 from the Ministry of Health, this research presents no risks to patients.

This study considered the international regulation for research with human beings (and it considered the Colombian research regulation (Resolution 8430 of 1993), classifying it as research with minimum risk. All patients signed the informed consent for the use of their clinical and personal information. This study was presented to and approved by the BIOMAB research committee (April 4, 2019, registered in folder 25).

Results

We included 1436 patients with a diagnosis of RA from a reference center in Bogotá (BIOMAB – Center for Rheumatoid Arthritis). The population was comprised of 273 (19%) male and 1163 (80.9%) female participants, with ages ranging from 18 to 87 years. The general characteristics of the population are presented in Table 1.

Regarding the RA characteristics in the population studied, the disease activity showed that 936 (65.2%) were in remission, 223 (15.5%) in low activity, 233 (16.2%) in moderate activity and 44 (3.1%) in high activity. In relation to pharmacological therapy, these were distributed as follows: 369 (25.7%) were being treated with biological drugs and 1067 (74.3%) with non-biological DMARDs. The presence of comorbidities different from RA was determined, finding other autoimmune diseases in 130 cases (9%), non-autoimmune diseases in 596 patients (41.5%) and in 211 subjects (14.7%) the coexistence of autoimmune and not-autoimmune pathologies, the remaining cases 499 (34.7%) did not report comorbidities.

Sleep disorders

The prevalence of sleep disorders was 31.1% (446/1436) with a median age of 58 years (Interquartile Range (IQR): 52-64) ($p = 0.008$). Of the 446 subjects, 377 (84.5%) had insomnia, 39 (8.7%) apnea syndrome - obstructive sleep apnea (OSA) and 30 (6.7%) circadian rhythm disturbances.

Clinimetric values according to sleep disorders

Regarding the activity of the disease, the median of the DAS28 at the time of the evaluation was 3.6 (IQR: 2.9-4.4), while the median of the HAQ functionality was 0.87 (IQR: 0.37- 1.62). The association between DAS28 and HAQ with sleep disorders was explored by finding: for DAS28 and insomnia (OR: 3.3, CI 95%: 2.5 - 4.3), DAS28 and OSA (OR: 2.2, CI 95%: 1.1- 5), DAS28, and alterations of the circadian cycle (OR: 9.3, CI 95%: 2.8-48.1). Regarding HAQ and insomnia (OR: 2.5, CI 95%: 1.9 - 3.3), HAQ and OSA (OR: 2.9, 95% CI: 1.4 - 5.8), and finally HAQ and alterations of the circadian cycle (OR: 4, CI 95%: 1.8 - 9.1). The detail of DAS28 and HAQ according to the presence of sleep disorders are presented in figure 1.

Factors related to sleep disorders

The activities performed by the patients during their free time were evaluated. This showed that 64 (4.5%) carried out self-care activities (healthy eating and personal hygiene); 195 (13.6%) recreational or leisure (working out, dance, activity groups for older adults); 370 (25.7%) practiced handicrafts (embroidery, painting, country art); 227 (15.8%) attended a patient educational group; 352 (24.5%) attended mixed activities; and 228 (15.9%) did not carry out any activity. The detail of the bivariate analysis is presented in Table 2.

Multivariate analysis

Variables such as schooling level, dyspareunia, smoking, sedentary lifestyle and history of dyslipidemia or diabetes were included. The proposed model was subjected to the Hosmer-Lemeshow goodness-of-fit

test (p-value: 0.3), documenting an adequate adjustment of the selected predictors. In a complementary way, it was established that the proposed model correctly classified 72% of the individuals. The adjusted epidemiological estimates are presented in detail in table 3.

