Rheumatoid Arthritis in Minorities

Guest Editors: Juan-Manuel Anaya, Adriana Rojas-Villarraga, Rubén Darío Mantilla, and Claudio Galarza-Maldonado

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Editorial Board

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Editorial

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Latin America and the Caribbean (LAC) is a rapidly growing region with almost 600 million inhabitants composed of Mexico, Central and South America, and the islands of the Caribbean [1, 2]. The Americas were first inhabited by people crossing the Bering Land Bridge from northeast Asia into Alaska well over 10,000 years ago. Native Americans descend from at least three streams of Asian gene flow [3]. Europeans arrived after 1492 following Christopher Columbus's voyages. African people were captured and taken to America by the transatlantic slave trade from the 16th to the 19th centuries. Hence, the population of LAC comprises a variety of ancestries, ethnic groups, and races, making the region one of the most diverse in the world. The specific composition varies from country to country: many have a predominance of European-Native American, or Mestizo, population; in others, Native Americans are a majority; some are dominated by inhabitants of European ancestry; some countries' populations are primarily Mulatto [4]. To a less extent, Black, Asian, and Zambo (mixed Black and Native American) are also identified regularly [4]. Noteworthy, ethnic self-identification is culturally and biologically complex and is not correlated with self-reported ancestry which should be no longer evaluated by questionnaire but rather by the use of ancestry informative markers (AIMs) at the molecular level [5].

The term majority refers to a group that controls economic, political, and social resources regardless of the population size. In this sense, LAC still meets most of the Feagin defining features of minority, including suffering discrimination and subordination, physical or cultural traits that set them apart, and a shared sense of collective identity and common burdens as well as socially shared rules [6]. LAC remains one of the world's most unequal regions [7]. Enormous cultural differences in health perceptions in LAC exist which correlate with individuals' economic and health conditions [8]. Lower-income groups recognize more health problems but are less tolerant to some of them than the rich [8].

There is an increased prevalence of chronic diseases in LAC which has been attributed to diverse causes, including ancestry, socioeconomic status (SES), the ageing of the population, and lifestyle factors such as smoking, physical inactivity, and excess of alcohol intake [8, 9]. Higher SES has been characterized by lower levels of Native American ancestry [9]. The prevalence of some autoimmune rheumatic diseases, including rheumatoid arthritis (RA), is higher than expected among some Amerindian groups highlighting ancestry as a factor influencing the risk of acquiring autoimmune diseases [10, 11].

In spite of setbacks, LAC is making important progress in research. The "Grupo Latino Americano de Estudio de Artritis Reumatoide (GLADAR)" is an example among several others (http://www.gladar.org/). From 2000 to 2010, LAC has seen a high growth of more than 9% per year in scholarly output, resulting in a nearly 70% increase in its share of world papers over the same period, to reach just under 4.4% of the world's annual output of scholarly papers in 2010 [12]. Latin

American research is growing fast and becoming more visible on a global scale. And this is not the only bibliometrically-observed improvement to LAC's scholarly output over the last few years. LAC's relative citation impact, albeit still under world average, has been improving by 1.6% per year from 2000 to 2010 and from about 70% of world average in 2000 to more than four-fifths in 2010 [12]. Improving research and human resources capacity in the region will require increasing research partnerships within and outside the region, between rich and poor countries, promoting collaborations between LAC research institutions and universities to boost postgraduate programs, and aligning research investments and outputs with the current burden of disease [7].

This issue of *Arthritis* offers five papers from LAC. The effect of illness on workers participation and productivity, more than any other consequence of disease, is important to a wide range of stakeholders both within and outside the healthcare sector. R. C. del Moral and colleagues from Argentina report how patients with RA with higher disease severity show higher work productivity compromise.

Three reports from the Center for Autoimmune Diseases Research (CREA) in Colombia are presented. J. C. Roldan et al. evaluated the global prevalence of autoimmune thyroid disease (AITD) in RA, stressing that AITD should be systematically assessed since it is a risk factor for developing diabetes and cardiovascular disease (CVD) in RA. A systematic literature review in Latin America on CVD in RA, led by J. C. Sarmiento-Monroy, indicates a high prevalence of CVD in LA patients (35.3%). Main nontraditional risk factors associated to CVD in this population are HLA-DRB1 shared epitope alleles, rheumatoid factor, markers of chronic inflammation, long duration of RA, steroids, familial autoimmunity, and thrombogenic factors. Authors propose to evaluate cardiovascular risk factors comprehensively in the Latin RA patient and to generate specific public health policies in order to diminish morbimortality rates. J. Amaya-Amaya and colleagues report the usefulness of patients-reported outcomes (PROs) in RA focus group. Authors evaluated 135 patients with RA during two different sessions of focus group interviews. Agreement was found between objective measurements assessed by the physician and subjective assessments done by the patients regardless of gender, educational level, and duration of disease. Application of PROs in daily routine offers enormous benefits with patients' adherence to treatment and cost reductions as the most important.

Finally, an elegant work from A. C. Machado-Díaz and colleagues from Cuba shows an increase of proinflammatory soluble interleukin-15 receptor alpha (IL-15Rα) in patients with RA as compared with osteoarthritic patients. In addition, their results evidence the presence of IL-15Rα in synovial fluids and suggest that its pro-inflammatory effect could be related to the induction of IL-6.

We hope readers of *Arthritis* will enjoy this special issue and be aware of the importance and promises to investigate factors influencing health in minorities. As García Marquez said "solidarity with our dreams will not make us feel less alone, as long as it is not translated into concrete acts of legitimate support for all the peoples that assume the illusion of having a life of their own in the distribution of the world" [13].

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Clinical Study

Work Productivity in Rheumatoid Arthritis: Relationship with Clinical and Radiological Features

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Objective. To assess the relationship between work productivity with disease activity, functional capacity, life quality and radiological damage in patients with rheumatoid arthritis (RA). *Methods*. The study included consecutive employed patients with RA (ACR'87), aged over 18. Demographic, disease-related, and work-related variables were determined. The reduction of work productivity was assessed by WPAI-RA. *Results*. 90 patients were evaluated, 71% women. Age average is 50 years old, DAS28 4, and RAQoL 12. Median SENS is 18 and HAQ-A 0.87. Mean absenteeism was of 14%, presenting an average of 6.30 work hours wasted weekly. The reduction in performance at work or assistance was of 38.4% and the waste of productivity was of 45%. Assistance correlated with DAS28 ($r = 0.446$; $P < 0.001$), HAQ-A ($r = 0.545$; $P < 0.001$) and RAQoL ($r = 0.475$; $P < 0.001$). Lower total productivity was noticed in higher levels of activity and functional disability. Patients with SENS > 18 showed lower work productivity than those with SENS < 18 (50 versus 34; $P = 0.04$). In multiple regression analysis, variables associated with reduction of total work productivity were HAQ-A and RAQoL. *Conclusion*. RA patients with higher disease severity showed higher work productivity compromise.

1. Introduction

Rheumatoid arthritis (RA) is a chronical inflammatory disease of unknown etiology that affects mostly patients at a productive age [1].

We have noticed that up to 70% of patients with RA will develop work impairment after 10 years of disease evolution and that the most significant increase in work impairment appears in the first year after the diagnoses [2].

Thanks to the progress made in the therapeutic management of the disease, many patients can continue working, though with different levels of work impairment [3]. In patients with RA, work productivity is affected mostly in those severely affected by the disease. However, patients with low disease activity show lower productivity than those who are under remission [4].

In 2009, in a descriptive work in which several centers of our country took part, we stated work impairment of 49% in patients with RA [5]. This fact motivated us to investigate the relationship between disease features and work impairment. The objective of the study is to assess the relationship between work productivity and disease activity, functional ability, quality of life, and radiological damage in patients with RA.

2. Patients and Methods

2.1. Design. During the period between March 2009 and July 2010, an analytical observational and cross-sectional study was done.

2.2. Patients. Consecutive RA patients were recruited from a rheumatology hospital in Ciudad Autónoma de Buenos Aires, Argentina. All participants were >18 years old, fulfilled the 1987 American College of Rheumatology (ACR) RA diagnostic criteria [6] and were proficient in the Spanish language. These patients were working in the last week and they accepted to take part of this research under signed informed consent. We excluded patients with other inflammatory arthropathy, fibromyalgia, illiteracy, or cognitive deficiency.

The following demographic features were assessed: age (years old), genre, level of education (years), socioeconomic level (by modified Graffar scale) [7], disease features: evolution time (months), disease activity and its categories by DAS28 [8], functional ability (HAQ A) [9], life quality (RAQoL) [10], functional class (Hochberg "91") [11], and radiological damage (Simple Erosion Narrowing Score: SENS) [12, 13], and work features: type of employment (according to the Occupational Uniform International Classification of 1988) [14] and the degree of work physical demand by Pujol scale [15].

To assess work productivity the "Work Productivity and Activity Impairment Questionnaire" for rheumatoid arthritis (WPAI-RA) [16] was used.

We also assessed if patients had showed changes in their work tasks due to RA and classified them into employed, hourly workers, or occasional workers.

Patients completed all questionnaires in the presence of their physician without assistance.

Instruments used in the study are as the follows.

(i) The DAS28 is an index similar to the original DAS, consisting of a 28 tender joint count (range 0–28), a 28 swollen joint count (range 0–28), ESR, and an optional general health assessment on a visual analogue scale (range 0–100). The DAS28 has a continuous scale ranging from 0 to 9.4, and the level of disease activity can be interpreted as low (DAS28 $\leq$ 3.2), moderate (3.2 < DAS28 $\leq$ 5.1), or high (DAS28 > 5.1) [8].

(ii) The HAQ-A is a self-response questionnaire which is used to measure functional status. Subscale scores range from 0 to 3, with higher scores indicating worse functional status [9].

(iii) The RAQoL consists of 30 questions with yes/no response format. Each affirmative answer carries a score of one point. The total score is calculated as the sum of all the affirmative answers. Scores range from 0 to 30, with higher scores indicating poorer QoL [10].

(iv) The Pujol scale classifies physical demand at work in five degrees: (1) sedentary: sitting or occasionally standing, lifting a maximum of 5 kl weight; (2) mild: walking or standing at a significant degree or when it is necessary to sit most of the time using arms and feet to push or pull objects, lifting a maximum of 10 kl weight (3) medium: usually lifting and carrying objects heavier than 12 kl up to 25 kl; (4) heavy: usually lifting and carrying objects heavier than 25 kl up to 50 kl; (5) very heavy: usually lifting and carrying objects heavier than 25 kl and occasionally heavier than 50 kl [15].

(v) The WPAI-AR consists of six questions: 1 = currently employed; 2 = hours missed due to health problems; 3 = hours missed due to other reasons; 4 = hours actually worked; 5 = degree of health-affected productivity while working (using a 0 to 10 visual analogue scale (VAS)); 6 = degree of health-affected productivity in regular unpaid activities (VAS). The recall period for questions 2 to 6 is of seven days. Four main outcomes can be generated from the WPAI-GH and expressed in percentages by multiplying the following scores by 100: (1) percentage of work time missed due to health problems = Q2/(Q2 + Q4) for those who were currently employed; (2) percentage of impairment while working due to health problems = Q5/10 for those who were currently employed and actually worked in the past seven days; (3) percentage of overall work impairment due to health problems $Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) \times (Q5/10))$ for those who were currently employed; (4) percentage of activity impairment due to health problems Q6/10 for all respondents. For those who missed work and did not actually work in the past seven days, the percentage of overall work impairment due to health will be equal to the percentage of work time missed due to health problems. The WPAI-AR was validated in patients with RA [16]. Work productivity is usually divided into two components: absenteeism and presenteeism. The former refers to work leave of absence related to the disease and the other represents work impairment caused by the disease but being present at work [3].

2.3. Statistical Analysis. Descriptive statistics were performed to calculate the means, standard deviations, medians, interquartile ranges, frequencies, and percentages.

Correlation between continuous numerical variables has been done by Pearson coefficient (r). For the proportional analysis among groups, chi squared test was applied. Comparison among groups of patients has been done by ANOVA with post-hoc analysis and Student's t-test with Levene test. Lineal regression analysis has been done taking the percentage of overall productivity loss as dependent variable. A value of $P \leq 0.05$ was considered significant.

3. Results

3.1. Population Characteristics. A total of 90 patients with RA were included in the study. Among the 90 patients, the average age was 50 years old and 71% were female. The

Table 1: Demographic characteristics.

Patients (n)	90
Age (mean ± SD)	50 ± 11
Female	64 (71%)
Years of schooling (mean ± SD)	10.2 ± 4.2
Socioeconomic level (n = 65)	
I	0
II	3 (4.6%)
III	20 (30.8%)
IV	39 (60%)
V	3 (4.6%)
Months of RA evolution (mean RIQ)	72 (24–120)
DAS 28 (mean ± SD)	4 ± 1
HAQ A (mean, RIQ)	0.87 (0.37–1.5)
RAQoL (mean ± SD)	12 ± 7
Functional class (n = 90)	
I	27 (30%)
II	47 (52%)
III	16 (18%)
IV	0
SENS (n = 59)	
(mean, RIQ)	18 (11–38)

SD: standard deviation; RIQ: range interquartile.

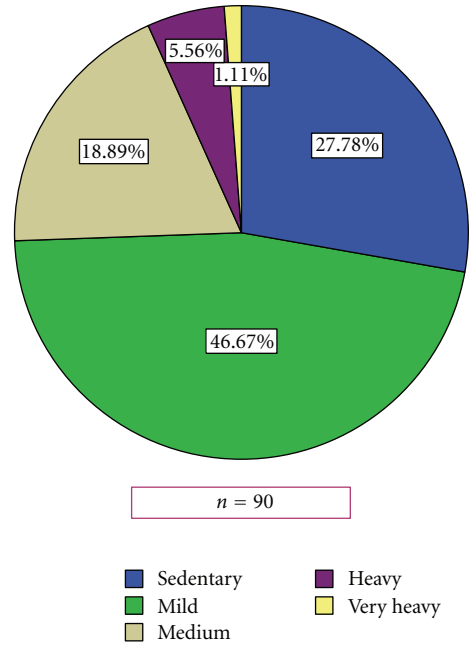

Figure 1: Work physical demand.

Table 2: Types of employment, according to the occupational uniform international classification.

	n (%)
Nonqualified sales and services workers	32 (35.6)
Office employees	14 (15.6)
Shop and market assistants	13 (14.4)
Metallurgy, mechanic construction, and kindred operators	10 (11.1)
Personal service and security service workers	6 (6.6)
Teaching professionals	6 (6.6)
Intellectual and scientific professionals	5 (5.7)
Construction operators	3 (3.3)
Facilities and machines operators and riggers/fitters	1 (1.1)
Total	90 (100)

sample's disease duration was 72 months since their first rheumatology visit. Demographic and disease features are shown in Table 1.

When this research work was being carried out, all included patients were working; therefore, the answer to the first question of the WPAI-AR was affirmative in all cases. 45% of patients were employed, 40% were working by the hour, and 15% were occasionally working.

Type of Employment. 32 patients were non-qualified sales and services workers (21/32 were working as household help staff). In Table 2, different types of employment have been observed.

Degree of Work Physical Demand (J. Pujol). Most patients were performing either a mild (46.7%) or sedentary job (27.8%). A minor proportion were doing jobs with intermediate physical demand (18.9%), heavy (5.6%), or very heavy (1.1%) (Figure 1). It is worth mentioning that 65% of patients have modified their tasks due to the disease.

3.2. Work Productivity Assessed by WPAI-AR (Table 3)

(1) Absenteeism (missed work hours due to RA): 63% of patients (n = 57) did not miss any work hours in the past week (absenteeism = 0%), although 25% of patients miss 8 or more work hours per week. The total average of missed work hours per week was 6.3 (SD 12.6), the average of hours worked during the last week was 34 (SD 20) and the average percentage of presenteeism being of 14%.

(2) Presenteeism(disease impact at work): 88.9% of patients (n = 80) presented some degree of work impairment. Among those with and without work impairment, the average percentage of presenteeism or reduction in work performance was 38.4%.

(3) Loss of overall productivity (absenteeism and presenteeism) was 45%.

(4) Impairment of daily life activities (DLA) outside work was 42%.

3.3. Correlation of Work Productivity with Disease Activity. Work impairment had a positive correlation with RA activity assessed by DAS28 (r = 0.446; P < 0.001).

Assessing the correlation between the loss of overall productivity and different activity categories by DAS28 (mild

Table 3: Work productivity according to WPAI-AR.

				Percentiles	
	n	mean	DS	25	median	75
Missed work hours due to RA	90	6.3	12.6	0	0	8
Missed work hours due to other reasons	90	5.2	13.8	0	0	6
Actually worked hours	90	34	20	18	32	48
Work affected by RA (0 a 10)	90	3.8	2.6	2	3.5	6
DLA impairment due to RA (0 a 10)	90	4.2	2.7	2	4	7.00
Percentage of absenteeism	90	14	24	0	0	20
Percentage of presenteeism	90	38.4	26	20	35	60
Percentage of overall productivity loss	90	45	30	20	45	70
Percentage of DLA compromise	90	42	27	20	40	70

WPAI: Work Productivity and Activity Impairment Questionnaire.
DLA: Daily life activities.

Table 4: Loss of overall productivity and RA activity.

DAS28	Percentage of overall work impairment		
	Media	IC 95%	
<3.2 $n = 26$	**25**	15–36	$P < 0.01$
3.2–5.1 $n = 39$	**46**	39–56	$P < 0.01$
>5.1 $n = 23$	**62**	51–74	$P < 0.01$

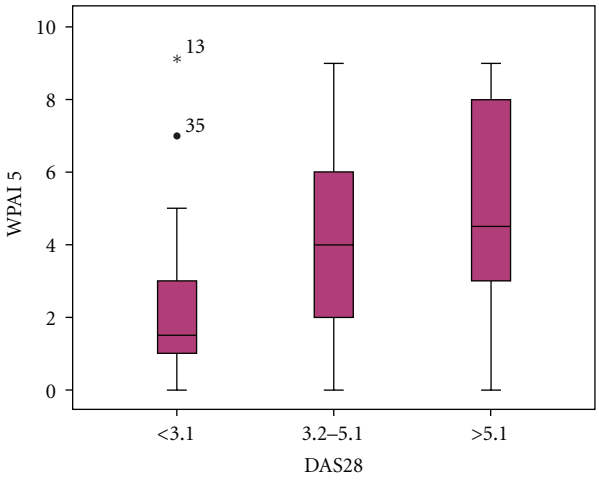

Figure 2: RA disease activity and work impairment.

<3.2, moderate 3.2–5.1, or severe >5.1), we have noticed significant statistical differences among them (Table 4).

The degree of work impairment due to RA measured in a numerical scale (0–10) was lower in patients with low disease activity ($P < 0.01$). With the exception of two cases (patient 13 and 35) (Figure 2).

The correlation among lost working hours according to different categories of RA activity by DAS28 (mild, moderate or severe) was assessed and we noticed that 75% of patients with mild RA activity have not shown any loss in work hours, and that only 10% of these lost 6 or more hours a week. However, 50% of patients with severe activity lost at least 8 work hours a week (Table 5).

3.4. Correlation between Work Productivity and Functional Ability. Work impairment in patients with severe activity had a positive correlation with functional ability assessed by HAQ A ($r = 0.545; P < 0.001$).

The correlation between loss of overall work production and the different levels of HAQ A (<0.5, 0.5 a 0.87 y > 0.87) was assessed. Work impairment was higher (61% IC95: 53–69) in those patients who showed an HAQ-A > 0.87, with significant differences ($P < 0.01$) compared with the other two groups.

Analyzing lost working hours, according to different levels of HAQ A (<0.5, 0.5 a 0.87 y >0.87), we have observed that only 10% of patients with low disability (HAQ A < 0.5) have had a work loss higher than 5 hours. On the other hand, 50% of patients with HAQ A > 0.87 lost no less than 5 working hours a week.

Degree of work impairment due to RA was higher in patients with HAQ A > 0.87 ($P < 0.01$) (Figure 3).

3.5. Correlation between Work Productivity and Life Quality. Impairment of work productivity due to RA had a positive correlation with lower life quality assessed by RAQoL ($r = 0,475; P < 0.001$). Patients that showed lower life quality (RAQoL $\geq$ 6) had a higher work productivity loss (50%) than those with lower values (overall work productivity loss 27%) ($P < 0.01$).

3.6. Correlation between Work Productivity and Radiological Damage. Work impairment due to RA had not a significant correlation with radiological damage assessed by SENS ($r = 0,2; P = NS$).

Dividing patients according to SENS median $\geq$18 ($n = 31$) versus SENS <18 ($n = 28$), we found a lower loss of overall productivity in those with less radiological damage (50 ± 31 versus 34 ± 25; $P = 0.04$).

Table 5: Loss of work hours and RA activity.

DAS28	Work hours loss percentiles						
	5	10	25	50	75	90	95
<3.2	0.00	0.00	0.00	0.00	0.00	6.00	9.30
3.2–5.1	0.00	0.00	0.00	0.00	6.00	15.90	36.00
>5.1	0.00	0.00	0.00	8.00	24.00	48.00	60.00

Table 6: Multiple lineal regression for work impairment.

	Non standardized coefficients		Standarized coefficients			IC 95% de B	
	B	Standard error	β	t	Sig.	Lower limit	Upper limit
(Constant)	10.840	10.470		1.035	0.306	−10.200	31.880
HAQ	21.610	7.568	0.505	2.856	0.006	6.402	36.818
EVA pain	0.111	0.152	0.103	0.731	0.468	−0.195	0.418
DAS28	−1.842	2.948	−0.096	−0.625	0.535	−7.767	4.082
RAQoL	1.094	0.507	0.276	2.156	0.036	0.074	2.113
SENS	0.155	0.213	0.084	0.728	0.470	−0.274	0.584
RA duration	−0.044	0.049	−0.105	−0.907	0.369	−0.142	0.054

Dependent variable: percentage of overall productivity loss.