Discussion

Currently, the management of RA is not only focused on the pharmacological treatment for the control of the activity of the disease, but also in the different disciplines that approach the patients from all aspects and their environment, in order to achieve a management comprehensive therapy that impacts on the prognosis of the disease and their quality of life (18). This strategy is the result of the parallel presence of comorbidities in patients with RA that worsen the functional prognosis of the patient, and which reaches 65.1% of the cases according to the literature (19), a figure similar to what was found in our study (65.2%). In the same way, we have identified the presence of unhealthy lifestyles such as sedentary lifestyle, and smoking or alcohol intake, which increase the burden of disease and increase the risk of incidence of other diseases or the direct complication of RA (20). This coincides with the results of this study since statistically significant associations were identified with a sedentary lifestyle (OR: 1.7 CI 95%: 1.3–2.2) and smoking (OR: 1.7 CI 95%: 1.1–2.6).

The pathophysiology of SDs in RA is still unclear; however, it could be explained by the role played by the immune system, considering that RA is a widespread chronic inflammatory process where humoral and cellular immunity is in constant activity. Thus, changes have been identified in the levels of IL-1, IL-2, IL-6, tumor necrosis factor (TNF), melatonin, intestinal vasoactive peptide, prostaglandins, as well as natural killer cells, which have been shown to be somnogenic and promote deep or slow-wave sleep (21–23). Consequently, these mediators are present in the central nervous system and are directly related to sleep, taking into account that in sleep deprivation these are increased (23), which suggests that during the presence of a chronic inflammatory process the characteristics of sleep may change. Additionally, chronic pain has been associated with quality of sleep or restful sleep, frequent awakenings during the night and time of sleep, becoming a cycle, because pain is also mediated by immunological mechanisms characteristic of RA (7). The study published by Regina et al states that TNF intervenes in narcolepsy, and has been associated with obstructive sleep apnea (OSA) and obstructive sleep apnea-hypopnea syndrome (OSAHS) as well as other SDs, results that are similar in this study, since it identified a relationship between OSAHS and disease activity (OR: 2.2, CI 95%: 1,1–5). This becomes relevant, taking into account that biological medicines are part of the therapy and apparently improve TNF levels (24, 25). Despite this statement, in this study no statistical association was observed between SDs and pharmacological management between conventional and biological DMARDs (OR: 0.9 CI 95%: 0.7–1.2).

SDs in patients with RA have reached prevalence between 38% and 42% (18, 26, 27), which are close to those found in this study (31.1%). These estimates contrast with other studies where prevalence are between 50% and 90%, including a systematic review conducted in 2012 where 23 studies were analyzed with results between 60% and 97% (8, 28, 29). These differences could be explained by the variety of

scales used to assess sleep disorders, as well as the specific and directed search since in most cases a comprehensive approach to the patient is not made.

With regards to the demographic characteristics of the population, the literature shows that SDs in patients with RA occur more frequently between the fifth and sixth decade of life (18), which for this study showed differences from the statistical point of view ($p = < 0.001$). In the same way, the association between schooling and socioeconomic classification was explored (Table 2) finding an association with the presence of SDs, which for the case of schooling the subjects with the highest academic level (secondary or university) have fewer SDs, assuming that there is a relationship between knowledge, understanding, and perception of the disease with adherence and self-care, hence the decrease in comorbidities (30). With respect to the realization of self-care activities, where the execution of manual activities, exercise, participation in social groups and collectives, the present study showed a significant association (Table 2), concordant with the literature, since it has been demonstrated to be a factor that reduces the clinical and symptomatic activity of RA and also decreases the appearance of comorbidities, directly impacting on the characteristics of sleep, specifically in restful sleep (31) .

Clinimetric values such as DAS28 and HAQ are related to the presence of SDs. Xu et al, in a study with 71 subjects with RA, determined that SDs affect the activity of RA (DAS28, $r = 0.46$, $p < 0.01$) and quality of life (HAQ, $r = 0.36$, $p < 0.01$), results that are not far from those found in our cohort of patients, which showed significant differences in these two scales with respect to the presence of SDs (Fig. 1). These values suggest a close relationship between these two pathologies that, according to the theories proposed in their physiopathology, the treatment with biological drugs and the comprehensive care programs that show an improvement in the activity of the disease and in the same way decreases SDs (27). In the same way, an association with metabolic pathologies such as diabetes and dyslipidemia could be determined ($p: < 0.001$), which can be explained by the association between nocturnal hypoxia and fragmentation of sleep and diabetes, since some studies have been able to identify sleep disturbances, increased oxidative stress, neurohumoral changes, and systemic inflammation, which favor insulin resistance. This relationship can be increased in the presence of an autoimmune process such as RA; however, due to the characteristics of this study, the temporal causal relationship cannot be determined (32).