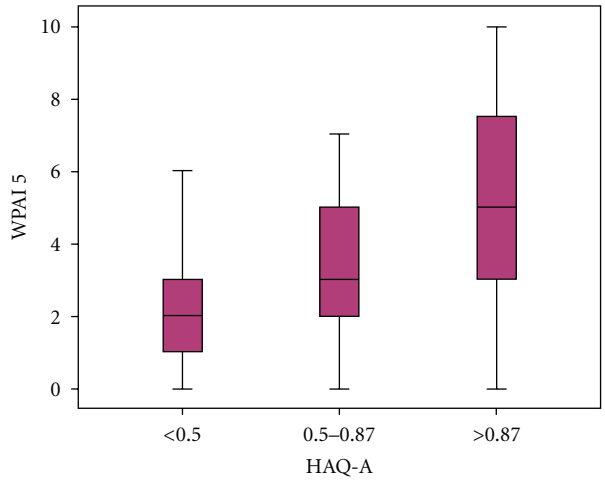

Figure 3: Functional status and work impairment WPAI (range 0–10).

3.7. Results of Multivariate Analysis. In the multiple regression analysis, considering work impairment as dependent variable, we found the HAQ-A and the RAQoL as unique associated variables. This model had a prediction power of 51% (adjusted $R^2 = 0.51$) (Table 6).

4. Discussion

In this work, we have found that work impairment in working patients with RA was of 45%. Those patients with higher degrees of disease activity assessed by DAS28 showed higher compromise of work productivity (in absenteeism as well as presenteeism). Our results are consistent with what Zhang and his partners found, who reported a moderate association between disease activity and absenteeism and a strong association with work impairment or presenteeism in 137 employed patients with early RA [17].

On the other hand, we have not found any association between disease activity and work productivity in a study done by Geuskens and partners in patients with inflammatory arthropathy of less than 12 moths of evolution [18].

Functional ability, assessed by HAQ, is one of the most frequent predicting factors associated with work impairment in several published studies [2, 19, 20]. We have also described an association between absenteeism and work impairment or presenteeism with functional ability [5]. Patients with RA disability corresponding to HAQ > 1.5 show a significant higher number of missed work days and of days with work impairment ≥50% than those with HAQ <0.5 [21]. Hazes and partners observed that patients with RA treated with certolizumab pegol and methotrexate that achieved a significant clinical improvement as regards pain and physical function reported significant higher increase in work productivity than those who did not achieve the same health improvement [22]. In our study, work impairment in patients with RA showed correlation with functional ability assessed by HAQ-A ($P < 0.001$), *being significantly higher in those patients that showed* HAQ-A > 0.87.

We have found a positive association between work impairment and lower quality of life assessed by RAQoL ($P <$

0.001*), and those patients with poor quality of life* (RAQoL ≥ 6) had more work productivity loss than those with better quality of life ($P < 0.01$).

As regards structural damage, we have not noticed any correlation with work productivity; however, dichotomizing the radiological compromise assessed by SENS according to the median value, we noticed that those patients with more radiological damage showed more work impairment ($P = 0.04$). In previous studies, an association between radiological damage and work impairment or lower indexes of full-time employment [23] has been described [17, 24], but as in our work, radiological compromise had no correlation with work productivity [24].

According to our findings, presenteeism was more compromised than work absenteeism (38.4% versus 14%, resp.). Besides, there was a great number of patients that were not absent at work (with 0% absenteeism), but that did show work impairment due to the disease. This is consistent with what was observed by Zhang and partners [25] who postulate that their results could be due to the fact that other factors would influence work absenteeism besides the disease features.

In our country, work disability figures ranging from 21% to 47% [21–27] have been informed. Studies have shown different factors associated with work disability in patients with RA, such as like a HAQ-A > 0.87, living under poverty line, functional classes III and IV, and a longer evolution of the disease.

Maldonado Ficco and partners informed in a study on 483 patients with early RA that 21% were unemployed, showed higher levels of disease activity, and worse functional ability, and had attended less school years than those who were working [26]. In another multicenter study done in our country over 172 employed patients, 40% of them showed a high risk of work instability (discrepancy between functional abilities of an individual and his/her work tasks). Besides, such instability was associated with HAQ-A ≥ 0.87, presence of erosions and functional class III and IV [28]. We have found that lower functional ability and worse quality of life are factors associated with work impairment

A limitation of this study is that patients with a lot of years of disease evolution could have changed their jobs adapting it to their limitations; in fact 65% of these patients have previously changed their work tasks.

5. Conclusion

In this study, we observed that patients with RA that show lower functional ability, lower life quality, higher levels of activity, and bigger radiological damage have a higher number of missed work hours (absenteeism) and higher work impairment (presenteeism). Factors associated with higher work impairment are lower functional ability and worse quality of life. Although at present thanks are to the improvement in the treatment of RA, a lot of patients can continue working. We could observe in this study that those with a bad control of the disease, in spite of being working, show different degrees of work impairment. Therefore, this aspect should be considered when assessing these patients' treatment evolution.

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Research Article

Autoimmune Thyroid Disease in Rheumatoid Arthritis: A Global Perspective

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Objective. To determine the prevalence and impact of autoimmune thyroid disease (AITD) in patients with rheumatoid arthritis (RA). *Methods*. Eight-hundred patients were included. The association between AITD and RA was analyzed was analyzed by bivariate and multivariate analysis. In addition, a literature review was done focusing on geographical variations. *Results*. In our cohort the prevalence of AITD was 9.8% while the presence of antibodies was 37.8% for antithyroperoxidase enzyme (TPOAb) and 20.8% for antithyroglobulin protein (TgAb). The presence of type 2 diabetes, thrombosis, abnormal body mass index, and a high educational level was positively associated with AITD. The literature review disclosed a geographical variation of AITD in RA ranging from 0.5% to 27%. Autoantibody prevalence ranges from 6% to 31% for TgAb, 5% to 37% for TPOAb, and from 11.4% to 32% for the presence of either of the two. *Conclusion*. AITD is not uncommon in RA and should be systematically assessed since it is a risk factor for developing diabetes and cardiovascular disease. These results may help to further study the common mechanisms of autoimmune diseases, to improve patients' outcome, and to define public health policies. An international consensus to accurately diagnose AITD is warranted.

1. Introduction

Autoimmune thyroid disease (AITD) is a term used to bring together a group of pathologies that has thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark [1, 2]. However, being a group of autoimmune diseases (ADs) clustered together, the clinical presentation varies among these diseases; it can be divided into those that cause hypothyroidism, hyperthyroidism, or both [3].

As organ specific ADs, this group of pathologies exhibits an autoantibody profile that may be composed of (1) antibodies directed against the thyroperoxidase enzyme (TPOAb), (2) antibodies directed against thyroglobulin protein (TgAb), and (3) antibodies directed against thyrotropin receptor (TSHrAb). In this last case, the antibodies can either block or enhance the receptor's activity. Furthermore, there is a T or B lymphocytic response that prevails and, ultimately, this will define the pathology that becomes manifest. Generally, T lymphocytes are the main cell type infiltrating the gland in Hashimoto's thyroiditis while a B response predominates and determines the presence of Grave's disease [3].

In general terms, those diseases where the clinical presentation is mainly a hypothyroid state include Hashimoto's thyroiditis. As originally described by Akaru Hashimoto in 1912 goiter was associated with this disease though today it may or may not be. The other disease is atrophic thyroiditis which is found with hypothyroidism in the absence of goiter. Conversely, Grave's disease, described by Robert Graves in 1835, is manifested by a hyperthyroid state that can be associated with diffuse goiter and sometimes with exophthalmos. Postpartum thyroiditis occurs in the first

postpartum year and it may start with a hyperthyroid state and end with a hypothyroid state that can be transient or permanent [4].

The prevalence of AITD in the general population varies between countries. A prevalence has been described of 5 to 15% in women and 1–5% in men [5]. The prevalence of thyroid autoantibodies has also been described. Hollowell et al. [6] described a prevalence of 13% for TPOAb and 11.5% for TgAb among the general population. This prevalence rises in spontaneously hypothyroid patients [7]. In other words, AITD can be regarded as the most common autoimmune endocrine disease.

Rheumatoid arthritis (RA), in turn, is a chronic, complex, and heterogeneous AD, in which there is a response directed towards the diarthrodial joints producing symmetric polyarthritis with progressive damage to the joints, bone destruction, and extra-articular manifestations (EAMs) such as cutaneous nodules, lung involvement, cardiovascular disease (CVD), episcleritis, and so forth. All of these lead to disability [8, 9], an increase in comorbidities [10], and premature mortality. Thus, the autoimmune compromise is systemic as opposed to AITD which is organ specific [11].

RA is the most common inflammatory arthropathy worldwide. The disease is three times more frequent in women than men with a prevalence of 0.5–1.0% in industrialized countries [12, 13] and less than 0.5% in Latin America [12, 14]. This region has a high admixture of cultures and ethnicities and thus RA genotypes and phenotypes differ between and within countries [15]. However, the prevalence rises with age and is highest in women older than 65 years [11]. The annual incidence is highly variable (12 to 1,200 per 100,000 population) [16] and is dependent on a variety of factors including gender, environmental (e.g., smoking [17], infectious diseases [18, 19]), ethnicity, and age [16]. With the exception of certain native populations, RA affects all populations worldwide. These variations are indicative of different genetic risks and hormonal exposures [20].

For several decades an increased occurrence of thyroid disorders in patients suffering from RA has been documented—both autoimmune and nonautoimmune in nature [21–24]. In addition, [25] rheumatologic and nonrheumatologic manifestations of AITD have been described. Within these manifestations, it is noteworthy that the most common symptoms are polyarthralgia and unclassified arthritis, which are the main features of RA.

ADs share similar mechanisms [12, 26–28]. In clinical practice some conditions support these commonalities. One of these corresponds to polyautoimmunity, which is defined as the presence of more than one AD in a single patient [29]. The multiple autoimmune syndrome (MAS), a form of polyautoimmunity, corresponds to the coexistence of three or more well-defined ADs [30]. The importance of these terms is due to the fact that patients with polyautoimmunity or MAS may have a modified disease course (with a worse prognosis or a better one) and a modified clinical presentation. Moreover, first degree relatives (FDR) of these patients are at increased risk of developing an AD [31]. Several studies have consistently mentioned association and clustering between ADs [32, 33].

Genetic background is, therefore, an important aspect in autoimmunity. Genetic risk factors shared among diseases have been described and AITD and RA are no exception [25, 34, 35]. Nevertheless, the etiology of ADs is complex in nature, which means that genetic, epigenetic, and environmental factors are responsible for the occurrence of these diseases. For certain ADs, genetic factors have been consistently found to be more important than environmental factors and vice versa [1, 2, 36, 37].

In AITD, numerous genes have been found to confer risk for the disease including HLA gene complex, CD40, CTLA4, PTPN22, TSH receptor gene, and thyroglobulin gene [2, 38–40]. While the term AITD lumps Graves' disease and Hashimoto's thyroiditis together, in the case of the former, genetic factors appear to be more important whereas the reverse is true in the latter [1, 2, 36, 37]. CD40, CTLA4, and PTPN22 genes as well as the HLA gene complex have also been implicated in the pathogenesis of RA [41]. In addition, shared environmental factors such as smoking [17] have been implicated in numerous studies as risk factors for AITD and for RA [2, 36].

Although AITD and RA share common physiopathological mechanisms, the connection between AITD and RA is a topic with no definite results so far. In Latin America and other regions, this association has not been thoroughly explored. It is important to establish if the presence of AITD in RA is linked with EAMs including CVD and the presence of a worse prognosis for RA (e.g., presenting erosions) [42, 43]. As a center for autoimmune research established in Latin America, we are mainly interested in unraveling the association between these diseases, to look for information from our region and to establish a solid base on which future research in this area may hold its ground.

The purposes of the study are (1) to determine the prevalence of AITD within an RA cohort of Colombian patients and determine the differences between these two groups regarding the prognostic features of RA as well as (2) to analyze the current information concerning the prevalence of AITD in RA patients and to evaluate any deviations on RA course due to AITD presence.

2. Patients and Methods

2.1. Study Population. This was a cross-sectional, analytical study in which 800 consecutive Colombian patients with RA were included. The subjects were being seen at the Center for Autoimmune Diseases Research (CREA) at the Universidad del Rosario in Bogota and Medellin between February 1996 and April 2012. All of them fulfilled the 1987 American College of Rheumatology classification criteria [44] and had AITD status investigated. The study was conducted in compliance with Act 008430/1993 by the Ministry of Health of the Republic of Colombia. The institutional review board of the Universidad del Rosario approved the study design.

Each patient was evaluated by a rheumatologist. The information on patient sociodemographic and cumulative clinical and laboratory data was obtained by interview, physical examination, and chart review. A household description

was obtained by questionnaire and a clinical evaluation of the affected family members was done using the same methodology as above. All data were collected in an electronic and secure database.

The sociodemographic variables included current age, age at RA onset, disease duration, educational status, socioeconomic status (SES), current occupational status, smoking habits, coffee consumption, and physical activity. The following are the definitions of these variables: age at onset: age at which patients began to suffer from pain, typical morning stiffness (more than 1 hour), and symmetrical inflammation of hand and/or foot joints; disease duration: difference between age at onset and the date of first participation in the study. It was dichotomized as having either more or less than 10 years of disease as our group had previously reported this to be a risk factor for CVD [45]. Educational level was recorded as years of education; the cohort was split into two groups with one group including those with less than 9 years of education (including preschool, primary, and the first 2-3 years of high school) and the other more than 9 years of education. This breakdown was based on the General Law of Education in Colombia [46, 47]. SES was categorized on the basis of national legislation and was divided into high status (3 to 6) and low status (1 and 2). For occupational status we focused on establishing if the patient worked on household duties exclusively.

Regarding clinical variables, we evaluated polyautoimmunity, MAS, familial autoimmunity, erosions, comorbidities, EAMs, systolic and diastolic blood pressure, body mass index (BMI), and waist circumference. The following are the definitions of these variables: polyautoimmunity and MAS as stated above. However, we evaluated polyautoimmunity as a variable without taking into account the presence of AITD. Familial autoimmunity was defined as the presence of any diagnosed AD in another FDR of the proband. We evaluated 6 ADs on the basis of international criteria namely: systemic lupus erythematosus (SLE), AITD, Sjögren's syndrome (SS), antiphospholipid syndrome (APS), psoriasis (PSO), and vitiligo (VIT) [48]. It is important to note that there are no international criteria for the diagnosis of AITD. These cases were classified on the basis of an abnormal thyrotropin (TSH) test, or history of thyroid hormone therapy, and the presence of either TPOAb or TgAb.

Erosions were defined as having at least one point on the Sharp/van der Heijde classification [49]. EAMs was defined as the presence of at least one of the following: skin ulcerations, nodules, episcleritis, vasculitis, neuropathy, pleural effusion, pulmonary hypertension or embolism, and CVD. The latter was categorized as positive if any of the following variables were present: hypertension (defined as having blood pressure >140/90 mm Hg or using antihypertensive medication) [50], coronary artery disease, occlusive arterial disease, carotid disease, or thrombosis.

The patients were asked about the presence of diabetes mellitus, defined as having a fasting plasma glucose level >7 mmol/L (126 mg/dL) or taking antidiabetic medication at the time of the assessment [51]. Diagnosis of dyslipidemia was given if patient had hypercholesterolemia, defined as taking lipid-lowering medication or having a fasting plasma total cholesterol >200 mg/dL, HDL <40 mg/dL, hypertriglyceridemia >150 mg/dL, or LDL cholesterol >100 mg/dL [52, 53]. Anemia was diagnosed if current hemoglobin was <12 g/dL, gastritis only if evidenced by esophagogastroduodenoscopy, periodontal disease was self-reported, and renal disease if serum creatinine measurement had values above 1.2 mg/dL.

Systolic and diastolic blood pressures were measured twice with at least 15 minutes between measurements and the average was recorded. A BMI $\geq 25\ kg/m^2$ (overweight and obesity) was considered abnormal [54]. Abnormal values of waist circumference (>102 cm for men, >88 cm for women) and waist-to-hip ratio (WHR > 0.9 for men, >0.85 for women) were considered indicators of abdominal obesity. Waist circumference was measured around the narrowest point between ribs and hips after exhaling and viewed from the front. Hip circumference was measured at the point of maximum extension of the buttocks when viewed from the side [55]. Abnormal WHR values are consistent with National Cholesterol Education Program Adult Treatment Panel III and World Health Organization definitions [56].

Medical treatment included the current or past use of methotrexate and other disease modifying antirheumatic drugs (DMARDs) such as sulfasalazine, D-penicillamine, azathioprine, cyclosporine, gold salts and leflunomide, steroid therapy, antimalarials (cloroquine, hydroxychloroquine), and biologic therapy (rituximab, infliximab, etanercept, abatacept, adalimumab, tocilizumab). Patients and their past medical records were evaluated for the current or past use of aspirin or hormone replacement therapy as well.

Relevant laboratory variables were also registered including erythrocyte sedimentation rate (ESR), hemoglobin levels, white blood cell count, platelet count, and serum high sensitive C-reactive protein (CRP) levels. Autoantibodies such as rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP), TPOAb, and TgAb antibodies were taken from the patient's clinical record. They were measured with enzyme-linked immunosorbent assay (QUANTA-Lite, INOVA, San Diego, CA, USA) following the manufacturer's protocol. Antibodies directed against either TSH receptor or thyroid hormones (THAb) were not assessed in the current study.

2.2. Statistical Analysis. First, univariate analysis was done on all members of this new cohort. Categorical variables were analyzed by frequencies. Kolmogorov-Smirnov normality test was done to evaluate normality for quantitative, continuous variables. Parametric data are expressed as mean and standard deviation (SD), and nonparametric data are described as median and interquartile range (IQR).

Second, bivariate analyses done in search of the association between different characteristics of RA and AITD were verified using chi-square test or Fisher's exact test when the factors were dichotomous. Parametric values were analyzed by Student's t-test. Nonparametric values were analyzed by Mann-Whitney U-test. A P value of less than 0.05 was considered significant.

A multivariate binomial logistic regression model was fit with AITD as the dependent variable. As independent variables, the model included those that were significantly associated in the bivariate analyses and those that were biologically and clinically plausible for this relationship. The adequacy of logistic models was assessed using the Hosmer-Lemeshow goodness-of-fit test. The Nagelkerke R^2 (i.e., pseudo-R^2) was used to estimate the percentage of variance explained by the model. Adjusted odds ratios (AORs) were calculated with 95% confidence intervals (CIs). Statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS, v.20, Chicago, IL).

2.3. Literature Search. We did a literature review with reference to polyautoimmunity between RA and AITD. The search was done using the following databases: PubMed, SciELO, EMBASE, Virtual Health Library (BIREME and LILACS), and Google Scholar.

Limits regarding language, age (all adults), and humans were taken into account. No limits regarding publication date was used. The following Medical Subject Headings (MeSH terms) were used: "Thyroiditis, Autoimmune" OR "Graves Disease" AND "Arthritis, Rheumatoid". In addition, each MeSH term was translated into DeCS (Health Sciences Descriptors), a tool that makes it possible to navigate between records and sources of information through controlled concepts organized in Spanish and English. This was done in order to search SciELO, BIREME, and Virtual Health Library databses. The DeCs terms and key words used were "artritis reumatoide" AND ("tiroiditis autoinmune" OR "enfermedad de graves").

The inclusion criteria were the following: only articles that used accepted classification criteria for RA had a definite diagnosis of AITD (presence of antithyroid antibodies and thyroid dysfunction), and that included RA as well as AITD. They were divided based on prevalence of AITD, prevalence of antithyroid antibodies, radiographic progression, and extra-articular manifestations. Articles were excluded if they were animal models, dealt with juvenile rheumatoid arthritis, or with other autoimmune diseases other than RA or AITD.

Those references from the articles that seemed to be relevant for our review were hand searched. Titles and abstracts were reviewed by two independent reviewers in search of eligible studies.

3. Results

3.1. Colombian Cohort. There were 81.3% women and we found that the prevalence of AITD was 9.8%. The presence of antibodies was 37.8% for TPOAb and 20.8% for TgAb. Characteristics of the cohort are illustrated in Table 1. Due to the nature of this study (i.e., cross-sectional) and the cohort beginning date (i.e., 1996) there is a proportion of patients in whom not all the data were assessed. Health assessment questionnaire (HAQ) and disease activity score (DAS28) were calculated on study entry date, but were not taken into account in the analyses due to their variability over time.

Table 1: Characteristics of 800 patients with RA.

Characteristic	
Age (years)	51.92 (12.19) [a]
Age at onset (years)	39.58 (12.35)[a]
RA duration (years)	10 (14) [b]
Educational level (years)	11 (9)[b]
Body mass index	24 (5.8)[b]
DAS28	3.63 (2.12)[b]
HAQ	1.05 (1.31)[b]
Sociodemographic	*n*/*N* (%)
Female	650/800 (81.3)
Low educational level	264/692 (38.2)
Low socioeconomic status	234/780 (30.0)
Current smoking	85/768 (11.1)
Household duties	254/684 (37.1)
Clinical aspects	
Type 2 diabetes	32/737 (4.3)
Dyslipidemia	184/752 (24.5)
Hypertension	208/752 (27.7)
Thrombosis	39/738 (5.3)
Cardiovascular disease	173/781 (22.2)
Body mass index > 25	394/681 (57.9)
Abdominal obesity	460/683 (67.4)
Aspirin use	105/653 (16.1)
Abnormal cholesterol	179/333 (53.8)
RA characteristics	
Disease duration > 10 years	393/703 (55.9)
Erosions	349/451 (77.4)
EAMs with CVD	402/793 (50.7)
Rheumatoid factor+	573/717 (79.9)
Anti CCP+	312/384 (81.3)
Methotrexate	702/794 (88.4)
DMARD (any)	783/794 (98.6)
Antimalarials	633/793 (79.8)
Steroids	705/793 (88.9)
Biological Agents	276/794 (34.8)
Autoimmunity	
Autoimmune thyroid disease	78/800 (9.8)
Systemic lupus erythematosus	11/709 (1.6)
Sjögren's syndrome	24/800 (3.0)
Polyautoimmunity	113/800 (14.1)
Polyautoimmunity [c]	35/800 (4.8)
MAS	17/714 (2.4)
Familial autoimmunity FDR	104/800 (13.0)
ANAs+	310/448 (69.2)
Anti Ro+	43/287 (15.0)
Anti La+	20/285 (7.0)
TPOAb+	51/135 (37.8)
TgAb+	26/125 (20.8)

ANAs: antinuclear antibodies; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; CVD: cardiovascular disease; DAS28: disease activity score; DMARD: disease modifying antirheumatic drugs; EAM: extra-articular manifestations; ESR: erythrocyte sedimentation rate; FDR: first degree relatives; HAQ: health assessment questionnaire; MAS: multiple autoimmune syndrome; RA: rheumatoid arthritis; TgAb: anti-thyroglobulin; TPOAb: anti-thyroperoxidase enzyme.

[a] Mean (standard deviation).

[b] Median (interquartile range).

[c] Without taking AITD into account.

Table 2: Bivariate analysis of categorical variables.

Characteristic	RA with AITD	RA without AITD	OR	95% CI	*P*
MAS	10/61 (16.39)	7/650 (1.08)	18.01	6.57–49.30	<0.0001
Type 2 Diabetes	12/72 (16.67)	20/665 (3.01)	6.45	3.00–13.83	0.008
Methotrexate	75/78 (96.15)	627/716 (87.57)	3.54	1.09–11.49	0.024
Female	72/78 (92.31)	575/719 (79.97)	3.01	1.2–7.05	0.008
Thrombosis	9/71 (12.68)	30/667 (4.50)	3.01	1.4–6.78	0.003
Anti La+	6/39 (15.38)	14/246 (5.69)	3.01	1.08–8.3	0.04*
Anti Ro+	11/39 (28.21)	32/248 (12.90)	2.65	1.20–5.84	0.013
Abnormal BMI	37/69 (53.60)	250/612 (40.8)	1.67	1.01–2.76	0.042
Low educational level	15/59 (25.4)	249/633 (39.3)	0.52	0.28–0.96	0.035
Abnormal cholesterol	17/43 (39.53)	162/290 (55.86)	0.51	0.26–0.99	0.045
RF+	50/73 (68.49)	523/644 (81.21)	0.50	0.29–0.85	0.01
Polyautoimmunity	78/78 (100)	35/722 (4.8)	N/A	N/A	N/A
TPOAb+	51/54 (94.44)	0/81 (0.00)	N/A	N/A	N/A
TgAb+	26/50 (52.00)	0/75 (0.00)	N/A	N/A	N/A

*Fisher's exact test.
95% CI: 95% confidence interval; AITD: autoimmune thyroid disease; BMI: body mass index; N/A: not assessed; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; TgAb: anti-thyroglobulin; TPOAb: anti-thyroperoxidase enzyme.

Table 3: Bivariate analysis of continuous variables.

Characteristic	RA with AITD Mean ± SD	RA without AITD Mean ± SD	*P*
Age	52.26 ± 12.39 **Median ± IQR**	51.88 ± 12.24 **Median ± IQR**	0.029
Educational level (*y*)	14 ± 7	11 ± 9	0.006
Body mass index	25.5 ± 6.3	23.9 ± 5.9	0.006

AITD: autoimmune thyroid disease; IQR: interquartile range; RA: rheumatoid arthritis; SD: standard deviation.

Table 4: Associated factors with AITD in RA (multivariate analyses).

Characteristic	*B*	AOR	95% CI	*P*
Thrombosis	3.19	24.41	2.73–218.43	0.004
Diabetes	2.61	13.61	1.61–114.96	0.016
BMI > 25	1.44	4.22	1.19–14.93	0.025
Rheumatoid factor+	0.95	2.58	0.33–19.88	0.36
Methotrexate use	0.90	2.48	0.27–22.36	0.418
Female	0.46	1.58	0.34–7.42	0.56
Abnormal cholesterol	−1.22	0.29	0.08–1.10	0.069
Duration disease > 10 years	−1.32	0.27	0.07–1.05	0.058
Low educational level	−1.82	0.16	0.03–0.88	0.036
Antimalarials	−2.29	0.10	0.02–0.57	0.01

95% CI: 95% confidence interval; AOR: adjusted odds ratio; BMI: body mass index.

In the bivariate analysis, significant differences among women, educational level, abnormal BMI, diabetes, thrombosis, hypercholesterolemia, presence of RF, and use of methotrexate were observed. Tables 2 and 3 show the relationships explored in the study population.

Table 4 depicts the multiple logistic regression analysis. Adjusted for gender and RA duration, the presence of diabetes, thrombosis, and abnormal BMI were positively associated in patients with polyautoimmunity (i.e., between RA and AITD). We found that there is a lower AITD frequency in the lowest educational level than in the highest one. This is also true when antimalarials are used (Table 4).

3.2. Literature Search Results. The searches in Medline, EMBASE, LILACS, and BIREME brought up 788 articles. Forty-nine were selected for further analysis based on their title and abstract. Using information from references, other studies that met the selection criteria were chosen. The articles were divided by measured outcomes that were considered relevant: radiographic progression, genetic analysis, prevalence of AITD, and prevalence of TPOAb or TgAb.

3.2.1. Prevalence of AITD (Figure 1). Seventeen studies identified RA as index disease and determined AITD prevalence in this group [23, 57–72]. The prevalence in RA cases ranged from 0.5% in Morocco [58] to 27% in Slovakia [71]. Within the studies analyzed, 10 studies were from Europe [23, 63–71] with prevalence ranging from 1% in Germany [65] to 27% in Slovakia [71]. Four studies were from the North American region [59–62] where prevalence ranged from 2.1% [61] to 9.8% [60]. Only two studies were from Africa were retrieved [57, 58] and one from the Middle East [72]. The search did not result in any article about Latin American or Asian populations. Table 5 gives a detailed view of the data.

3.2.2. Prevalence of Autoantibodies (Figure 1). Twenty studies reported the prevalence of autoantibodies against thyroid antigens [23, 57, 70, 73–89]. The prevalence for TgAb ranged from 5% in men from the UK [88] and 6% regardless of gender in Egypt [57] to 31% in RA patients from Japan [79]; the prevalence for TPOAb was within the range of 5% in

Table 5: Prevalence of AITD diagnosis in RA patients.

Author publication date	Location	Study population	Diagnostic criteria of RA	Diagnostic criteria of AITD	Number of Cases	Frequency	Prevalence %
Africa							
Mousa et al. 2012 [57]	Egypt	F: 80% A: 36.3	ACR 1987	Lab.	217	12	5.5
Benamour et al. 1992 [58]	Morocco	F: 87.4% A: 34	ARA	N/A	404	2	0.5
America							
Cárdenas et al. 2012*	Colombia	F: 81.3% A: 51.92	ACR 1987	Lab.	800	78	9.8
Shiroky et al. 1993 [59]	Canada	F: 76. A: 58.7	ARA	Biopsy	119	7	4.2
Becker et al. 1963 [60]	USA	N/A	ARA	Histology	51	5	9.8
Linos et al. 1980 [61]	USA	F: 74.1% A: N/A	ARA	N/A	521	11	2.1
McCoy et al. 2012 [62]	USA	F: 69% A: 55.8 ± 15.7	ACR	Lab.	650	40	6.1
Europe							
Hijmans et al. 1961 [23]	Europe#	N/A	ARA 1959	N/A	86	7	8.1
Pongratz et al. 2000 [63]	Austria	F: 88.3% A: N/A	ARA	N/A	383	35	9.1
Caron et al. 1992 [64]	France	N/A	N/A	N/A	131	21	16
Herrmann et al. 1990 [65]	Germany	F: 86% A: N/A	N/A	US, Lab.	201	2	1
Biro et al. 2006 [66]	Hungary	N/A	ARA	Lab.	185	9	4.9
Somers et al. 2009 [67]	UK	F: 92% A: N/A	GPRD	GPRD	22888	337	1.5
Thomas et al. 1983 [68]	UK	F: N/A A: 52	N/A	NR	295	8	2.7
Chan et al. 2001 [69]	UK	F: 90% A: N/A	ARA	Lab.	64	2	3.0
Przygodzka and Filipowicz-Sosnowska 2009 [70]	Poland	F: 100% A: 56 ± 13	ACR	Lab.	100	16	16.0
Lazúrová et al. 2009 [71]	Slovakia	F: N/A A: 52.2 ± 2	N/A	US, Lab.	68	19	27.0
Middle East							
Zayeni et al. 2010 [72]	Iran	F: 87.1% A: 49.05	N/A	Lab. Clinical examination	224	39	17.4

Location not stated. Collaboration between the UK and The Netherlands.
* Current series.
N/A: Not available; F: Proportion of females; A: Age at time of assessment (standard deviation); ARA-ACR: RA diagnostic criteria 1987; UK: United Kingdom, US: Ultrasound, USA: United States of America, GPRD: General Practice Research Database; Lab.: Laboratory criteria.

Egypt [74] to 37% in Italy [80]. This search included 2 studies from Brazil [76, 77] and one from Argentina [75] which were the only countries from Latin America that had published literature on this topic. Some studies did not discriminate the frequency of each autoantibody [23, 76]. Ruggeri et al. [81] show the assessment of THAb at three points in time. Further information can be obtained from Table 6.

3.2.3. Extra-Articular Manifestations. In our search CVD was the sole EAMs found. Articles by McCoy et al. [62] and Raterman et al. [21] agreed that the presence of hypothyroidism, including Hashimoto's thyroiditis, is a risk factor for CVD in patients with RA. McCoy and colleagues found a hazard ratio of 2.7 (95% CI: 1.1–6.3) [62].

3.2.4. RA Severity. One full text article and three abstracts were located that dealt with this topic.

4. Discussion

In our cohort the prevalence of AITD was 9.8% while the presence of antibodies was 37.8% for TPOAb and 20.8% for TgAb. Type 2 diabetes (AOR: 13.61; 95% CI: 1.61–114.96; $P = 0.016$), thrombosis (AOR: 24.4; 95% CI: 2.72–218.42; $P = 0.004$), and abnormal BMI (AOR: 4.22; 95% CI: 1.19–14.93; $P = 0.025$) were positively associated in patients with polyautoimmunity (i.e., RA and AITD) while the lowest educational level (AOR: 0.16; 95% CI: 0.03–0.88; $P = 0.036$) as well as the use of antimalarials (AOR: 0.10; 95% CI: 0.18–0.57; $P = 0.01$) were negatively associated with this coexistence.

There is a worldwide prevalence of AITD in RA that varies considerably, ranging from 0.5 % in Morocco [58] to 27% in Slovakia [71]. Thyroid-specific antibody prevalence ranges from 6 to 31% for TgAb [57, 79], 5 to 37% for TPOAb [74, 80], and from 10.4 to 32% for the presence of

Table 6: Prevalence of TPOAb and TgAb in RA patients.

Author publication date	Location	Study population	Number of Cases	Diagnostic criteria of RA	Frequency		Prevalence %	
					TPOAb	TgAb	TPOAb	TgAb
Africa								
Assal et al. 2009 [73]	Egypt	F: 66.6% A: 26.8	30	ACR 1987	2	9	6.0	30.0
El-Sherif et al. 2004 [74]	Egypt	N/A	20	N/A	N/A	N/A	5.0	30.0
Mousa et al. 2012 [57]	Egypt	F: 80% A: 36.3	217	ACR 1987	22	13	10.1	6.0
America								
Cárdenas et al. 2012*	Colombia	F: 81.3% A: 51.92	125–135**	ACR 1987	51	26	37.8	20.8
Rivero et al. 1974 [75]	Argentina	N/A	50	N/A	N/A	10	N/A	20.0
Innocencio et al. 2004 [76]	Brazil	N/A	25	ACR 1987	8		32.00	
Gonçalves et al. 2009 [77]	Brazil	F: 86% A: 50 ± 10	72	ACR 1987	11	9	15.3	12.5
Asia								
Porkodi et al. 2004 [78]	India	N/A	N/A	N/A	21	13	2.8	1.8
Nakamura et al. 2008 [79]	Japan	F: 82.76% A: 61 ± 14	29	N/A	9	9	31.0	31.0
Europe								
Hijmans et al. 1961 [23]	Europe#	N/A	86	ARA 1959	9		10.4	
Atzeni et al. 2008 [80]	Italy	F: 81% A: 47 ± 16	70	ACR 1987	26	16	37.0	23.0
Ruggeri et al. 2002 [81] ≠	Italy	N/A	N/A	N/A	N/A	N/A	1975–1982: 0 1990–1992: 12 1998-1999: 26	
Genth et al. 1978 [82]	Germany	N/A	105	N/A	15	7	14.3	6.7
Andonopoulos et al. 1996 [83]	Greece	N/A	101	N/A	N/A	N/A	12.9	N/A
Raterman and Nurmohamed 2012 [84]	NL	N/A	N/A	ACR 1987	N/A	N/A	15	N/A
Magnus et al. 1995 [85]	Norway	N/A	100	N/A	N/A		§	
Przygodzka and Filipowicz-Sosnowska 2009 [70]	Poland	F: 100% A: 56 ± 13	100	ACR 1987	15	12	15.0	12.0
Buchanan 1965 [86]	Scotland	F: 100%	N/A	N/A	N/A	N/A	N/A	24.4
Yavasoglu et al. 2009 [87]	Turkey	F: 82%	82	ARA 1959	13	10	15.9	12.3
Silman et al. 1989 [88]	UK	N/A	N/A	N/A	N/A	N/A	males: 5 females: 15	males: 5 females: 11
Middle East								
Al-Awadhi et al. 2008 [89]	Kuwait	F: 79.1% A: 38.3	177	ACR 1987	12	6	6.7	3.4

N/A: Not available; F: Proportion of females; A: Age at time of assessment (standard deviation); NL: The Netherlands; UK: United Kingdom; USA: United States of America.
*Current series.
**See text for details.
#Location not stated. Collaboration among UK and NL.
§Compared to the prevalence in the normal population, patients with rheumatoid arthritis have a higher prevalence of both antibodies.
≠ Prevalence assessed in three time points. Only valid for thyroid hormone antibodies (THAb).

either of the two [23, 76]. This high prevalence variability may be explained by certain factors. Firstly there are difficulties on diagnosing AITD because it relies on the fact that there must be a diagnosis of thyroid dysfunction *a priori*. However there has been much of a debate regarding how to define hypothyroidism or hyperthyroidism; the normal reference range is not universally accepted and thus authors and clinicians worldwide accept different normal ranges.

The debate is more intense when establishing the normal upper limit for TSH values; several authors have addressed this issue but there has been no consensus [90–96]. Wartofsky and Dickey [91], and the Wickham cohort propose a TSH range around 2.5 IU/mL [97] while Surks et al. [94] and the American Academy of Clinical Endocrinologists (AACE) [98] support a TSH upper limit of 5 IU/mL. Jensen et al. and Hamilton et al. [90, 95] found a normal upper TSH level of 4.1 IU/mL, which is more clinically acceptable in order

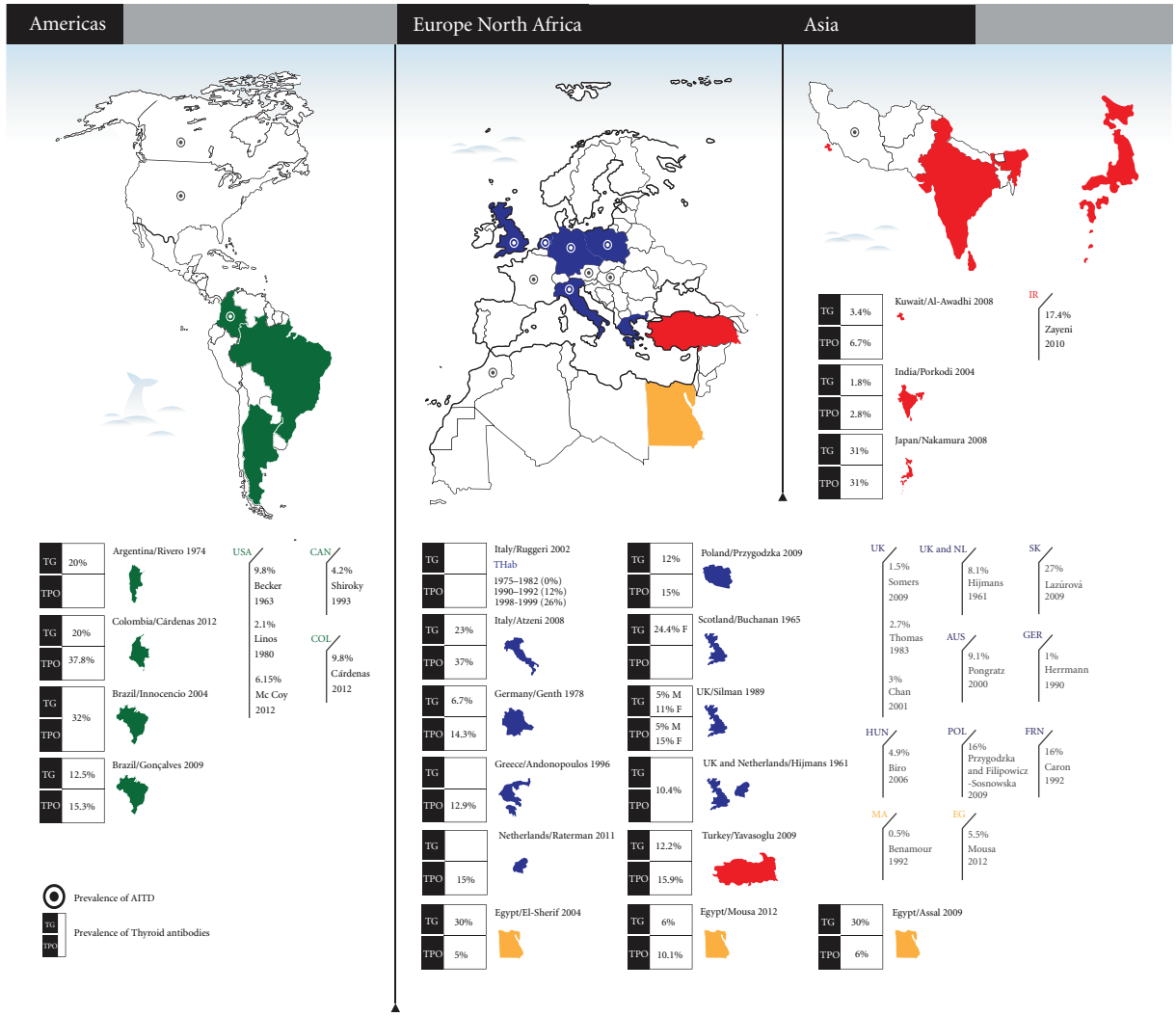

Figure 1: Prevalence of AITD and antibodies worldwide.

for initiating therapy. Secondly, the TSH assay methods have changed with time, improving its diagnostic accuracy [96]. This may hold true for other assays. Older studies may have not detected low levels of a given laboratory value and thus report a false negative result. This could explain the results of Ruggeri et al. [81] in which the prevalence of THAb are increasing with time.

A third explanation involves iodine intake. It is well known that iodine has a particular property of inducing autoimmune response against the thyroid [99–101]. Epidemiological studies support this statement as they have found an increasing incidence of AITD, particularly Hashimoto's thyroiditis, with increasing iodine intake (0.2% for low, 1% for normal, and 1.3% for high intake) [48]. Besides, a rise in Hashimoto's thyroiditis prevalence was encountered after adjustment of iodine supplementation [102]. Given this, and accepting the fact that iodine supplementation/intake is not evenly distributed among countries [103], it is plausible to think that this may also contribute to the heterogeneous prevalence of AITD in RA found around the globe.

When polyautoimmunity was assessed without taking into account AITD, a prevalence of 5% was found, which is relatively high. This is linked to a positive association between Ro and La antibodies and AITD. Both of these findings are supported by the "Autoimmune Tautology" [27].

Surprisingly, the association between AITD and EAMs did not become apparent in the literature search nor in our cohort. Although CVD is linked to the presence of EAMs [104], an increased cardiovascular risk is observed within this subset of patients with an OR of 3.1 in the bivariate analysis and an AOR of 24 when adjusted for potential confounders and variables of clinical interest. This is the reason CVD is considered an EAM and a major predictor of poor prognosis [16] and increased RA medical costs [105].

The aforementioned relationship found is supported by other studies. McCoy et al. [62] found that Hashimoto's disease had an HR of 2.1 (95% CI: 1.2–3.8) for CVD in patients with RA in a retrospective cohort. By perpetuating an inflammatory state RA is also considered as a novel risk factor for CVD. This has been shown in a large number of

reports [22, 106, 107] and was also demonstrated in our cohort previously [45, 104].

Furthermore, higher ESR, CRP, and TNF-α titers, the occurrence of RA vasculitis, and RA lung disease emerged as strong disease-specific predictors of cardiovascular mortality. This also holds even after accounting for demographics, traditional cardiovascular risk factors such as diabetes, sedentary lifestyle, obesity, smoking, and relevant comorbidities [108]. It has been proposed that an altered lipid profile is responsible for excess of CVD in patients with AITD [109]. However, Taddei et al. [110] in a case-control setting compared patients with subclinical hypothyroidism and autoimmune thyroiditis versus controls. They found that low grade systemic inflammation was responsible for endothelial dysfunction and impaired nitric oxide availability independent of lipid profile alterations [111]. Moreover, McCoy et al. [62] found that thyroxine supplementation was significantly associated with CVD, which supports the fact that the administration of this medication does not decrease the occurrence of this outcome. Autoimmunity itself may be an independent risk factor for CVD.