It is important to mention that the presence of SDs can be associated with other comorbidities such as obesity (33), chronic pulmonary pathologies, neurodegenerative processes, which can be the main cause of SDs as a result of a chronic inflammatory process, as well as for other causes before the diagnosis of RA, however, it has been argued that concomitance with RA can trigger or potentiate SDs due to changes related to pain and the impacts of immunological mediators on the central nervous system, for which disease activity can be associated (25, 34).

According to what has been described, the recommendations for the treatment of RA should be aimed at achieving the objectives of activity in a comprehensive care program (35, 36), which takes into account the quality of life of the patient and the incidence of SDs that directly impact the symptom control, the

prevention of structural damage and their functional integration into society (37, 38). These interventions of cognitive and behavioral order are effective for pain management and coping, and other general patient health aspects, displaying objective improvement in pain rating, the number of affected joints, decrease in reports of sexual alterations, the incidence of psychiatric pathologies, and SDs (7, 39).

Finally, it is relevant that health professionals who are part of the comprehensive treatment team explore the different comorbidities that occur in patients with RA, which for the case of SDs, symptom identification would allow a marked improvement in the quality of the patient's life and, therefore, better control of the disease.

Limitations

Considering that this study was based on historical clinical records, the interdisciplinary group did not evaluate patients with specific scales for this type of disorder at the time of admission. The antecedents that the patients had in their medical history were taken into account, and the expertise of the interdisciplinary group made up of rheumatologists, psychologists, physiatrists, physiotherapists, pharmaceutical chemists and nurses in this type of alterations according to the DSM-V manual at the time of clinical assessment. This limitation could underestimate or overestimate the prevalence of SDs. In the same way, we consider that this study exclusively explores the timeless relationship between RA and SDs, due to the characteristics of the design; however, we consider that it may be relevant for the scientific community because it explores the relationship between activity of the RA or functional disability and the presence of SDs.

Conclusions

It was determined that the prevalence of SDs was 31.1%. According to the evidence, it could be concluded that there is an association between the presence of sleep disorders and the activity of the disease (DAS28), functional capacity (HAQ), and factors of good prognosis according to literature such as the performance of leisure activities and a better level of schooling. Similarly, multivariate analysis identified the importance of somatic symptom disorder and the schooling of the patient as factors associated with sleep disorders. These results suggest a comprehensive approach to the RA patient in order to identify and treat comorbidities that ultimately have an impact on the disease's prognosis.

Declarations

Financing

This project was supported by BIOMAB IPS, a referral center for patients with rheumatological diseases.

Conflicts of Interest

None of the authors declare a conflict of interest regarding this article

Author contribution statement

All authors participated in the conception, collection, analysis and writing of the article

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Tables

Table 1. General characteristics of the population

Variable	Women (n = 1163)		Men (n = 273)		Total (n = 1436)	
	n	%	n	%	n	%
Socioeconomic classification *						
I-II-III (Low)	1079	92.8	259	94.8	1338	93.2
IV-V (High)	84	7.2	14	5.1	98	6.8
Civil status						
Single	176	15.1	32	11.7	208	14.5
Married	687	59.1	175	64.1	862	60
Divorced	217	18.6	52	19	269	18.7
Widowed	83	7.1	14	5.1	97	6.8
Scholarship						
Illiterate	68	5.9	27	10	95	6.6
Elementary	495	42.7	149	54.6	644	44.9
Secondary education	397	34.2	72	26.3	469	32.7
University	200	17.2	25	9.2	225	15.7
Occupation						
Unemployed	34	2.9	16	5.9	50	3.5
Employee	392	33.7	95	34.8	487	33.9
Home	347	29.8	16	5.9	363	25.3
Retired	390	33.5	146	53.5	536	37.3
Age † - Median (IQR ‡)	55	(50-59)	60	(54-64)	56	(50-60)
AR time of evolution †- Median (IQR ‡)	11	(6-16)	10	(6-16)	11	(6-16)
Time receiving AR treatment † - Median (IQR ‡)	5	(3-8)	5	(3-8)	5	(3-8)

* Classification and definition of socioeconomic classification according to the National Administrative Department of Statistics (DANE-Colombia), † Years, ‡ Interquartile range p25-p75.

Table 2. Bivariate analysis between the associated risks factors and the presence of sleep disorders.

	Sleep disorders						
Variable	YES (n = 446)		NO (n=990)		OR	95% CI	p- value*
	n	%	n	%			
Age - Median (IQR)	58 (52-64)		55 (49-59)		-	-	<0.001 ‡
Sex – female	362	81.1	801	80.9	1	0.7-1.3	0.9
Sociodemographic classification							
(I-II-III) Low Vs. (IV-V-VI) High	426	95.5	912	92.1	1.8	1.1-3.1	0.01
Scholarship							
Secondary or university education vs. Illiterate or primary education	160	36.1	534	53.9	0.4	0.3-0.6	<0.001
Lives alone	88	19.7	162	16.3	1.2	0.9-1.6	0.1
Risk factors							
Smoking	49	10.9	64	6.4	1.7	1.1-2.6	0.003
Alcoholism	8	1.7	14	1.4	1.2	0.4-3.2	0.5
Sedentary lifestyle	162	36.3	245	24.7	1.7	1.3-2.2	<0.001
Metabolic Diseases *	100	22.4	144	14.5	1.6	1,2-2,2	<0.001
Cardiovascular / Cerebrovascular diseases	51	11.4	108	10.9	1.1	0.7-1.5	0.7
Concomitant autoimmune pathologies	115	25.7	226	22.8	1.1	0.8-1.5	0.2
Leisure activities-self-care	358	80.2	850	85.8	0.6	0.4-0.9	0.007
Late AR diagnosis	434	97.3	958	96.7	1.2	0.5-2.6	0.5
Treatment with biological DMARD	110	24.6	259	26.1	0.9	0.7-1.2	0.5
Psychological history							

Mood disorder	115	25.7	243	24.5	1	0.8-1.3	0.6
Somatoform disorders	74	16.5	94	9,4	1.8	1.3-2.6	<0.001
Eating disorders	12	2.6	28	2.8	0.9	0.4-1.9	0.8
Dementia	9	2	13	1.3	1.5	0.5-3.9	0.3
Sexual disorders							
Dissatisfaction	36	8.1	89	8.9	0.8	0.5-1.3	0.5
Loss of sexual desire	24	5.3	39	3.9	1,3	0.7-2.3	0.2
Dyspareunia	75	16.8	83	8.3	2.2	1.5-3.1	<0.001
Premature ejaculation	15	43.3	21	2.1	1.6	0.7-3.3	0.1
Orgasmic decrease	12	2.6	31	3.1	0.8	0.3-1.7	0.6
DAS28							
Activity Vs. No activity	322	72.2	396	40	3.8	3-5	<0.001
HAQ							
Disability Vs. Without disability	184	41.2	176	17.7	3.2	2.5-4.1	<0.001

† Chi2 test. ‡ Wilcoxon nonparametric test. Values p <0.05 were considered statistically significant. * Diabetes or dyslipidemia

Table 3. Multivariate analysis associated risks factors and the presence of sleep disorders.

Variable	OR †	95% CI	p-value
DAS28	3.1	2.4-4	<0.001
HAQ	2.4	1.8-3.1	<0.001
Somatoform disorders	1.5	1-2.2	0.016
Scholarship	0.5	0.4-0.6	<0.001

† Logistic regression

Figures

Figure 1

Distribution of DAS28 and HAQ values according to the presence of sleep disorders. 1A. DAS28, 1B. HAQ. The Wilcoxon statistical test was used for the two hypotheses contrast according to the data distribution.