As both diseases increase inflammatory parameters and cytokines and cause endothelial dysfunction, a relationship between polyautoimmunity (RA and AITD) and the occurrence of CVD is not surprising.

Although antimalarial use was not significant in the bivariate analysis, we decided to keep the variable in the multivariate analysis. This is because this medication has been associated with a better cardiovascular outcome, improved glycated hemoglobin in patients with type 2 diabetes mellitus [112], enhanced glycemic control in patients with RA and SLE, and a reduced risk of developing diabetes mellitus in those patients [113, 114] in several reports. Furthermore, these medications influence cardiovascular risk by lowering total cholesterol levels [115, 116], which strengthens the hypothesis that reducing inflammation is important in reducing the risk of CVD in RA patients. This seemed to be the case with our RA patients with AITD.

It is noteworthy that most of the retrieved articles were from Europe followed by North American countries such as United States and Canada. This could be linked to the theory that Hashimoto's thyroiditis is the most frequent cause of spontaneously acquired hypothyroidism in industrialized countries. Few developing countries have data on AITD prevalence. These are Egypt, Iran, and Morocco. The latter reports the smallest prevalence of what we found in our literature search.

Considering thyroid antibodies, the prevalence is also heterogeneous. It is widely accepted that among these thyroid antibodies the most frequent is TPOAb compared to TgAb [6]. This has happened in almost all the studies that reported data on both antibodies [57, 70, 77, 80, 82, 87], and in our cohort. Nonetheless, this is not the case in the article from Japan by Nakamura et al. [79] in which they found the same prevalence for both antibodies. In addition, two studies from Egypt, one by El-Sherif et al. [74] and the other by Assal et al. [73], found an increased prevalence of TgAb, respectively. However, the study by Mousa et al. [57] found a higher prevalence for TPOAb in Egypt. A small sample size in these situations may be the best explanation for these contradictory findings. In Latin America, Rivero et al. [75], in an Argentinean setting, found a prevalence of 20% for TgAb while Gonçalves et al. [77] in Brazil found a prevalence of 15% for TPOAb and 7% for TgAb. Ruggeri et al. [81] demonstrated an increasing prevalence of THAb with time; pathologies different from AITD (RA and SS) exhibit increasing prevalences as well. It is noteworthy that this study also demonstrates that beyond an association of RA with Hashimoto's thyroiditis, antibodies to thyroid hormones (i.e., T3 and T4) may also foster the development of hypothyroidism.

Nevertheless, as the first study in Latin America that describes the relationship, our results do not differ from what has been reported in other latitudes. We report a prevalence of 9.8% of AITD in RA subjects, a TPOAb prevalence of 37.78%, and a TgAb prevalence of 20%. Although a prevalence of TgAb that was similar to Rivero's was found, the antibody prevalences in this study differ from those mentioned earlier by Gonçalves et al. [77]. Almost two times more of each antibody was found in our study than what they reported. In addition the AITD prevalence in RA patients is higher than in the general population from Latin America. According to Marsiglia the prevalence of AITD in the general population in Venezuela is 4.2% [117].

With respect to RA severity we only found one abstract that assessed the link between AITD and RA. Charles et al. [118] did not found a relationship between the presence of thyroid antibodies and the occurrence of anti-CCP although they did with PTPN22R620W allele. Likewise, in our cohort we did not find a correlation between AITD and proxy variables for RA severity such as erosions, biologic agent use, the presence of anti-CCP [119], and EAMs (data not shown). The reason why this association between AITD and RA severity has not been studied is not immediately apparent. One cannot but hypothesize that many of these studies are cross-sectional in nature and because the importance of DAS28 and HAQ is along a timeline, it is not relevant to include these variables in the analysis.

In nonautoimmune hypothyroidism however, Cojocaru-Gofita et al. [120] found that women with AR and clinical hypothyroidism had a higher DAS28 score compared to RA women without clinical hypothyroidism. Kang et al. [121] found that in Korean patients with AR subclinical or clinical hypothyroidism was associated to the occurrence of positive titers of anti-CCP. Also, Delamere et al. [122] found that thyroid dysfunction is associated with increased mean duration and incidence of morning stiffness. It is important to consider these reports because some of these patients may have AITD and this could be related to the severity of RA. Figure 2 illustrates the main symptoms in patients with AITD and AR.

The importance of this Colombian cohort is worth considering. We attempt to add further knowledge with respect to the characteristics of RA in minorities in Latin America, a region about which literature on this topic is scarce.

We are aware of our study limitations. First of all, information bias could be present in our analysis as not

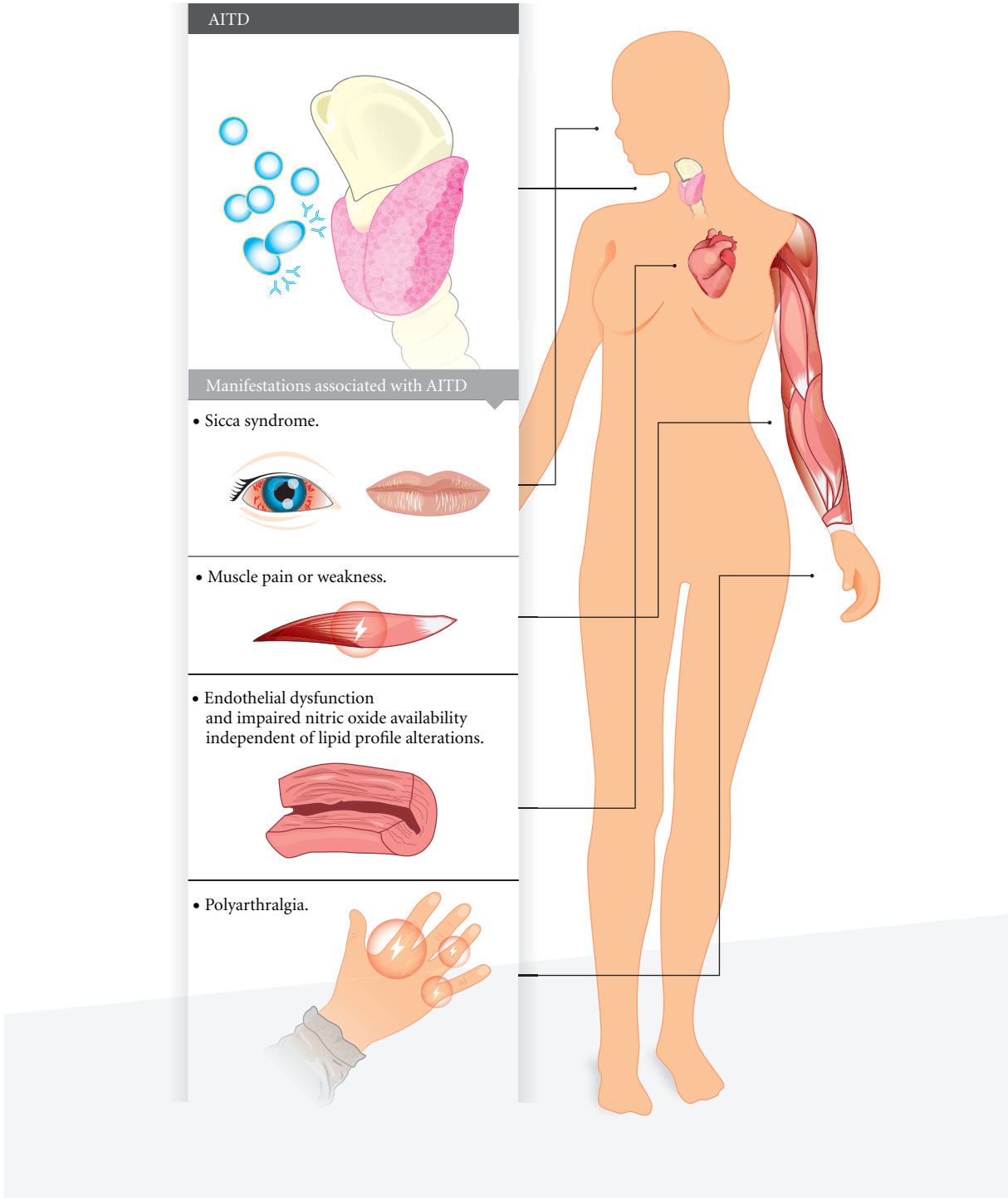

Figure 2: AITD manifestations in patients with RA. AITD manifestations may resemble those presented by RA. Some symptoms are exacerbated when both diseases co-occur. See text for details.

all patients with RA were systematically evaluated for all the variables. This is the case for thyroid antibodies, which were only assessed in patients that had some type of thyroid disturbance. This included 135 patients for TPOAb and 125 for TgAb. Secondly, the cross-sectional nature of the study does not allow us to infer causality. Another limitation is one that is linked to all searches—some articles may have escaped our search and, thus, some regions may have been overlooked. Additionally, the articles found had small sample sizes. It is important to consider the heterogeneity in the definition of AITD as well. In contrast, our strengths are our number of participants, a well-described cohort of RA

patients, and the multicenter validation of RA cases. To our knowledge, this is the first paper that addresses this particular topic from a global perspective.

There were more patients with TPOAb and TgAb than with a clinical diagnosis of AITD. Linked with the idea that autoantibodies are predictors of disease [123, 124], it is important to remain vigilant in following the clinical course of these patients; TPOAb and TgAb are known to predict AITD. This was demonstrated in the Wickham cohort [97]. Patients within accepted TSH reference range and having the aforementioned antibodies had a greater risk of developing overt hypothyroidism (i.e., AITD). Also TPOAb has been shown to predict development of AITD in pregnant women [125]. A careful assessment of those patients with a normal range of TSH but presenting specific antibodies should be done.

To conclude, we have found that AITD is not uncommon in RA patients. The range has its lower limit in 0.5% and it goes up to 27%. For TgAb, this prevalence ranges from 6% to 31% and for TPOAb, also from 5% to 37%. The prevalence of AITD and antibodies in our cohort falls within these ranges. Our literature search indicates that literature is scarce and, therefore, more research is needed on this topic, particularly in developing countries. The findings in this study justify a prospective analysis that follows RA patients diagnosed with AITD. They also support routine screening for CVD among these patients. These results may help to further study the common mechanisms of autoimmune diseases, to improve patients' outcome, and to define public health policies. An international consensus to accurately diagnose AITD is warranted.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Cardiovascular Disease in Rheumatoid Arthritis: A Systematic Literature Review in Latin America

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Background. Cardiovascular disease (CVD) is the major predictor of poor prognosis in rheumatoid arthritis (RA) patients. There is an increasing interest to identify "nontraditional" risk factors for this condition. Latin Americans (LA) are considered as a minority subpopulation and ethnically different due to admixture characteristics. To date, there are no systematic reviews of the literature published in LA and the Caribbean about CVD in RA patients. *Methods*. The systematic literature review was done by two blinded reviewers who independently assessed studies for eligibility. The search was completed through PubMed, LILACS, SciELO, and Virtual Health Library scientific databases. *Results*. The search retrieved 10,083 potential studies. A total of 16 articles concerning cardiovascular risk factors and measurement of any cardiovascular outcome in LA were included. The prevalence of CVD in LA patients with RA was 35.3%. Non-traditional risk factors associated to CVD in this population were HLA-DRB1 shared epitope alleles, rheumatoid factor, markers of chronic inflammation, long duration of RA, steroids, familial autoimmunity, and thrombogenic factors. *Conclusions*. There is limited data about CVD and RA in LA. We propose to evaluate cardiovascular risk factors comprehensively in the Latin RA patient and to generate specific public health policies in order to diminish morbi-mortality rates.

1. Introduction

RA is the most common inflammatory arthropathy worldwide with a prevalence of 0.5–1.0% in industrialized countries [1]. The annual incidence is highly variable (12 to 1,200 per 100,000 population) and is dependent on a variety of factors, including sex, ethnicity, and age [2]. RA is a chronic, multiorganic, and complex disease with an autoimmune basis. The disease is three times more frequent in women than men [1]. RA can damage virtually any extraarticular tissue due to a systemic proinflammatory state. Cardiovascular disease (CVD) is considered an extraarticular manifestation (EAM) [3] and a major predictor of poor prognosis [2]. Several studies have documented a high prevalence of CVD in many autoimmune diseases (ADs) [2, 4–14]. Several traditional risk factors such as obesity, dyslipidemia, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), hypertension, physical inactivity, advanced age, male gender, family history of CVD, hyperhomocysteinemia, and tobacco have been associated with CVD in RA patients [15–20]. In fact, seropositive RA may, like diabetes, act as an independent risk factor for CVD [21]. A proinflammatory state [7], insulin resistance [22], hyperhomocysteinemia [23], and oxidative stress [24] are common characteristics of both RA and atherogenesis. Nevertheless, excessive cardiovascular events observed in RA individuals are not fully explained by these traditional risk factors [7, 24]. Hence, there is an increasing interest in identifying "nontraditional" [4, 5] novel risk factors (i.e., genetic polymorphisms, autoantibodies, medication, duration of RA, high disease activity, development of EAM and many others) in order to explain the development

of early endothelial dysfunction, increased intima-medial thickness (IMT), and finally, accelerated atherosclerosis [25]. The finding and understanding of these predisposing factors will allow us to better describe cardiovascular subphenotypes including hypertension, stroke, coronary artery disease (CAD), angina, myocardial infarction (MI), arrhythmias, ventricular diastolic dysfunction [26, 27], congestive heart failure (CHF), thrombosis, and peripheral arterial disease [16, 28].

Life expectancy of patients with RA is three to ten years less than that of the general population [29]. Although it is well established that cardiovascular mortality is higher in RA, the reasons for this remain elusive [30]. Currently, ischemic heart disease (IHD) secondary to atherosclerosis is the most prevalent cause of death associated with CVD in patients with RA [31]. CVD accounts for 30–50% of all deaths in RA patients [3]. Thus, RA added to CVD as the leading cause of death around the world [32, 33] requires us to take these diseases more seriously. Therefore, doctors need to be more committed to assessing, monitoring, and treating cardiovascular risk factors in the early stages as well as to promoting lifestyle changes in order to diminish morbimortality rates in RA individuals.

Hispanics are considered a minority group due to a mixed ethnicity (so called *mestizos*) that is mainly derived from a European and Amerindian inheritance [34]. Therefore, they represent a unique population. So far, some studies of RA have documented differences in health status, disease prevalence, treatment outcomes, and healthcare use among different ethnic groups [35, 36] which suggest that minority health disparities influence RA. Moreover, CVD is still one of the most important comorbidities in this subpopulation due to augmented mortality secondary to accelerated atherosclerosis, systemic inflammation, and MI or stroke [37–39].

RA is not uncommon in LA, the geographical area defined by Mexico, Central America, South America, and the islands of the Caribbean [1]. Overall,RA affects 0.5% of LA [40]. In Argentina, Spindler et al. [41] reported an overall prevalence ratio (per 1,000) of 1.97 (95% CI: 1.8–2) for both sexes, 0.6 (95% CI: 0.49–0.73) for men and 3.2 (95% CI: 2.9–3.5) for women. Peláez-Ballestas et al. [42] found a prevalence of 0.7–2.8% in Mexican patients. In an isolated African Colombian population, a prevalence of 0.01% was reported [43]. However, CVD has not been systematically assessed in LA and only a few studies have evaluated some of the traditional and nontraditional risk factors, cardiovascular subphenotypes, and mechanisms underlying the accelerated atherosclerosis that is characteristic of this population. Therefore, in this study, a systematic review of CVD in LA patients with RA was done.

2. Material and Methods

2.1. Search Strategy. A systematic literature review of articles on CVD and RA in LA was carried out in the following databases: PubMed, LILACS, SciELO, and Virtual Health Library (VHL). It included articles published between January 1947 and May 2012. Two reviewers did the search independently (SMJC and HDAC) while applying the same selection criteria described below. The search results were compared and disagreements were resolved by consensus. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in data extraction, analysis, and reporting [44].

The search was done in PubMed, using the following Medical Subject Headings (MeSH terms): "Arthritis, Rheumatoid," "Latin America," "Ethnic Groups," "Minority Groups," "Latin America/Epidemiology," "Latin America/Ethnology," "Brazil," "Mexico," "Colombia," "Chile," "Cuba," "Panama," "Venezuela," "Bolivia," "Peru," "Argentina," "Uruguay," "Paraguay," "Ecuador," "Nicaragua," "Surinam," "French Guiana," "Guatemala," "Honduras," "Belize," "Costa Rica," "El Salvador," "Puerto Rico," "Dominican Republic," and "Haiti." Each one of them was cross-referenced with the following MeSH terms: "Cardiovascular Diseases," "Hypertension," "Thrombosis," "Stroke," "Myocardial Infarction," and "Coronary Artery Disease." Each term was cross-referenced for the greatest number of results. No limits regarding language, period of publication, or publication type were used. In a quality control assessment of the first systematic search, it was evident that some publications were missed when only MeSH terms were used. Therefore, a second search was done by implementing key words. In the second search, also without limits, MeSH terms ("Hispanic Americans" and some of the previously described terms such as "Arthritis, Rheumatoid;" "Latin America" and "Minority Groups") and key words (Rheumatoid Arthritis was matched with every country and Hispanics with RA) were included.

A similar strategy was followed for the other databases. Each MeSH term was translated into DeCS (Health Sciences Descriptors) in order to explore sources of information in Portuguese, Spanish, and English through SciELO, LILACS and VHL databases. The following terms were selected: "Artritis Reumatoide," "América Latina," "Salud de Minorias," "Grupos Étnicos," "Brasil," and "Haití" (24 countries, as well as PubMed). Then each of the terms was cross-referenced with the following: "Enfermedades Cardiovasculares," "Hipertension," "Embolia y Trombosis," "Accidente Cerebrovascular," "Infarto del Miocardio," and "Enfermedad Coronaria" for the first search. Each term was cross-referenced for the greatest number of results. Once again, no limits were used. For the second search in SciELO, some of the DeCS terms and keywords included were Artritis Reumatoid, América Latina, Salud de Minorias, Grupos Étnicos, "Enfermedades Cardiovasculares," "Hipertension," "Embolia y Trombosis," "Accidente Cerebrovascular," "Infarto del Miocardio," and "Enfermedad Coronaria." Both Spanish (Artritis Reumatoide) and English (Rheumatoid Arthritis) key words were matched with every country (Brazil to Haiti). "Artrite Reumatoide" was included as an additional term for Brazil in the search for articles published about CVD in this country. Likewise, in two remaining databases—LILACS and VHL (all sources)—both Spanish (Artritis Reumatoide) and English (Rheumatoid Arthritis) key words were matched with every country (Brazil to Haiti). As in SciELO, "Artrite Reumatoide" was included as an additional term for Brazil.

2.2. Study Selection, Data Extraction, and Quality Assessment. A study was included if (a) the abstract was available, (b) it contained original data, and (c) it used accepted classification criteria for RA and measured cardiovascular risk factors (traditional, nontraditional) and/or any of the cardiovascular subphenotypes. Articles were excluded from the analysis if they dealt with juvenile idiopathic arthritis or were done on animal models (i.e., murine models) instead of RA patients. Studies were also excluded if they were reviews or case reports, if they discussed topics not related to CVD, and/or were not done on an LA population. Those references from the articles that seemed to be relevant for the present paper were hand-searched and were included in the discussion. Abstracts and full text articles were reviewed to find eligible studies. Duplicate papers were excluded.

Three blinded reviewers (SMJC, AAJC, and HDAC) organized selected articles on the basis of publication source, author, cardiovascular outcome, and traditional and nontraditional cardiovascular risk factors as well as subphenotypes evaluated. Moreover, a descriptive analysis from these data was completed. Articles were not included in the analysis when there was a lack of inclusion criteria, insufficient data, and statistical significance. A database with pertinent information from these studies which included authors, name of study, country, language, study design, number of patients, objective, cardiovascular outcome, method of hypothesis testing, results, limits/bias of the study, and reference was created. Disagreements between the reviewers were resolved by consensus. Each record was classified based on the quality score of the studies that was assigned by applying the levels established by the Oxford Centre for Evidence-based Medicine 2011 in order to evaluate the risk of bias [45].

3. Results

3.1. Systematic Literature Review. There were 3,897 articles identified in the first and 1,285 articles in the second search in PubMed (total of 5,182). Additional records identified through other sources included 206 articles from SciELO in the first search and 273 in the second one, 34 and 465 from LILAC, and 2,496 and 1,427 from VHL. Therefore, the database searches provided a total of 10,083 publications. Of these, 9,998 studies were discarded because they did not meet the eligibility criteria. After this exclusion, 85 articles were assessed and duplicates were identified (64 papers). A total of 21 full text articles were assessed for eligibility. Finally, only 16 articles [25, 30, 46–59] that had interpretable data and fulfilled the eligibility criteria were included. Of the selected articles, there were 5 from Mexico, 3 from Brazil and Colombia, 2 from Argentina, and 1 from Chile, Cuba and Puerto Rico, respectively. Seven were cross-sectional, 6 were case controls, 2 descriptive/retrospective, and only one corresponded to a cohort study. Half the studies had a sample size that was less than 100 patients. The flow chart for systematic literature review and articles included in the analysis are shown in Figure 1.

3.2. Risk Factors, Physiopathological Changes, and Subphenotypes of CVD. The prevalence of CVD in LA patients with RA was 35%. Several *traditional* cardiovascular risk factors such as dyslipidemia [25, 30, 48, 50, 51, 53, 55, 56, 58, 59], hyperhomocysteinemia [30, 48], smoking [25, 30, 48, 50], T2DM [25, 48, 50, 53, 56, 58], MetS [25, 50, 53], hypertension [30, 48–50, 52–56, 58], male gender [25, 46, 48, 49, 52–55], obesity [25, 49, 50, 52], physical inactivity [25, 50], and family history of CVD [25, 55] were reported. Several studies were associated with *nontraditional* risk factors, previously described in the literature, such as HLA-DRB1 shared epitope (SE) allele [25], rheumatoid factor (RF) [25, 30, 46, 49, 52, 55, 57, 58], anticyclic citrullinated peptide antibody (anti-CCP) [25, 55], and other autoantibodies [51]. These included anticardiolipins (aCL), anti-β2 glycoprotein I (anti-β2GPI), antioxidated low-density lipoprotein (anti-oxLDL), and antiheat shock proteins 60/65 antibodies (anti-HSP 60/65) [52]. Other nontraditional factors include long duration of RA (>10 years) [25, 55], markers of chronic inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [48, 49, 52, 55], high disease activity score-28 (DAS-28) [25, 49, 52, 57] and simplified disease activity index (SDAI) [52], presence of EAM [25, 46, 55, 57], medications like methotrexate (MTX) [25, 30, 49], and steroids [25, 30, 55–57, 59]. The last factors described were thrombogenic factors such as von Willebrand factor (vWF) [49] and fibrinogen [52], and novel risk factors like poliautoimmunity (defined as the presence of more than one autoimmune disease in a single patient) [25, 46, 55, 58], and familial autoimmunity [25] (diverse autoimmune diseases cooccurring within families). These factors and their respective prevalence or associations are depicted in Table 1.

Many groups described endothelial dysfunction, an increased IMT, and atherosclerosis plaque in RA patients [25, 49, 51, 52]. A broad spectrum of cardiovascular subphenotypes including stroke, CAD, MI, hypertension, thrombosis, peripheral arterial disease, and ventricular diastolic dysfunction were described in LA individuals with RA. Hypertension was the most common outcome in almost all studies with an overall prevalence of 28% (range 11.2–80.6%) [25, 48, 50, 53–56, 58, 59]. The average prevalence of CAD and stroke was 9% [47, 54, 58] and 2.5% [30, 46, 48, 58, 59], respectively. Figure 2 shows the prevalences of CVD in LA and the Caribbean.

4. Discussion

To date, the literature evaluating CVD outcomes in LA individuals with RA is scarce. Only a few studies have assessed the classic and nontraditional risk factors in this subpopulation.

4.1. Cardiovascular Disease as the Leading Cause of Mortality in LA. CVD is the leading cause of mortality worldwide. On the American continent, the prevalence and incidence of CVD is growing at an alarming rate. The World Health Organization (WHO) forecasts that the number of deaths in the region attributed to CVD will increase by more than

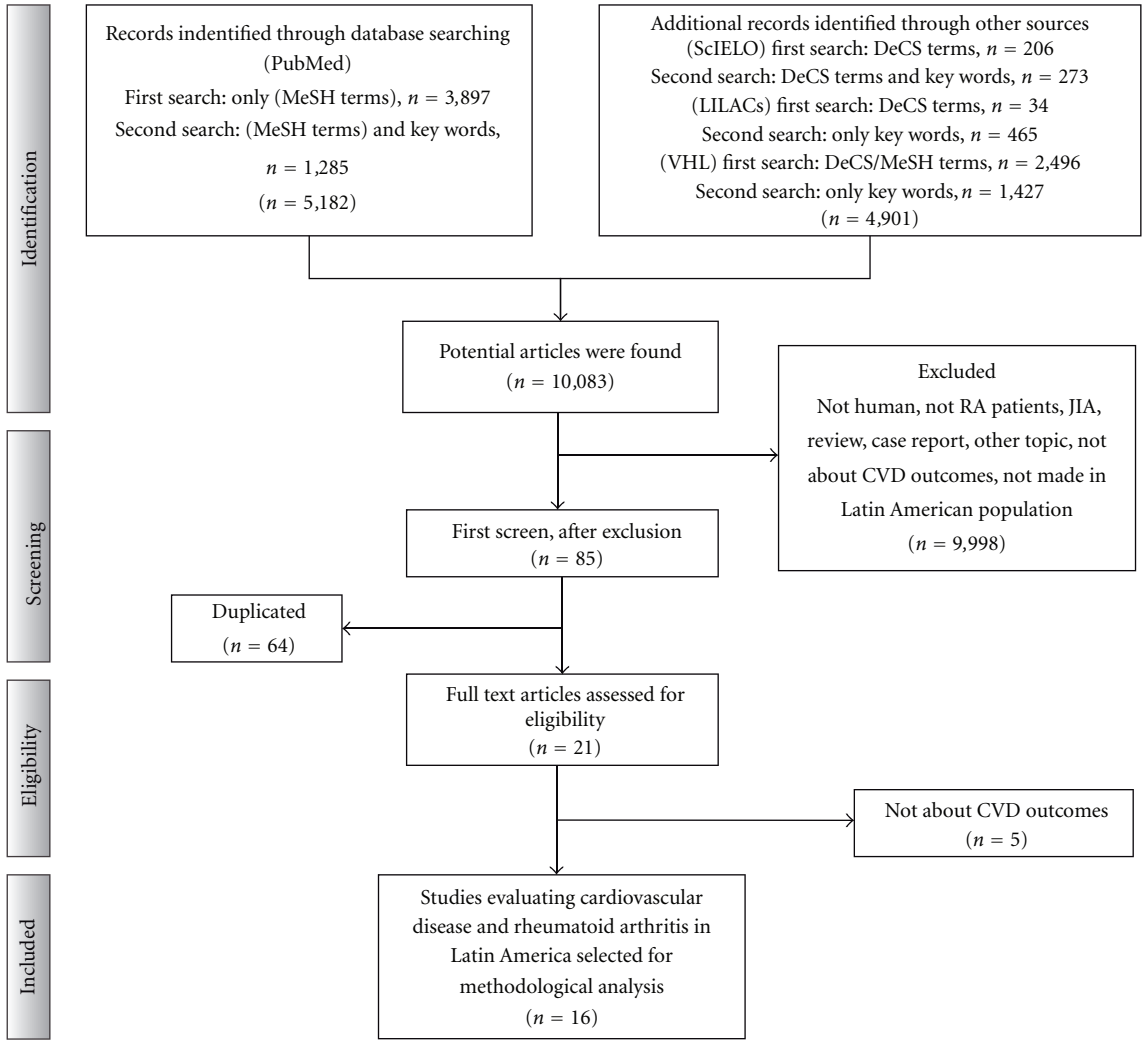

Figure 1: Flow chart of the systematic literature review; VHL: virtual health library; RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis; CVD: cardiovascular disease.

60% between 2000 and 2020 unless preventive measures are taken [60]. Thus, this chronic disease is one of the major causes of death around the world [33]. Thanks to the CARMELA initiative study, many traditional factors have been described in LA population such as hypertension, dyslipidemia, obesity, smoking, T2DM, and MetS [61].

Table 2, which was adapted from the Pan American Health Organization report [62], shows the mortality rates of CVD in the Americas as of 2007–2009 in terms of IHD and cerebrovascular disease. The data on this table is organized by country and region thus making it possible to contrast mortality rates from these two diseases in the United States of America (USA) and Canada with LA and the Caribbean. Generally, high rates of death were mostly observed in developed countries such as USA and Canada 136.3/100,000 people. Incidence of mortality in LA and the Caribbean due to IHD and cerebrovascular disease is 55.8/100,000 and 44.8/100,000 people, respectively. Individuals living in developed countries have more risk factors, for example, inappropriate life styles, that contribute to a higher rate of death from CVD. Thus, it is important to promote healthy habits among the general population and in patients with an early diagnosis of RA in order to prevent CVD. In specific LA countries, numbers show high rates of IHD in countries such as Cuba (140.1/100,000 people) and Puerto Rico (100.7/100,000 population). The importance of the numbers lies in the fact that they can be analyzed from the perspective of increased risk of CVD in RA in comparison to the general population. Therefore, it is important to discriminate mortality CVD rates by patients with chronic inflammatory diseases (i.e., RA).

LA has a growing population and it is a very dynamic region with an estimated population of 515 million. As mentioned before, the RA prevalence reported in LA is considered to be less than 0.5% [63, 64]. The heterogeneity across LA is expected due to the high degree of admixture between subpopulations. Hispanic/Latino populations are the result of a two-way admixture between Amerindian

Table 1: Traditional, nontraditional risk factors, physiopathological changes, and subphenotypes of cardiovascular disease and rheumatoid arthritis in Latin America.

Ref.	Country	Author	Prevalence of CVD in RA (%)	*N*	Cardiovascular outcome measured			
					Traditional risk factors of CVD *n/N* (%)	Nontraditional risk factors of CVD *n/N* (%)	Physiopathological changes in CVD *n/N* (%)	Subphenotype of CVD described *n/N* (%)
[46]	Mexico	Orozco-Alcalá et al.[a]	44.7	38	Male gender 12/38 (31.6)	Polyautoimmunity 6/38 (15.8); RF 32/38 (84.2); EAM 16/38 (42.1); GC 9/38 (23.7); RA duration over 10 years 17/38 (44.7)	N/A	Stroke 10/38 (26.3), MI 3/38 (7.9), CHF 3/38 (7.9), acute pulmonary embolism 1/38 (2.6)
[47]		Espinola-Zavaleta et al.	14.3[b]	37 (14 with RA)	Dyslipidemia[c]: TGL 106.2 ± 55.1[†]; male gender 2/14 (14.3)	RA duration 8.2 ± 7.1[c]	N/A	Alterations in myocardial perfusion: Subclinical CAD 2/14 (14.3)[b]
[48]		Lopez-Olivo et al.	13.8	152 RA patients/153 controls	Obesity: BMI 25 (16–36)[‡], dyslipidemia: hypercholesterolemia 5/152 (3.3), T2DM 8/152 (5.3), male gender 26/152 (17.1)[§], hyperhomocysteinemia 31/152 (20.4)[§] and smoking 56/152 (36.8)[§]	RF 149 (0–3,050)[‡]; CRP (mg/dL) 17 (3–126)[‡§]; RADAR 1.0 (0.1–2.7)[‡], HAQ-Di 0.7 (0–2.7)[‡]; MTX 14/31 (45.2)[d]	N/A	Hypertension 17/152 (11.2), stroke 4/152 (2.6)
[49]		Daza, et al.[e,f]	7.3[g]	55 RA patients/22 controls	Obesity: BMI 27.51 ± 4.05/24.48 ± 3.73[§]	RF 506.5 (347.1–665.8)[‡]/13.3 (5.8–20.8)[§]; CRP (mg/dL) 1.48 (1.05–1.9)[‡]/0.6 (0.02–1.2)[§], ESR 28.47 ± 14.48[†]/9.65 ± 3.56[§]; DAS 28 4.77 (4.5–5.1)[‡]; MTX 45/55 (81.8), SSZ 6/55 (10.9), GC 8/55 (14.5); vWF 145.6 ± 30.1[†]/121.8 ± 37.2[§]	IMT 0.67 ± 0.18[†]/0.58 ± 0.10 (mm)[§], atherosclerosis plaque 4/55 (7.3)	N/A
[50]		Zonana-Nacach et al.	24.5[#]	192 (107 RA and 85 SLE patients)	Obesity 49/192 (25.5), dyslipidemia 49/192 (25.5), T2DM 14/192 (7.3), MetS (18.7), physical inactivity 75/192 (87), and smoking 28/192 (14.6)	RA duration 135 ± 112[†] (months); Housewife 102/192 (53)	N/A	Hypertension 47/192 (24.5)

Table 1: Continued.

Ref.	Country	Author	Prevalence of CVD in RA (%)	*N*	Cardiovascular outcome measured			
					Traditional risk factors of CVD *n/N* (%)	Nontraditional risk factors of CVD *n/N* (%)	Physiopathological changes in CVD *n/N* (%)	Subphenotype of CVD described *n/N* (%)
[52]		Pereira et al.[i]	14.1[g]	71 RA patients/51 controls	Male gender[j] 7/71 (9.9)	CRP[k] (mg/L): 8.64 ± 8.27[†]/19.75 ± 25.08, ESR[k]: 24.1 ± 14.6[†]/34.07 ± 23.54; DAS 28: 4.24 ± 1.02[†]/4.64 ± 1.05; SDAI[k]: 35.54 ± 12.34/48.5 ± 30.28[§]; MTX[k] (mg/w): 20 ± 5/19.09 ± 5.74, GC[k] (mg/day): 7.25 ± 2.75/7.72 ± 3.59; fibrinogen[k] 326.04 ± 113.56[†]/371.94 ± 121.08[§]	IMT[j]: 0.72 ± 0.17/0.67 ± 0.15 (mm). Carotid plaquesj (IMT > 1.5 mm) 10/71 (14.1)/1 (1.9)[§]	N/A
[51]	Brazil	Pereira et al.[l]	14.1[g]	71 RA patients/53 controls	Dyslipidemia[k]: CT 243.3 ± 31.2/191.54 ± 36.21[§], male gender[j] (9.9/13.9)	Same data from [52] and autoantibodies: RF[k]: 195.10 ± 281.71[†]/308.13 ± 584.46, anti-CCP (79/1.9), aCL (IgG 5.6/3.8, IgM 7/3.8), anti-B2GPI (IgG 1.4/1.9, IgM 4.2/1.9), anti-HSP 60 (14.1/7.5), anti-HSP 65 (36.6/17), anti-LPL antibodies (2.8/1.9)	IMT[j]: 0.72 ± 0.17/0.67 ± 0.15 (mm). Carotid plaquesj (IMT > 1.5 mm) 10/71 (14.1)/1 (1.9)[§]	N/A
[53]		de Cunha et al.	80.6[#]	283 RA patients/226 controls	Obesity: BMI 26.6 ± 5.1[†]/26.8 ± 4.3, dyslipidemia: HDL 58.9 ± 16.4[†]/52.7 ± 12.1[§], LDL 109.9 ± 33.2/122.8 ± 37.7[§], T2DM 32/283 (11.3)-6/226 (2.7)[§], MetS 111/283 (39.2)-44/226 (19.5)[§], male gender 50 (17.7)/34 (15)	N/A	N/A	Hypertension[m] 228 (80.6)/95 (42)

Table 1: Continued.

Ref.	Country	Author	Prevalence of CVD in RA (%)	*N*	Cardiovascular outcome measured			
					Traditional risk factors of CVD *n/N* (%)	Nontraditional risk factors of CVD *n/N* (%)	Physiopathological changes in CVD *n/N* (%)	Subphenotype of CVD described *n/N* (%)
[54]		Pineda et al.[n]	32.4	41	Male gender 12/41 (29)	N/A	N/A	Hypertension (24.2), CAD 9/41 (8.2)
[25]	Colombia	Rojas-Villarraga et al.[o]	41[#]	140	Obesity 23/140 (16), dyslipidemia 49/140 (35), T2DM 6/140 (4), MetS 61/140 (44), physical inactivity 119/140 (85), male gender 16/(23), family history of CHD 22/140 (16), ever smoking 61/140 (44)[§], and history of hormone replacement therapy 10/140 (7)	Poly-autoimmunity 31/140 (22); family history of autoimmunity 29/140 (21)[§]; HLA-DRB1 SE 60/136 (46)[§]; RF 85/134 (63)[§], anti-CCP antibodies 73/94 (78); CRP 5.9 ± 15[†], ESR 38.9 ± 25.1[†]; DAS 28 4.4 ± 1.4[†], HAQ 1.7 ± 0.7[†]; EAM 60/140 (43); MTX 131/140 (94), GC 131/140 (94); RA duration 13.8 ± 8.5[§]	Early endothelial dysfunction 44/140 (31)[§], increased IMT 75/140 (54)[§], atherosclerosis plaque 10/140 (7)[§]	Hypertension 57/140 (41)
[55]		Ortega-Hernandez et al.[o]	32	538	Dyslipidemia 64/534 (10), male gender 80/538 (15)	Polyautoimmunity 48/538 (9); RF 246/385 (64)[§], anti-CCP antibodies 146/183 (80); CRP 8.65 ± 20.21[†], ESR[†] 38.86 ± 25.93§; EAM 113/538 (21); GC 39/486 (8); RA duration 12.53 ± 8.08[§]	N/A	Hypertension 128/534 (24), thrombosis 43/534 (8)
[56]	Argentina	Larroudé et al.	13.9[#]	137	Dyslipidemia 89/137 (65), T2DM 2/137 (1.45), and male gender N/A 11/137 (8)	GC 71/137 (51.8)	N/A	Hypertension 19/137 (13.9)
[57]		Lascano et al.[p]	47	32 RA patients/32 controls	N/A	RF 27/32 (84); ESR 28 ± 15[†]; DAS 28 4.3 ± 1.4[†]; EAM 8/32 (25); GC 21/32 (66); RA duration 10.2 ± 8.4[†]	N/A	Ventricular diastolic dysfunction 15/32 (47)
[30]	Chile	Cisternas et al.[q]	46.4	54 RA patients/32 controls	Obesity: BMI 26 (18–39)[‡], dyslipidemia 18/54 (33), male gender 7/54 (13), family history of CVD 9/54 (17), hyperhomocysteinemia 38/54 (70)[§], and smoking 21/54 (39)	RF 50/54 (92), aCL[‡] IgM 3 (0.53–23)/1.6 (0.21–10.6) IgG 4.3 (0.3–85)/2.5 (0–12.3); CRP 0.73 (0.04–5.96)[‡]/0.31 (0.05–2.88)[§], ESR 27 (3–99)[‡]; MTX 41/54 (75), GC 42/54 (77); RA duration 9.5 (0.2–32)[‡]	N/A	Hypertension 21/54 (39), stroke 2/54 (3.7), stable angina 2/54 (3.7)

Table 1: Continued.

Ref.	Country	Author	Prevalence of CVD in RA (%)	*N*	Cardiovascular outcome measured			
					Traditional risk factors of CVD *n/N* (%)	Nontraditional risk factors of CVD *n/N* (%)	Physiopathological changes in CVD *n/N* (%)	Subphenotype of CVD described *n/N* (%)
[58]	Cuba	Acosta et al.[r]	34.1	172	Dyslipidemia 10/172 (5.8), T2DM 16/172 (9.3), and male gender 29/172 (16.9)	Polyautoimmunity 2/172 (1.1); RF 52/85 (61.1)	N/A	Hypertension 46/172 (26.7), stroke 1/172 (0.5), CAD 8/172 (4.6), and peripheral vascular disease 4/172 (2.3)
[59]	Puerto Rico	Santiago-Casas et al.[s]	55.9	214	Dyslipidemia[§] (9.1)-(52.7)-(58.4) T2DM[§] (9.1)-(52.7)-(58.4) MetS (18.2)-(39.6)-(43.4) Smoking (4.5)-(11.0)-(7.9)	RF (52.4)-(52.9)-(57.1); ESR (81.0)-(92.2)-(91); Steroids[§] (54.5)-(78.0)-(82.2); RA duration[‡] (3.4 ± 2.9)-(9.5 ± 8.2)-(13.6 ± 10.7)	N/A	Hypertension (13.6)-(40.7)-(76.2), MI (0)-(2.2)-(9.1), angina pectoris (0)-(1.1)-(4.0), stroke (0)-(1.1)-(8.0), peripheral artery disease (0)-(1.1)-(5.0), and CHF (0)-(1.1)-(5.0)

CVD: cardiovascular disease; RA: rheumatoid arthritis; RF: rheumatoid factor; EAM: extraarticular manifestations; GC: glucocorticoids; N/A: not available; MI: myocardial infarction; CHF: congestive heart failure; TGL: triglycerides; CAD: coronary artery disease; BMI: body mass index; T2DM: type 2 diabetes mellitus; CRP: C-reactive protein; RADAR: rapid assessment of disease activity in rheumatology; HAQ-Di: health assessment questionnaire disability index; MTX: methotrexate; ESR: Erythrocyte Sedimentation Rate; DAS-28: Disease Activity Score-28; SSZ: sulfasalazine; vWF: von Willebrand Factor; IMT: intima-medial thickness; MetS: metabolic syndrome; SDAI: simplified disease activity index; TC: total cholesterol; anti-CCP: anti-cyclic citrullinated peptide antibodies; aCL: anticardiolipins antibodies; anti-B2GPI: anti-β2 glycoprotein I antibodies; anti-HSP 60/65: anti-heat shock proteins 60/65 antibodies; anti-LPL: antiLipoprotein lipase antibodies; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

[a]Only descriptive study, which evaluated causes of mortality in adult patients with RA.

[b]By echocardiogram and gammagraphy.

[c]Data from patients with RA 14/37 (37.8).

[d]Data from patients with hyperhomocysteinemia (>15 μmol/L).

[e]Exclusion criteria: patient with traditional cardiovascular risk factors.

[f]Only female were included, each with at least 5 years of duration of the disease and between 35 and 54 years of age.

[g]Not CVD subphenotype measured. Prevalence regarding presence of atherosclerosis plaque.

[h]Only female were included.

[i]Exclusion criteria: smoking, diabetes and hypertension pregnancy, renal failure, chronic hepatopathy, nephrotic syndrome, hypothyroidism and use of statins/fibrates.

[j]RA patients versus controls.

[l]Exclusion criteria: smoking, diabetes, and hypertension.

[m]High blood pressure was defined above 130/85 mmHg.

[n]The objective was to analyze causes and direct costs of hospitalization of Colombian patients with RA.

[o]Sample population was originally from Northwestern Colombia. They are considered ethnically different.

[p]Exclusion criteria: any symptoms of heart disease or risk factors for CVD.

[q]Subjects over 60 years were excluded.

[r]Only cohort, 6 years followup. Low mortality rate 9/32 (5.2%).

[s]Three age group (<40 y)-(40–59 y)-(>60 y). Elder people (>60 y) have more probability to develop CVD independent of RA.

[†]Mean ± standard deviation.

[‡]Median (interquartile range).

[#]Prevalence of CVD regarding the only subphenotype described.

[§]P values < 0.05 were considered significant.

Figure 2: Cardiovascular disease in rheumatoid arthritis in Latin America and the Caribbean; LA: Latin America; CA: Central America; SA: South America; C: Caribbean. [a]General cause of death was evaluated. CVD was the highest. [b]Subclinical coronary artery disease. [c]Hypertension and stroke. [d]Not CVD subphenotype measured. Prevalence regarding presence of atherosclerosis plaque. [e]Hypertension [f]References [48, 49] report data from the same cohort of patients. Hence, the prevalence of CVD and risk factors is identical. [g]Hypertension and atherosclerosis plaque. [h]Hypertension and coronary artery disease. [i]Hypertension and thrombosis. [j]Ventricular diastolic dysfunction. [k]Hypertension, stroke, and stable angina. [l]Hypertension, stroke, coronary artery disease, peripheral vascular disease. [m]Hypertension, myocardial infarction, angina pectoris, stroke, and peripheral vascular disease, and congestive heart failure.

and European populations or of three-way admixture of Amerindian, European, and West African populations [65].

Some studies have documented differences in the health status of, disease prevalence in, treatment outcome in, and healthcare use by different ethnic groups. Yazici et al. [35] compared patients from different ethnic groups with early RA using disease activity measures, identifying possible differences in patterns of clinical severity. They found that Hispanic patients with RA scored the worst in all self-report measures compared to Caucasians and African Americans with statistically significant differences in the Modified Health Assessment Questionnaire (MHAQ) functional score, psychological distress, and morning stiffness [35]. In a study of RA patients, Bruce et al. [36] demonstrated disparities between Caucasians and African Americans and Hispanics in disability, pain, and global health. Pain was worse in the latter two groups and global health was worse in Hispanics. The results of this exploratory study suggest that in a relatively similar cohort of patients with RA, minority health disparities exist [36]. Moreover, the prevalence of MI is high in Hispanics living in the USA, and coronary events are presented by people younger than in other minorities [48].

Table 2: Cardiovascular disease mortality in the Americas*.

Region	Annual deaths average (thousands)[a]	Mortality rate from IHD[a,b]	Mortality rate from cerebrovascular disease[a]
		Total	Total
Americas	6,447.2	87.4	45.1
North America	2,885	136	45
Canada	262.8	109	41.4
United States of America	2,621.7	139	45.4
Latin America and the Caribbean	3,562.2	55.8	44.8
Latin America	3,510.8	56	44.9
Mexico	549.4	54.1	27.5
Central American Isthmus	226.1	41.9	24.4
Belize	1.2	30.9	25.7
Costa Rica	20.4	48.4	21.3
El Salvador	41	56	22.4
Guatemala	80.5	25.5	16.4
Honduras	37.5	N/A	N/A
Nicaragua	27.5	54.2	32.8
Panama	18.1	57.2	51.5
Latin Caribbean	270.5	N/A	N/A
Cuba	83.9	140	80.6
Dominican Republic	60.1	N/A	N/A
French Guiana	0.9	N/A	N/A
Haiti	90	N/A	N/A
Puerto Rico	29.1	101	40.1
Andean Area	722.5	58.7	35.7
Bolivia	72.9	N/A	N/A
Colombia	260.6	74.1	38.7
Ecuador	74.5	25.6	34.1
Peru	161.4	27.8	26.6
Venezuela	153.1	81.4	41
Brazil	1.261.1	60.4	62.2
Southern Cone	481.3	49.1	51.2
Argentina	315.6	46.8	48.2
Chile	98.2	47.1	46.8
Paraguay	36.1	50.3	55.5
Uruguay	31.3	85.4	103
Non-Latin Caribbean	51.3	63.4	63.8
Guyana	4.4	80.9	70.3
Suriname	3.8	47	72

*Adapted from [62]. The values were obtained from "Corrected Mortality" data. These values were computed by applying a correction algorithm for mortality underregistration and a redistribution algorithm for deaths from ill-defined causes. The methodology used is presented in Health Statistics from the Americas. 2006 edition (http://www.paho.org/HSA2006).
[a]Values are expressed in incidence rates/100.000 population (2007–2009).
[b]IHD: ischemic heart disease.
N/A: not available.

Nevertheless, only two studies in LA assessed mortality in RA patients. Orozco-Alcalá et al. [46] showed that there were no differences between RA patients and the general population concerning causes of death. Acosta et al. [58] demonstrated a mortality rate of 5.2% in a six-year followup. For both, the most frequent cause of death was CVD in 44.7% and 22.2% of the cases, respectively. In the other selected articles, a wide range of prevalence for CVD was

reported (13.8–80.6%). The highest prevalence was indicated by Santiago-Casas et al. [59] in Puerto Rican patients (55.9%) when the demographic characteristics, clinical manifestations, comorbidities, pharmacological profile, and functional status of different age groups were determined. Nevertheless, the fact that elderly people (>60 years) have a higher probability of developing CVD whether or not they have RA had to be taken into account for calculating the prevalence of CVD in Puerto Rico. Cisternas et al. [30] evaluated cardiovascular risk factors in Chilean patients with RA and reported a prevalence of 46.4% for CVD. For Brazil [51, 53], Colombia [25, 54, 55], and Argentina [56, 57], a similar prevalence was indicated (47.4, 35.1 and 30.5%, resp.). In Mexico, five studies [46–50] reported an overall prevalence of 20.9% for CVD in RA patients.

4.2. Traditional Risk Factors, CVD, and RA. RA is a relatively frequent AD, which is chronic in nature, and these patients are doubly at risk of developing any CVD subphenotype with respect to the non-RA population [66, 67]. In fact, IHD secondary to atherosclerosis is the most prevalent cause of death associated with CVD in patients with RA [30]. The worldwide prevalence of hypertension in RA is between 49 and 77% [5]. It is considered the most common comorbiditiy in Hispanic patients with RA. The most frequent classic risk factor for CVD in this systematic literature review (with more than 2,000 RA patients included) was hypertension as well. Nevertheless, a lower prevalence (27.9%) than that reported previously in other countries was found. Many of these predisposing factors have been described in LA studies: hypertension [30, 36, 53–55, 58, 59, 61, 68, 69], T2DM [25, 48, 50, 53, 56, 58], dyslipidemia [25, 58, 59, 70], MetS [17, 25, 50, 53, 68, 69, 71], and hyperhomocysteinemia [22, 25, 48, 72]. For details, see Table 3.

4.3. Nontraditional Risk Factors, CVD, and RA. Since there is no classification system for nontraditional risk factors, we would like to propose one. Our recommendation is to divide them into genetic, AD associated, and others. The genetic group includes both HLA and non-HLA genes. HLA-DRB1 SE alleles are related to chronic inflammation, endothelial dysfunction, premature death, and CVD itself [25, 73–80]. The non-HLA genes include polymorphisms in the endothelin-1 and methylene tetrahydrofolate reductase genes. Endothelin-1 enhances CVD by endothelial dysfunction and hypertension [81]. Methylene tetrahydrofolate reductase has been related to atherosclerosis and the clinical response to some Disease-Modifying Antirheumatic Drugs (DMARDs) [82]. Others genes are TNFA rs1800629 and NFKB1-94ATTG ins/del polymorphisms. These are associated with predisposition to cardiovascular complications in patients with RA, as subclinical and accelerated atherosclerosis [83, 84]. However, other gene polymorphisms placed outside the HLA region and not strongly associated with susceptibility to RA and CVD. Rodríguez-Rodríguez et al. [85] showed a potential influence of the CCR5Δ32 deletion on the risk of CV disease among patients with RA. This may be due to a protective effect of this allelic variant against the development of vascular endothelial dysfunction.

The AD associated factors include a broad spectrum of autoantibodies as well as RA characteristics. The autoantibodies include RF [25, 49, 86], anti-CCP, aCL, anti-B2GPI, anti-HSP 60/65 [25, 30, 51, 55], and anti-oxLDL [30, 87, 88]. The RA characteristics are inflammatory basis [39, 89, 90], high disease activity [91], long duration [25], systemic involvement [56, 76, 92], treatment (systemic steroids) [93–95], and others, recently described, such as polyautoimmunity [25, 46, 55, 58] and familial autoimmunity [25].

Other issues, such as thrombogenic factors, which include vWF and fibrinogen levels, are related to CVD as well [49, 96, 97]. Several new cardiovascular risk factors in RA have received only modest attention and the different studies have shown contradictory results in LA patients. Each of these factors contribute to an impaired endothelial function, increased IMT, accelerated atherosclerosis, and finally, manifest CVD. For details, see Table 3.

4.4. Discovering Novel Nontraditional Risk Factors. Despite of all the traditional risk factors that have been associated with CVD in RA patients, the literature on it with respect to LA and the Caribbean is still scarce. Even though it has been generally accepted that systemic activity is related to chronic inflammation and accelerated pathogenic processes leading to cardiovascular compromise, it is important to assess other novel factors in patients that may also contribute. Therefore, we believe further research is needed in order to establish other factors that are not currently taken into account. To date, there are no systematic reviews of literature involving LA patients as a minority group.

After the systematic search was done, 2,119 RA patients from different LA countries were included and evaluated for cardiovascular outcomes in studies ranging from 1993 to 2012 (see Supplementary Table 1 in Supplementary Material available online at doi:1155/2012/371909). Common limiting factors in the sixteen studies analyzed included a lack of prospective follow up of RA patients and a general limitation on sample sizes. Most of the studies were either cross-sectional or case-control which in terms of evidence place them at level 4 [45]. Moreover, 50% of the studies included in the analysis had sample sizes of more than 100 RA patients. The rest of them had limited numbers of patients included, which was another common limit or bias found in the retrieved studies. Furthermore, the lack of adequate statistical methods and hypothesis testing in some of the studies should be noted. This was the case for four of the studies, which were descriptive or did not calculate P values, adjusted odds ratio or confidence intervals.

There is insufficient literature regarding CVD in LA patients with RA. Although the number of patients assessed is not negligible, when the geographical area of LA, the diversity, and the admixture of the population are considered, there is a need to include true cohorts to ensure more decisive conclusions.

Table 3: Traditional and non-traditional risk factors associated with cardiovascular disease and rheumatoid arthritis in Latin America.

Risk factor associated with CVD		Comments	Reference(s)
Traditional			
	Hypertension	Increases the risk to suffer IHD or stroke with an important impact on mortality in patients with RA	[16]
	T2DM	Patients with RA have a similar risk of developing CVD when compared to the same risk in patients with T2DM. Unfortunately, when there is a coexistence of both diseases, this risk is increased by three times	[69]
	Dyslipidemia	Altered lipid profiles in RA patients are related with higher probability of IHD by accelerating atherosclerosis	[25, 70]
	MetS	Is characterized for an alteration in production/secretion of proinflammatory adipokines and leads to increased activity of RA and accelerating atherosclerosis	[68, 71]
		Studies about the prevalence of MetS in LA patients have not achieved definitive conclusions, although its presence has been directly associated with a worse prognosis	[53]
		In RA patients, was related with pain and functional status, suggesting disease activity. Therefore, a better control of disease activity may reduce CVD risk	[50]
	Hyperhomocysteinemia	Homocysteine is considered as biomarker for atherosclerosis and a risk factor related with CAD and stroke	[22, 72]
		There is still controversy about whether hyperhomocysteinemia is a causative agent of cardiovascular damage or only an epiphenomenon of inflammation	[48]
		A high prevalence of this biomarker in Mexican patients with RA had a statistical association with male gender and higher radiological damage	[48]
		High homocysteine concentration can be an important risk marker for CVD in Chilean patients with RA, as it was significantly associated	[30]
Nontraditional			
Genetic	HLA-DRB1 SE alleles	Related with chronic inflammation, endothelial dysfunction, and premature death for CVD	[73–75]
		Associated with severe RA and with more EAM, high activity, and systemic inflammation	[74–77, 79]
		Being a carrier of a single copy of HLA-DRB1 SE were significantly associated with an increased risk of atherosclerotic plaque in RA Colombian patients	[25]
AD associated	Polyautoimmunity	Some articles included patients with poliautoimmunity, but no correlation with CVD subphenotypes was described	[25, 46, 55, 58]
	Familial autoimmunity	Was associated with presence of atherosclerotic plaque in RA Colombian patients.	[25]
	RF positivity	High titers have been established to be a predictor of CVD due to immune complex formation and tissue injury. It has been shown that such immune complexes from RF can be deposited in the endothelium and through inflammatory reactions generate endotelial disfunction and atherosclerotic process	[86]
		RF seropositivity was significantly associated with an increased risk of endothelial dysfunction in RA Colombian patients	[25]
		A statistical association between increased IMT, atherosclerosis plaque, and presence of RF was described in Mexican population with RA	[49]
	anti-oxLDL	Promote instability and rupture of the atheromatous plaque within the coronary arteries	[24, 88]
		Only one LA study evaluated this antibodies, but no correlation with CVD was found	[30]
	Other autoantibodies	The presence of plaques was higher in Brazilian patients with RA, but no correlation between IMT or plaques and autoantibodies were found	[51]
		Other autoantibodies were assessed in LA population, such as aCL, anti-β2GPI, anti-HSP 60/6, and anti-CCP antibodies with no association regarding CVD outcomes	[25, 30, 51, 55]
	Inflammatory markers	The association of inflammatory pathways with CVD is complex and is composed of several intermediate factors, including dyslipidemia, homocysteinemia, insulin resistance, and endothelial dysfunction	[89]

Table 3: Continued.

Risk factor associated with CVD		Comments	Reference(s)
		May accelerate atherogenic processes, either by the accentuation of known pathways of plaque formation or by the onset of additional immune pathways	[90]
	Disease activity	The lipid profile in RA depends on disease activity. Higher disease activity leads to depressed levels of total cholesterol. However, HDL cholesterol levels are even more depressed, resulting in a more unfavourable atherogenic index	[90]
	Long duration of RA (>10 years)	Implies more time for chronic inflammatory process to generate sequelae such as atherosclerosis and endothelial dysfunction	[39]
		Were significantly associated with an increased risk of atherosclerotic plaque in RA Colombian patients	[25]
	EAM	Is an indirect indicator of disease severity and systemic compromise. Patients are considered to have three times higher risk to develop CVD	[55, 76]
	GC	Could enhance cardiovascular risk owing to their potentially deleterious effects on lipids, glucose tolerance, insulin production and resistance, blood pressure, and obesity. On the other hand, it may actually decrease the risk of atherosclerosis and CVD by suppressing inflammation, which paradoxically may improve glucose intolerance and dyslipidaemia	[93]
Others	Thrombogenic factors	vWF has been recognized to induce a procoagulant state Represent a biomarker of endothelial dysfunction	[96, 97]
		The measurements of the IMT together with the vWF serum levels could give valuable information about the artery status and the atherosclerosis process in early stages in Mexican patients with RA without cardiovascular risk factors	[49]

CVD: cardiovascular disease; IHD: ischemic heart disease; RA: rheumatoid arthritis; T2DM: type 2 diabetes mellitus; LA: Latin America; MetS: metabolic syndrome; SE: shared epitope; RF: rheumatoid factor; IMT: intima-medial thickness; anti-oxLDL: anti-oxidized low-density lipoprotein antibodies; aCL: anticardiolipins antibodies; anti-B2GPI: anti-β2 glycoprotein I antibodies; anti-HSP 60/65: antiheat shock proteins 60/65 antibodies; anti CCP: anti-cyclic citrullinated peptide antibodies; HDL: high-density lipoprotein cholesterol; EAM: extra-articular manifestations; GC: glucocorticoids; vWF: von Willebrand factor.

4.5. Assessing CVD in RA Patients. Heart disease in patients with RA is a major concern. Rheumatologists often face the question of how to treat and prevent CVD. To appropriately do so, we need to answer three important questions. *(1) How do we estimate the risk of CVD in RA?* Unfortunately, neither the Framingham Risk Score nor Reynold's Risk Score were designed to estimate risk in RA patients. The European League Against Rheumatism published their recommendation on estimating cardiovascular risk in RA; however, this has not been validated yet. *(2) Which actions decrease CVD risk?* Eating a well-balanced diet, exercising on a regular basis, quitting smoking, and maintaining a healthy weight have a positive impact on cardiovascular health. Targets based on the individual risk profile of every patient also have to be set. Well-established risk factors such as blood pressure, LDL levels, and hemoglobin A1C need to be considered. Treatments that reduce these risk factors include angiotensin-converting enzyme inhibitors, statins, and, in some patients, metformin. *(3) What should be the target of all these efforts?* That question raises more questions. Inflammation in RA is a risk factor for CVD which can be treated effectively, but can targeting "inflammation" decrease CVD risk in RA? Should the target be remission, a low CRP level, or lack of swollen joints? Is targeting specific inflammatory pathways more effective for reducing cardiovascular risk than other therapies? There are many unanswered questions and a lot of controversy about how to best address cardiovascular risk in patients with RA. Therefore, a comprehensive multidisciplinary approach is the first step towards addressing this complex issue and to optimize patient outcomes [98].

5. Conclusions

RA and CVD share common pathophysiology mechanisms (i.e., systemic and chronic inflammation) with secondary accelerated atherosclerosis that can explain the high mortality rates and augmented risk of ischemic events in these patients. Therefore, early or subclinical atherosclerosis should be assessed in every patient through the measurement of IMT in carotid arteries and other inflammatory markers on a regular clinical basis.

LA patients are ethnically different from other populations and have a worse disease course due to their different genetic burden that could be the cause of a higher prevalence of EAM. Trying to extrapolate previous results from countries with patients from a different ethnic group to our subpopulation could be a mistake.

Although there is an evident association of traditional risk factors and cardiovascular compromise in RA patients, they do not completely explain the high rates of CVD in these patients. Thus, novel risk factors which are related to autoimmunity are now becoming a more important focus

of attention. This is the reason why we propose to separate traditional and nontraditional risk factors and evaluate them comprehensively and in a multidisciplinary fashion.

There is a lack of literature about CVD in Hispanic patients as demonstrated by this systematic search. To make matters worse, literature evaluating nontraditional risk factors is scarce. This should be a challenge to the rheumatologist to do research in these fields in order to elucidate the underlying mechanisms involved for the benefit of the patient.

Unfortunately, LA patients receive lower quality diagnostic assessment and treatment choices than Caucasian patients due to difficulties in access to health services and delayed diagnosis. Cardiovascular compromise in RA patients is a therapeutic challenge and doctors need to be committed to assessing, monitoring, and treating cardiovascular risk factors in the early stages as well as generating effective public health policies in developing LA countries so that morbimortality rates can be decreased promptly.

Abbreviations

CVD:	Cardiovascular disease
RA:	Rheumatoid arthritis
LA:	Latin America
EAM:	Extraarticularmanifestations
T2DM:	Type 2 diabetes mellitus
MetS:	Metabolic syndrome
AD:	Autoimmune disease
IMT:	Intima-medial thickness
CAD:	Coronary artery disease
MI:	Myocardial infarction
CHF:	Congestive heart disease
IHD:	Ischemic heart disease
VHL:	Virtual health library
SE:	Shared epitope
RF:	Rheumatoid factor
Anti CCP:	Anti-cyclic citrullinatedpeptide antibodies
aCL:	Anticardiolipin antibodies
Anti-B2GPI:	Anti-β2 glycoprotein I antibodies
Anti-oxLDL:	Antioxidized low-density lipoprotein antibodies
Anti-HSP 60/65:	Antiheat shock proteins 60/65 antibodies
CRP:	C-Reactive Protein
ESR:	Erythrocyte sedimentation rate
DAS-28:	Disease activity score-28
SDAI:	Simplified disease activity index
MTX:	Methotrexate
vWF:	von Willebrand factor
WHO:	World Health Organization
MHAQ:	Modified Health Assessment Questionnaire
DMARDs:	Disease nodifying anti rheumatic drugs.

Conflict of Interests

The authors declare no conflict of interests.

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Research Article

Usefulness of Patients-Reported Outcomes in Rheumatoid Arthritis Focus Group

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Objective. Patient-reported outcomes (PROs) have become an essential part of the assessment of patients with rheumatoid arthritis (RA). We aimed to evaluate the agreement and correlation between PROs and the physician's measurements. *Methods*. This was a cross-sectional analytical study in which 135 patients with RA were clinically evaluated during two different sessions of focus group interviews. Rheumatologist recorded 28 swollen (SJCs) and tender joint counts (TJCs). The patients filled out the PROs instruments (MDHAQ, RADAI, RAPID3, 4, and 5 and self-report articular index (SAI) diagram for pain and joint swelling). DAS28 was calculated (C-reactive protein). An adjusted multiple lineal regression model was done (DAS28 as dependent variable). *Results*. Highly significant agreements were found between SJC and TJC registered by the physician and patient. There was moderate correlation between DAS28 with patient SJC ($r = 0.52$), patient TJC ($r = 0.55$), RADAI ($r = 0.56$), RAPID3 ($r = 0.52$), RAPID4 ($r = 0.56$), RAPID5 ($r = 0.66$), and VAS-Global ($r = 0.51$). Likewise, we found moderate to high correlations between CDAI and SDAI with all variable measurements done by the patients. The resulting predictive equation was DAS28(CRP) $= 2.02 + 0.037 \times$ RAPID4 $+ 0.042 \times$ patient SJC. *Conclusion*. PROs applied in focus groups interview are a useful tool for managing patients with RA regardless of gender, educational level, and duration of disease.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, complex, heterogeneous, and widely known autoimmune disease (AD). It is characterized by the presence of long-standing inflammation of the diarthrodial joints resulting in symmetric polyarthritis and synovial membrane hypertrophy with progressive damage to the joints, bone and cartilage destruction, and deformity. However, the autoimmune compromise is systemic and thus, leads to extra articular manifestations (EAMs) including cutaneous nodules, lung involvement, cardiovascular disease (CVD), episcleritis, and vasculitis [1–3]. All of these lead to an increase in comorbidities [4, 5], disability [6, 7], impaired quality of life [8, 9], and premature mortality, which is two times the general population [10, 11].

The disease is more frequent in women than men [5, 12, 13]. The age at onset is commonly situated around the 30s with a peak in the fifth decade of life according to the majority of epidemiological studies [14]. Several incidences and prevalence of the disease have been reported during the last few decades which suggest a high admixture of cultures, ethnics, environmental, genetic, and epigenetic factors. The majority of studies carried out in Northern Europe and North America estimate a prevalence of 0.5-1.1% [12, 15]. Studies from developing countries report lower prevalence (between 0.1–0.5%) even in Latin America population [12, 16]. The worldwide incidence rates (cases per 100

inhabitants) oscillate from 0.01 in Southern Europe to 0.3 in Asia [12]. Furthermore, the incidence increases with age and seems to reach a plateau as of the age of 60 [13]. Incidence in the United States, in turn, is estimated to be 25 per 100,000 persons for men and 54 per 100,000 persons for women [3].

Considering that RA is the most common inflammatory arthropathy worldwide and causes multiple disabilities, an inadequate assessment of clinical status can lead to inappropriate treatment and undesirable outcomes. It is necessary to implement clinical measures to determine the degree of activity and disease involvement. Traditionally, evaluation of RA has centered around physician-generated assessments in clinical outpatient care with many restrictions such as a limited amount of time in consultation, absence of a gold standard for diagnosis and subsequent followup [17, 18], and the lack of patient participation [19–21].

Currently, the evaluation of a RA patient involves aspects of the disease pathophysiology (i.e., measurement of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, antibodies, and X-ray), disease activity, functional capacity, structural damage, pain, fatigue, and quality of life. All these allow a better and more objective assessment, which includes the most relevant long-term outcomes [22], presence or absence of comorbidity, drug toxicity, psychological and social consequences, prognosis, premature mortality, and high disease costs [6, 19, 23–25].

In recent years, there has been a growing interest in the assessment of patients with RA from the patient's perspective. Patient-reported outcomes (PROs) in RA are processes in which the patient completes some forms (i.e., questionnaire, scales, self-administered index (SAI) diagram) and objectively evaluates the disease. It has been found to be as or more informative than physician-assessed measurement because it allows the information necessary for clinical and therapeutic decisions to be collected. The information is organized into quantitative data and used to make decisions as well as assess the prognosis and most probable outcomes for the patients [24, 26–30].

In both clinical practice and research, the PROs, though they are self-report tools, have been designed, validated, reliable and reproducible world-wide [31–34]. Most studies have been able to demonstrate agreement between self-administered and observed-derived assessment of joint counts, and so forth [17, 30, 35–39]. This agreement allows these qualitative data to be summarized and converted into quantitative data classified by scores. This makes an objective and reproducible assessment that can be used over time possible during the visits to the rheumatologist.

In order to demonstrate the agreement and correlation present between PROs and the measurements from the physician in RA patients, a cross-sectional study was done to evaluate the agreement and usefulness of PROs in comparison to objective measurements during a focus group of Colombian RA patients.

2. Material and Methods

2.1. Study Population. This was a cross-sectional analytical study in which 135 consecutive patients with RA were included. All of them fulfilled the 1987 American College of Rheumatology classification criteria [40] and were seen at three different outpatient clinics in Bogota, Colombia. Also, they were contacted by telephone, brought together, and clinically evaluated during two different sessions of focus group interviews. Each session included approximately 70 patients. This study was undertaken between November 2010 and January 2011 and done in compliance with Act 008430/1993 issued by the Ministry of Health of the Republic of Colombia. The ethics committee of the Universidad del Rosario approved the study design.

The focus groups interview methodology was coordinated by a rheumatologist who explained the concept of PROs, the activities, and the tools used for gathering the information (i.e., questionnaires and SAI diagram [38]). After that the patients filled out the questionnaires with information about sociodemographic and cumulative clinical data. Most patients were able to complete the instruments with no problem. However, if requested by the patient, ten health care providers helped them complete the questionnaires. After the focus group interview, physicians through chart, radiographic review, and telephone interview confirmed the data collected.

The questionnaires used by the patients for the self-report were

(a) multidimensional health assessment questionnaire R729-NP2 (MDHAQ), Spanish version [41];

(b) pain visual scale analogue (VAS-Pain) (0–10);

(c) self-administered, rheumatoid arthritis disease activity index (RADAI), where the patient self-reported tender joints on a scale of 0–3 from 8 bilateral joint groups (0–10) [30];

(d) global assessment by visual scale analogue (VAS-Global) (0–10);

(e) swollen joint count (SJC) and tender joint count (TJC) in the SAI [38], (Figure 1).

Each patient was examined by a rheumatologist who determined:

(a) out of a total of 28 joints the physician identified and TJC by physical examination. This examination was blinded and done independently of the questionnaires filled out by the patients;

(b) global assessment by visual scale analogue (MD-Global) (0–10);

(c) anthropometric measurements;

(d) after the informed consent was signed, a blood sample was drawn for the CRP measurement.

These composite indices were determined in each patient:

(a) RAPID3: (routine assessment of patient index data) [42]. This is a PROs-based index that uses the three core set criteria evaluated by the patient, that is, physical function (from MDHAQ), VAS-Pain, and VAS-Global (scale 0–10);

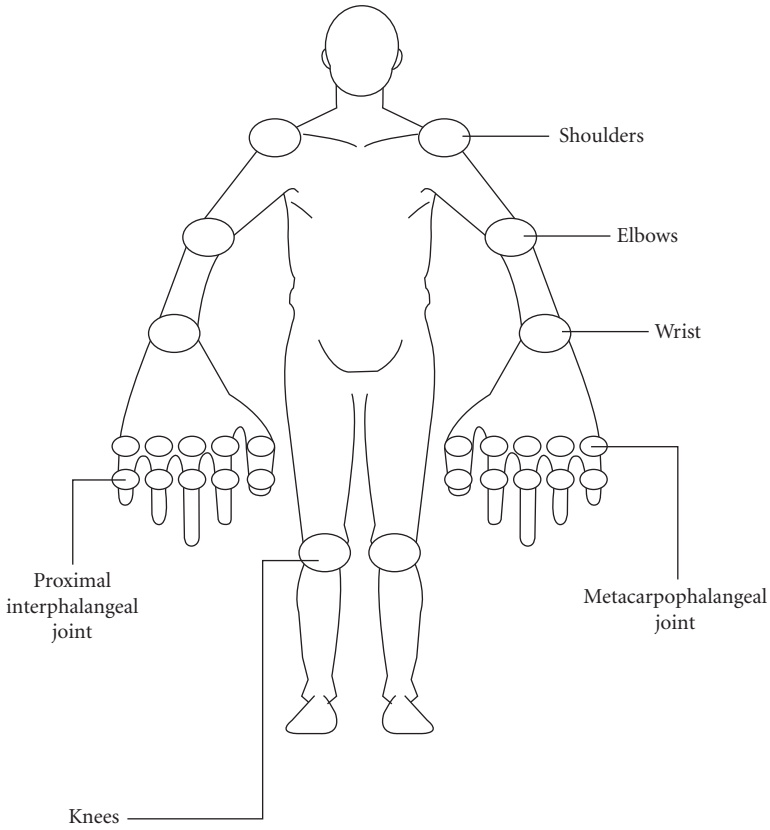

Figure 1: Self-administered index (SAI) Modified from [38].

(b) RAPID4: [43] this includes the same variables as RAPID3 plus RADAI (Scale 0–10);

(c) RAPID5: [43] this includes the same variables as RAPID4 plus MD-Global (Scale 0–10);

(d) DAS28-CRP: (disease activity score-28 joints) [44]. It is made up of the TJC and SJC on 28 joints determined by physician and CRP (mg/L). The equation is as follows: $\text{DAS28} = 0.56 * \sqrt{(\text{TJC}28)} + 0.28 * \sqrt{(\text{SJC}28)} + 0.36 * \ln(\text{CRP} + 1) * 1.10 + 1.15$;

(e) SDAI: simplified disease activity index [45] is the algebraic sum of the following five parameters: TJC and SJC on 28 joints determined by the physician, CRP level in mg/dL, patient VAS-Global, and MD-Global;

(f) CDAI: clinical disease activity index [46] is the algebraic sum of the SDAI items minus the CRP level;

(g) conversion from MDHAQ to the original health assessment questionnaire (HAQ) though Anderson's model [47].

The sociodemographic variables included current age, age at RA onset, disease duration, educational status, socioeconomic status (SES), current occupational status, smoking habits, coffee consumption, and physical activity. The following are the definitions of these variables (Table 1): age at onset is age at which patients began to suffer from pain, typical morning stiffness (more than 1 hour), and symmetrical inflammation of hand and/or foot joints. Disease duration is difference between age at onset and the date of first participation in the study. It was divided into either more or less than 10 years of disease as our group had previously reported this to be a risk factor for poor prognosis (i.e., CVD) [48]. Educational level was recorded as years of education. These data were dichotomized into two groups with one group including those with less than 9 years of education (including preschool, primary, and the first 2-3 years of high school) and the other group more than 9 years of education. This breakdown was based on the General Law of Education in Colombia [49, 50]. SES was categorized on the basis of national legislation and was divided into high status (3 to 6) and low status (1 and 2). For occupational status, we focused on establishing if the patient worked at household duties exclusively.

Regarding clinical variables, polyautoimmunity, multiple autoimmune syndrome (MAS), familial autoimmunity, erosions, comorbidities, EAMs, systolic and diastolic blood pressure, body mass index (BMI), and waist circumference were evaluated. The following are the definitions of these variables. Polyautoimmunity is the presence of more than one autoimmune disease in a single patient [51]. MAS corresponds to the coexistence of three or more well-defined ADs [51]. In order to define these two, we evaluated 6 ADs on the basis of international criteria, that is, systemic lupus erythematosus (SLE) [52], autoimmune thyroid disease (AITD), Sjögren's syndrome (SS) [53], antiphospholipid syndrome

Table 1: Characteristics of 135 patients with RA evaluated in the current study.

Characteristic	Mean ± SD
Age	53.63 ± 11.28
Age at onset	40.5 ± 12.14
Characteristic	Median ± IQR
Duration of the disease	12 ± 14
Educational level (years)	11 ± 10
Body mass index	24.14 ± 5.69
Waist-hip ratio	0.92 ± 0.09
Systolic blood pressure	120 ± 20
Diastolic blood pressure	70 ± 11
C-Reactive protein	0.39 ± 1.06
DAS28	2.75 ± 1.30
HAQ	0.99 ± 1.19
TJC physician	2 ± 4
SJC physician	2 ± 4
TJC patient	7 ± 13
SJC patient	4 ± 8
SDAI	13.72 ± 14.45
CDAI	13 ± 13.50
Variable	*n*/*N* (%)
Sociodemographic	
Female	106/135 (78.5)
Low educational level	59/133 (44.4)
Low socioeconomic status	52/132 (39.4)
Ever smoking	50/134 (37.3)
Household duties	49/135 (36.3)
Clinical aspects	
Diabetes	5/135 (3.7)
Dyslipidemia	28/135 (20.7)
Hypertension	56/135 (41.5)
Thrombosis	6/135 (4.4)
Osteoporosis	42/135 (31.1)
Occlusive arterial disease	3/135 (2.2)
Cardiovascular disease	63/135 (46.7)
Abnormal body mass index	61/133 (45.9)
Abdominal obesity	106/134 (79.1)
Physical activity	44/135 (32.6)
RA characteristics	
Typical morning stiffness	100/134 (74.6)
Duration disease > 10 years	78/135 (57.9)
Erosions	71/108 (65.7)
Nodules	40/135 (29.6)
EAMs	47/135 (34.8)
EAMs with CVD	87/135 (64.4)
Rheumatoid factor +	106/124 (85.5)
Anti CCP +	58/70 (89.2)
Methotrexate	121/135 (89.6)
DMARD	128/135 (42.2)
Antimalarials	106/135 (78.5)
Steroids	122/135 (90.4)
Biological agents	57/135 (42.2)
Alternative medicine	73/130 (56.2)
Autoimmunity	
Systemic lupus erythematosus	1/135 (0.7)
Autoimmune thyroid disease	13/135 (9.6)
Sjögren's syndrome	4/135 (3)
Antiphospholipid syndrome	2/135 (1.5)
Vitiligo	1/135 (0.7)
Scleroderma	1/135 (0.7)
Polyautoimmunity	19/135 (14.1)
MAS	3/135 (2.2)
Familial autoimmunity FDR	22/135 (16.3)
Familial autoimmunity SDR	5/135 (4.4)
ANAs +	63/99 (63.6)

RA: rheumatoid arthritis; SD: standard deviation; IQR: interquartile range; DAS28: disease activity score; HAQ: health assessment questionnaire; TJC: tender joint count; SJC: swollen joint count; SDAI: simplified disease activity index; CDAI: clinical disease activity index; EAMs: extraarticular manifestations; CVD: cardiovascular disease; Anti-CCP: anticyclic citrullinated peptide; DMARD: disease modifying-antirheumatic drugs; MAS: multiple autoimmune syndrome; FDR: first degree relatives; SDR: secondary-degree relatives; ANAs: antinuclear antibodies.

(APS) [54], scleroderma (SSc) [55], and vitiligo [56]. Familial autoimmunity was defined as the presence of any diagnosed AD in any first-degree relatives (FDR) of the proband [57]. AITD was confirmed on the basis of an abnormal thyrotropin (TSH) test or history of thyroid hormone therapy and the presence of either antibodies, antithyroperoxidase enzyme (TPOAb), or antithyroglobulin protein (TgAb).

Erosions were defined as having at least one unequivocal cortical bone defect evaluated by two blinded researchers (a rheumatologist and a radiologist) [58]. EAMs was defined as the presence of at least one of the following: skin ulcerations, nodules, episcleritis, vasculitis, neuropathy, pleural effusion, pulmonary hypertension or embolism, and CVD. The latter was categorized as positive if any of the following variables were present: hypertension (defined as having a blood pressure >140/90 mm Hg or using antihypertensive medication) [59], coronary artery disease, occlusive arterial disease, carotid disease, or thrombosis [60].

The patients were asked about the presence of diabetes mellitus**,** defined as having a fasting plasma glucose level > 7 mmol/L (126 mg/dL) or taking antidiabetic medication at the time of the assessment [61]. Diagnosis of dyslipidemia was given if the patient had hypercholesterolemia, defined as taking lipid-lowering medication or having a fasting plasma total cholesterol >200 mg/dL, HDL < 40 mg/dL, hypertriglyceridemia > 150 mg/dL, or LDL cholesterol > 100 mg/dL [62]. Anemia was diagnosed if current hemoglobin was <12 g/dL, gastritis only if evidenced by esophagogastroduodenoscopy, periodontal disease was self-reported, and renal disease if the serum creatinine measurement had values above 1.2 mg/dL.

Systolic and diastolic blood pressures were measured twice with at least 15 minutes between measurements and the averages were recorded. A BMI $\geq 25\,kg/m^2$ (overweight and obesity) was considered abnormal [63]. Abnormal values of waist circumference (>102 cm for men, >88 cm for women) and waist-to-hip ratio (WHR; >0.9 for men, >0.85 for women) were considered indicators of abdominal obesity. Waist circumference was measured around the narrowest point between ribs and hips after exhaling and viewed from the front. Hip circumference was measured at the point of maximum extension of the buttocks when viewed from the side [64]. Abnormal WHR values are consistent with National Cholesterol Education Program Adult Treatment Panel III and World Health Organization definitions [65].

Medical treatment includes the current or past use of methotrexate and other disease modifying antirheumatic drugs (DMARDs) such as sulfasalazine, D-penicillamine, azathioprine, cyclosporine, gold salts and leflunomide, steroid therapy, antimalarials (chloroquine, hydroxychloroquine), and biological therapy (rituximab, infliximab, etanercept, abatacept, adalimumab, or tocilizumab). Patients and their past medical records were evaluated for the current or past use of aspirin or hormone replacement therapy as well.

Relevant laboratory variables were also registered including ESR, hemoglobin levels, white blood cell count, platelet count, and highly sensitive CRP serum levels. Autoantibodies such as rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP), antinuclear antibodies (ANAs), Ro, La, RNP, Sm, IgG, and IgM anticardiolipins, and TPOAb and TgAb antibodies were taken from the patient's clinical record. They were measured with enzyme-linked immunosorbent assay (QUANTA-Lite, INOVA, San Diego, CA, USA) following the manufacturer's protocol. Antibodies directed against either TSH receptor or thyroid hormones (THAb) were not assessed in the current study.

2.2. Statistical Analysis. First, univariate analysis was done. Categorical variables were analyzed by frequencies. Kolmogorov-Smirnov normality test was done to evaluate normality for quantitative variables. Parametric data are expressed as mean and standard deviation (SD), and nonparametric data are described as median and interquartile range (IQR).

Agreement and correlation between patient and rheumatologist variables were evaluated by the statistic tests described in the footnote of Table 2. We considered correlations between 0.5 and 0.7 to be moderate and correlations of more than 0.7 to be high [66, 67].

To assess predictors for DAS28 (objective measurement), variables that had significant correlations with DAS28 (dependent variable) were entered as independent variables in the multiple lineal regression model (multivariate analyses). Those variables were patient SJC and TJC (SAI diagram), RADAI and RAPID4. The last two were considered crude data (values between 0–48 and, 0–40 respectively). MDHAQ, VAS-Global, VAS-Pain, and RAPID3 were not included due to the fact that these are contained in RAPID4, RAPID5 was also excluded because it included MD-Global (an objective measurement). This model was adjusted by gender, duration of the disease, and educational level. The adequacy of lineal regression models was assessed using the Durbin-Watson goodness-of-fit test. Statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS, v.20, Chicago, IL, USA).

3. Results

Table 1 describes the main sociodemographic, clinical, and autoimmune characteristics. Out of a total of 135 patients, 78.59 % were women. The most frequently reported occupation was household duties at 36.3% (49/135), and the most frequently reported comorbidity was osteoporosis at 31.1% (42/135).

A positive RF was registered as positive in 85.5% and anti-CCP was positive in 89.2% of the cases (Table 1). A total of 64.4% of the patients had at least one EAMs with the presence of CVD and nodules being the most frequent (Table 1). Steroids and methotrexate were the most frequently used medications. Polyautoimmunity was present in 14.1% with AITD as the most frequent coexistent AD.

According to the calculation of the RAPID3, 4, and 5, 53.3% (72/135), 51.8% (70/135), and 27.4% (37/135) respectively, had high scores, which indicated severe activity of the disease. Table 2 shows the correlation of values between the measurements done by the rheumatologist and patient. Highly significant ($P < 0.0001$) agreements were found between SJC and TJC registered by the physician and patient. There was a moderate correlation ($P < 0.0001$) between DAS28 with patient SJC ($r = 0.52$), patient TJC ($r = 0.55$), RADAI ($r = 0.56$), RAPID3 ($r = 0.52$), RAPID4 ($r = 0.56$), RAPID5 ($r = 0.66$), and VAS-Global ($r = 0.51$). Likewise, we found moderate to high correlations between CDAI and SDAI with all variable measurements done by the patients. The correlation between either CDAI or SDAI and RAPID5 was the highest ($r = 0.82$ and $r = 0.85$).

In the multiple lineal regression model (Table 3), the resulting predictive equation was DAS28(CRP) $= 2.02 + 0.037 \times$ RAPID4 $+ 0.042 \times$ patient SJC. Other independent variables were not significant in the DAS28 prediction. The educational level, duration of the disease, and gender did not have an influence on the predictive model. The explanation from the model was 40% (R^2). Correlations between the residuals (Durbin Watson = 2.26) and multicollinearity between independent variables (variance inflation factor < 10) were not found.

4. Discussion

In the current study, agreement was found between objective measurements assessed by the physician and subjective assessments done by the patient, which highlight the agreement between SJC and TJC as well as the correlation between activity index (CDAI and SDAI) and all the variables measured by the patient. Even though these tools are widely known since they provide the physician with information about the disease course and red flags, they are not usually applied in the daily routine with individual patients but rather in clinical research [17, 24, 68]. We also found that RAPID4 and SJC from patients can be used to predict DAS28.

Table 2: Agreement and correlations* between values finding by PROs and physician**.

Values physician/ Values patient	SJC physician	TJC physician	DAS28	MD-Global	CDAI	SDAI
SJC patient	0.772[b]	0.499	0.525	0.531	0.563	0.541
TJC patient	0.429	0.75[b]	0.552	0.493	0.611	0.598
RADAI	0.393	0.604	0.56	0.399[a]	0.667	0.646
RAPID3	0.372	0.594	0.523	0.361[a]	0.731	0.706
RAPID4	0.402	0.625	0.562	0.395[a]	0.75	0.726
RAPID5	0.53	0.709	0.662	0.511[a]	0.829	0.851
MDHAQ	0.246[d]	0.491	0.442	0.304[a]	0.531	0.531
VAS-Global	0.396	0.583	0.517	0.026[c,e]	0.754	0.725
VAS-Pain	0.323	0.508	0.434	0.314[a]	0.632	0.606

*Correlations were evaluated by spearman's rank correlation coefficient. except:
[a]Correlation by Kendall's Tau *b* test.
[b]Agreement by Kendall's *W* test.
[c]Agreement by Weighted kappa.
**All data $P < 0.0001$, except in [d]$P = 0.004$ and [e]$P = 0.241$.
PROs: patient-reported outcomes; SJC: swollen joint count; TJC: tender joint count; DAS28: disease activity score with 28 joints; MD-Global: global assessment by visual scale analogue from physician; CDAI: clinical disease activity index; SDAI: simplified disease activity Index; RADAI: self-administered rheumatoid arthritis disease activity index; RAPID: routine assessment of patient index data; MDHAQ: multidimensional health assessment questionnaire; VAS-Pain: pain assessment by visual scale analogue; VAS-Global: global evaluated by patient in visual scale analogue.

Table 3: Predictors of DAS28 with PROs variables.

	β*	P
Constant	2.021	<0.001
RAPID4	0.037	0.03
Patient SJC	0.042	<0.001
RADAI	0.073	0.48
Patient TJC	0.009	0.49
Gender	−0.123	0.44
RA duration	0.029	0.83
Education level	0.127	0.35

PROs: patient reported outcomes; β: beta coefficient; P: P value; RAPID: routine assessment of patient index data; SJC: swollen joint count; TJC: tender joint count; RA: rheumatoid arthritis.
*The beta coefficients give a measure of the contribution of each variable to the model. A large value indicates that a unit change in this predictor variable has a large effect on the criterion variable (DAS28).

Therefore, we confirmed that the PROs, administered in focus group sessions with RA patients, are an objective approach to disease [42].

4.1. General Aspects of PROs Instruments. Quantitative assessment in RA differs from the assessment of many other clinical conditions because a single gold standard measurement is not available to evaluate the complete individual disease activity of the patient. Practicing rheumatologists might have insufficient time to do a complete disease activity and functional status evaluation during every patient visit [19]. Most standard rheumatology care continues to be handled largely on the basis of laboratory tests (i.e., CRP, ESR, antibodies) and radiographic scores combined with subjective judgment without formal quantitative joint counts or patient questionnaires [68, 69]. Nonetheless, concerning functional status, patient questionnaires provide the most significant prognostic clinical measurement for all important long-term outcomes of RA including functional status, work disability, costs, joint replacement surgery, and premature death [70, 71]. However, psychological issues, depression, and anxiety, among others, are also important to evaluate through scales and questionnaires [72]. All these objective measurements assist the physician in guiding assessment, management, and prognosis for each patient, while these are filled out in the waiting room [20, 41, 73].

Nevertheless, objective measurements are not without some limitations. These include the time required to compute and interpret the scales. For instance, calculating the DAS28-CRP or DAS28-ESR requires a calculator, computer or web site, and the time spent is 114 seconds. Computing CDAI takes 106 seconds [18, 41, 74–76]. Furthermore, each one requires different scales and cutoff points to interpret it. In contrast, RAPID3 on an MDHAQ can be calculated in 5 to 10 seconds [41].

Additionally, a complete joint count, which is usually not done by a large percentage of rheumatologists, is necessary. Sometimes the fact that they do not do the joint count causes them to lose interest in the use of these measurements [38, 41, 42, 68, 77]. Another disadvantage is that the primary concerns of patients and their families are not addressed [78, 79].

Due to the difficulties and limitations mentioned above, PROs have been designed to guide clinical care complemented by objective measurements done by the physician. A PROs are any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy [80]. PROs instruments are used to measure these patient reports. Common examples of PROs include

quality-of-life and health status measurements, patient satisfaction and experience, psychological distress, pain, and self-efficacy. The common feature of PROs measurements is their grounding in the patient's perspective. PROs assessments are typically obtained through self-administered questionnaires, self-report scales, mannequins, and so forth. in the waiting area, by telephone, via postal mail, or online. PROs have been implemented globally and have correlated significantly with objective values in rheumatologic diseases and other chronic pathologies (i.e., cancer, asthma, hypertension, heart disease, stroke, psychiatric illness, migraines, diabetes) [26, 80–84].

Standardized patient measurement tools, rather than laboratory tests, are the most significant quantitative predictors of severe outcomes in many chronic diseases [24, 75]. These PROs instruments are useful for monitoring patient status over time due to their validity, reliability, feasibility, and their sensitivity to change. All these features can improve and optimize the time in the visit to the doctor by providing additional time for a complete physical examination. Otherwise, PROs improve the physician-patient relationship [38, 85], ease implementation of educational tools, which strengthens self-assessment of doctor care, diminish feelings of disability and risk of depression, promote a return to an active role in society, and strengthen social support. Furthermore, the patients become active participants in their followup, their adherence to the treatment improves, and there is greater disease control and a better prognosis [81–83].

In recent years, there has been growing interest in the assessment of patients with RA from the patient's perspective. The importance of PROs has been increasingly recognized over the years, and there are several reasons for the growing popularity of assessing PROs in rheumatology.

Patient medical history may be recorded as standardized "scientific" quantitative data on validated self-report questionnaires. Data from patient questionnaires are as effective as or more effective than laboratory tests and joint count data in discriminating active from control treatments in clinical trials and outpatient clinical care [29, 79, 86]. For instance, the most significant marker for predicting premature mortality over 5 years in patients with RA is a score for functional capacity in activities of daily living on a patient questionnaire rather than currently available laboratory tests, radiographs, or other imaging data [22, 87]. In a study of patients who had an extensive baseline evaluation in 1973 and were reviewed 9 years later in 1982, patient responses regarding capacity to carry out their usual activities predicted mortality 5 years later more effectively than any known clinical measure. Patients who could do fewer than 80% of their daily living activities "with ease" according to a questionnaire experienced a 5-year survival of about 50%, which is in the same range as patients with Stage IV Hodgkin's disease and 3-vessel coronary artery disease [88, 89]. Similar findings have been reported by Sokka et al. [90], Callahan et al. [89], and Wolfe et al. [91] with functional status measured by HAQ and MDHAQ.

4.2. Grade of Agreement between Physician and Patient Measurements. RAPID3 is an index proposed for the assessment and management of patients with RA that includes only the 3 patient-reported American College of Rheumatology (ACR) Core Data Set measurements, without formal joint count, for RA: physical function, pain, and VAS-global of status. It can be calculated in 5 to 10 seconds, in contrast to the 90 to 94 seconds for a formal 28-joint count, 106 seconds for a CDAI, and 114 seconds for a DAS28 [42]. Leeb et al. [17, 73] reported a substantially lower agreement between RAPID3 and DAS28, $r = 0.32$ and RAPID3 and CDAI, $r = 0.37$. In contrast, Pincus et al. [35, 92] demonstrated Spearman rank order correlation coefficients of 0.66 for DAS28-ESR with RAPID3, 0.50 for DAS28-CRP with RAPID3, and 0.74 for CDAI with RAPID3. All of these were highly significant ($P < 0.001$). Our findings are similar with Spearman's rank correlation coefficients of 0.52 for DAS28-CRP with RAPID3 and 0.73 for CDAI with RAPID3. Both of these were highly significant ($P < 0.001$).

Likewise, RAPID4 measures a construct of RA clinical status similar to DAS28 and CDAI because it includes RAPID3 and RADAI, a validated self-report joint count. RAPID4 can be calculated in about 19 seconds [93]. So far we have found agreement between RAPID4 and TJC, DAS28, CDAI, and SDAI, and there was no correlation with SJC. This could be due to the fact that the tender joint sub-score contributed only 17% of the total RAPID4 score [94] and that RADAI includes only painful joints.

RAPID3, RAPID4, and RAPID5 give similar results that distinguish between active disease and that controlled by treatment in RA clinical trials just as ACR improvement criteria do. All of these correlate significantly with DAS28 [35, 43, 70, 95]. Our findings agree with the above results and the correlation coefficients were 0.52, 0.56, and 0.66 between DAS28 and RAPID3, RAPID4, and RAPID5, respectively.

As noted, the joint count is the most specific measurement to assess RA. Several types of self-report joint counts have been reported since the 1980s showing correlation at levels of $r = 0.44$–0.87 with traditional TJC [30, 36, 96, 97]. RADAI self-report joint count correlates significantly with a physician/assessor TJC [30, 98, 99] as we demonstrated in the present study ($r = 0.60$, $P < 0.001$).

MDHAQ is a PROs instrument developed to include 6 complex activities of daily living which reflect status of patients currently seen by rheumatologists [74]. The reports of the HAQ and MDHAQ suggest that patient self-report data were generally more reliable than data elicited by a health professional observer, and these have been correlated with activity indices such as DAS28, CDAI, and SDAI [100–104] which is correlated with our findings. The greater reliability of self-reported data can be largely explained by the fact that the measurement was done only once by a single observer, the patient, rather than the two observers (i.e., the patient and a health professional) [93].

CDAI and SDAI, in turn, are measurements having a moderate to high correlation with all variables measured by the patient in the present study. For instance Rintelen et al. [105] also found a highly significant relationship between SDAI/CDAI levels and the patient's pain rating (SDAI: $r = 0.660$, $P < 0.001$; CDAI: $r = 0.671$, $P < 0.001$). SDAI was

highly correlated with the patient VAS-Global ($r = 0.72$, $P < 0.001$) in our cohort just as Leeb et al. [103] had shown in 2004.

4.3. Advantages and Weakness of PROs. The correlations between measurements taken by the physician and the patients show advantages in their management and prognosis of their disease. PROs had reported an association and are far more significant than laboratory tests or radiographs [24] for predicting, as mentioned above, premature mortality, costs, work disability, joint replacement, and premature death [106–110]. Other benefits of PROs in RA are the capacity to distinguish active disease from that controlled by treatment as DAS28 and CDAI do. The three also have a significant correlation with joint counts, ESR, and X-ray scores and are equally or proportionately as informative as the ACR 20, 50, 70 or DAS. Therefore, the patient may serve as his own "control" over time [20, 78]. In addition, they are more reproducible and less likely to improve with a placebo than traditional joint counts, ESR, X-ray scores, and physical measurements. It allows differentiation between case and control groups in phase III clinical trials and the modification in the treatment of placebo groups [20, 92, 111–113].

On basis of PROs, the physician can arrange strategies for monitoring patients at each visit based on the fact that the scores are available on a flow sheet, which allows the latest visit to be compared to previous ones before seeing the patient. Low cost and easy application are other features of these questionnaires and scales [24, 78]. Thus, physicians need little time to calculate questionnaires, (i.e., MDHAQ, RAPID) without mathematic formulas, advanced calculators, or quantitative articular count [18, 74, 76]. This has been reasonably shorter than the time necessary to calculate a DAS28 or a CDAI [17, 114, 115].

The questionnaire should be distributed to each patient at each visit. They complete the PROs instruments which are valid, reliable, effective, easily administered, and scored as a component of the infrastructure of standard rheumatology care [93]. Thus, the PROs instruments help the patient prepare for the visit by completing it in the waiting area prior to seeing the physician. The clinician, in turn, prepares for the visit and saves time by reviewing them before seeing the patient [116], then, scans the systems review and records the number of positives on the symptom checklist and reviews the recent medical history in order to improve accuracy and completeness of critical information [20, 70, 93, 98, 106].

However, most visits of patients with RA to rheumatologists include neither a formal quantitative joint count nor use of questionnaires [68]. This situation may be due to limitations that PROs instruments have, which includes the fact that about 20% of the patients may need some help to complete even a simple self-report questionnaire [117]. Furthermore, floor effects are seen, that is, patients may have normal HAQ scores but nonetheless feel that there are functional limitations [104]. Other times, the physicians do not check the patient's clinical status, and the patients felt unhappy after completing questionnaires if there was no evidence that the information was reviewed by a health professional [104]. Some authors have reported that specialized questionnaires are too cumbersome for usual clinical care, and short questionnaires are needed.

Sometimes the PROs instruments are nonspecific and measurements may show improvement in the patient status due to other situations unrelated to RA. They are subject to cultural differences (i.e., pain scores are highest in Latin Americans patients and lowest in Asian patients), must be translated into and validated in various languages, and may be subject to gaming by certain patients to give desired answers [20, 78, 110].

Other authors had shown disparities between physician and patient measurements. Studenic et al. [118] found patients and physicians often differed in the perception of RA disease activity, quantified by VAS-Global and MD-Global. This was due to a worse perception of pain by the patient, while for SJC, the worse perception was by the physician. The two discrepancies explain 65% of the discordance between patient and physician measurements.

4.4. Limitations and Conclusions. The present study had some limitations. The focus groups could be one of them since some patients may influence others and affect their answers. This could raise questions about its reproducibility both collectively and individually. In addition, measurements of test–retest reliability were not done because each focus group gathered only once, and an intragroup correlation cannot be done.

Through this study, we can conclude that PROs can be administered collectively without any specialized guidelines thus providing a space for group education. Therefore, PROs can be done in rheumatology practice using the processes and instruments described above. This practice will help to advance rheumatology as a specialty and improve the lives of millions of people with RA due to the fact that patient questionnaires can be collected easily, completed in a limited time, and done in all clinical practices. These questionnaires can be completed for patients at each visit regardless of gender, educational level, age, or duration of disease as demonstrated here. PROs are not intended to be a substitute for objective scores such as the DAS28 determined during physician visits, in other words, they do not replace the clinical judgment or a careful articular examination. On the contrary, they are complementary. Together, they act synergistically and allow the physician and patient to reach a consensus evaluation in order to achieve and support a long-term improvement of the patient's condition through better treatment.

We encourage clinicians to implement quantitative measurements about patient status in RA using PROs, since they are standardized, efficient, and effective. These appear wellsuited to a continuous quality improvement approach in standard patient care, contributing to provide data regarding functional status, pain, global status, fatigue, and psychological status that cannot be obtained any other way. We hope that implementation in rheumatology centers could provide the benefits described in this paper, increasing treatment adhesion, costs reduction and lead to a better outcome in RA.

Abbreviations

AD:	Autoimmune disease
AITD:	Autoimmune thyroid disease
ANAs:	Antinuclear antibodies
Anti-CCP:	Anticyclic citrullinated peptid
APS:	Antiphospholipid syndrome
BMI:	Body mass index
CDAI:	Clinical disease activity index
CRP:	C-reactive protein
DAS28:	Disease activity score-28 joints
DMARDs:	Disease modifying antirheumatic drugs
EAMs:	Extraarticular manifestations
ESR:	Erythrocyte sedimentation rate
FDR:	First-degree relatives
HAQ:	Health assessment questionnaire
IQR:	Interquartile range
MAS:	Multiple autoimmune syndrome
MD-Global:	Global assessment by visual scale analogue by physician
MDHAQ:	Multi-dimensional health assessment questionnaire
PROs:	Patient-reported outcomes
RA:	Rheumatoid arthritis
RADAI:	Rheumatoid arthritis disease activity index
RAPID:	Routine assessment of patient index data
RF:	Rheumatoid factor
SAI:	Selfadministered index
SD:	Standard deviation
SDAI:	Simplified disease activity index
SES:	Socioeconomic status
SJC:	Swollen joint count
SLE:	Systemic lupus erythematosus
SS:	Sjögren's syndrome
SSc:	Scleroderma
TgAb:	Antithyroglobulin protein
TJC:	Tender joint count
TSH:	Thyrotropin
TPOAb:	Anti-thyroperoxidase enzyme
VAS-Global:	Global evaluated by patient in visual scale analogue
VAS-Pain:	Pain visual scale analogue
WHR:	Waist-to-hip ratio.

Conflict of Interests

The authors declare no conflict of interests.

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Research Article

Proinflammatory Soluble Interleukin-15 Receptor Alpha Is Increased in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease in which many cytokines have been implicated. In particular, IL-15 is a cytokine involved in the inflammatory processes and bone loss. The aim of this study was to investigate the existence in synovial fluid of soluble IL-15Rα, a private receptor subunit for IL-15 which may act as an enhancer of IL-15-induced proinflammatory cytokines. Soluble IL-15Rα was quantified by a newly developed enzyme-linked immunosorbent assay (ELISA) in samples of synovial fluid from patients with RA and osteoarthritis (OA). The levels of IL-15Rα were significantly increased in RA patients compared to OA patients. Also, we studied the presence of membrane-bound IL-15 in cells from synovial fluids, another element necessary to induce pro-inflammatory cytokines through reverse signaling. Interestingly, we found high levels of IL-6 related to high levels of IL-15Rα in RA but not in OA. Thus, our results evidenced presence of IL-15Rα in synovial fluids and suggested that its pro-inflammatory effect could be related to induction of IL-6.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which imbalances in pro- and anti-inflammatory cytokines promote induction of autoimmunity, inflammation and joint destruction [1]. IL-15 is a proinflammatory cytokine associated with several autoimmune diseases, particularly rheumatoid arthritis. [2, 3]. Three different functional forms of IL-15 have been identified: the soluble cytokine [4], IL-15R-independent membrane-bound IL-15 [5, 6] and membrane-IL-15 anchored through IL-15Rα [7]. IL-15Rα is a unique high affinity private α chain that together with the IL-2 receptor, IL-2Rβ chain and the IL-2Rγ chain subunits constitute a trimeric receptor for IL-15 on cell membranes. Also, IL-15Rα may be secreted as a functional soluble molecule (s-IL-15Rα) and could behave as an agonist by forming a complex with IL-15 which is 100-fold more efficient than the noncomplexed soluble cytokine or as an antagonist for IL-15 [8–10].

In addition, s-IL-15Rα may activate a reverse signaling through interaction with IL-15R-independent membrane-bound IL-15, activating MAPKs (mitogen-activated protein kinases) and increasing production of several proinflammatory cytokines such as IL-6, IL-8, and tumor necrosis factor α [5, 6, 11]. This bidirectional signaling has also been described for most members of TNF ligand family contributing to multiple stages of immune regulation [12].

Soluble IL-15 has been detected in synovia of patients with RA mainly expressed by macrophages, fibroblasts, and endothelial cells [13, 14], and there it recruits circulating memory T cells in the synovial membrane and may up regulate TNFα, IL-17, and other proinflammatory cytokines [15–17]. Moreover, soluble IL-15 appears to be an important contributor to osteoclastogenesis contributing to bone erosion [18–20]. Membrane IL-15 has been detected in synovial tissue of RA patients. However, the role of IL-15R-independent membrane-bound IL-15 in RA has not been completely studied until now, and no data has been

reported so far concerning the existence of natural sIL-15Rα in synovial fluid of RA patients, two elements necessary to induce proinflammatory cytokines through reverse signaling that could contribute to pathogenesis of RA. Existence of different IL-15-activating signaling pathways for inducing inflammation in RA could imply use of different antagonists depending on the specific induced pathway(s).

We had previously identified P8 peptide as an IL-15Rα antagonist that may be inhibiting reverse signaling [21]. Therefore, we focused our study on determining the presence of soluble IL-15Rα in synovial fluid and its potential role in inducing reverse signaling through membrane-bound IL-15 on cells from synovial fluid. Interestingly, we found higher levels of IL-15Rα in RA compared with OA, and also we found that there is a positive relationship between these high levels of IL-15Rα and high levels of IL-6 in RA but not in OA. Furthermore, we demonstrated in an *in vitro* experiment that IL-15Rα induced secretion of IL-6 in cells from synovial fluid of an RA patient. These results suggest the role of sIL-15Rα as an inducer of the pro-inflammatory cytokine IL-6 through a reverse signaling in RA.

2. Subjects and Methods

2.1. Patients and Samples. Synovial fluids were obtained from the knee joints of 35 patients. Eighteen (18) of them with established RA were receiving treatment with oral methotrexate (MTX) and low-dose prednisone. They were moderate or nonresponders to MTX with a mean DAS28 of 4.7 and had shown inflammation and abundant synovial fluid in the cavities of synovial joints. The rest (17) were OA patients. All patients were from the Rheumatology Service at Ameijeiras Brothers Hospital. Permission was obtained from the local ethics committee, and all patients gave written informed consent. Patient demographics are listed in Table 1.

Synovial fluid was directly aspirated from the inflamed joint and collected into tubes, immediately after we added hyaluronidase type IV (H3884, Sigma, USA) at 10 ug/mL to synovial fluid, and mixed by inversion followed by spinning at 1000 g for 10 min within 30 min of sample collection. The acellular portion of synovial fluid (synovial liquid) was stored at −70°C before subsequent analysis. Cells were collected for flow cytometry and cell stimulation experiments.

2.2. Measurement of Serum IL-15Rα. We have developed an enzyme-linked immunosorbent assay (ELISA) format to measure serum levels of IL-15Rα as we have previously described [21]. The 96-well microtiter plates (Costar, Corning Inc., NY, USA) were treated with 2% glutaraldehyde solution for 2 h at 37°C. After two washes with water, plates were coated with 10 μg/mL of P8 peptide/well, and the plates were then incubated at 4°C overnight. After three washes with phosphate buffered saline pH 7.4 (PBS) containing 0.05% Tween 20, nonspecific binding sites were blocked by incubation for 1 h at 37°C in PBS containing 1% BSA. The blocking solution was replaced by samples (synovial liquid diluted 2-fold in PBS, containing 0.01% BSA and 0.05% Tween 20 or different concentration of recombinant IL-15Rα-Fc (147-IR, R&D) in the same buffer). All the samples were in triplicate. Following incubation at 37°C for 2 h, we did three washes with PBS containing 0.05% Tween 20. IL-15Rα was detected with specific antibody against IL-15Rα (AF247, R&D System). The bound IL-15Rα was detected with HRP-conjugated goat antihuman IgG (A0170, Sigma, USA) by incubation at 37°C for 1 h, followed by 5 washes with PBS, 0.1% Tween 20. The reaction was visualized by adding the substrate solution (3,3′,5,5′-tetramethylbenzidine [TMB]), and absorbance at 450 nm was measured with an ELISA plate reader (Biotrak GE, Healthcare, USA). The detection limit was 0.25 nM.

Table 1: Patient demographics.

	RA ($n = 18$)	OA ($n = 17$)
Sex (M/F)	4/14	9/8
Age (years)	49 ± 14.19	64 ± 9.8
Disease duration (years)	13 ± 11	10 ± 2.6
Rheumatoid factor (±)	6/12	—
DAS28	4.37 ± 1.23	—
DMARD (MTX)	16	—

Demographics showing age, sex, and duration of disease, where available; RF: rheumatoid factor status; DAS28: disease activity score; DMARD: disease-modifying antirheumatic drug.

2.3. Immunoassays for IL-6. Interleukin-6 concentrations were measured in duplicate using commercially available ELISA kits purchased from R&D Systems (Quantikine Human IL-6, D6050). The detection limit was 3.12 pg/mL.

2.4. Western Blot Analysis. We precipitated IL-15Rα from the synovial fluid with cold acetone. Proteins were separated on 12.5% SDS-PAGE and transferred to nitrocellulose membranes. Membranes were blocked in 5% nonfat dry milk in Tris-buffered saline (TBS) (pH 8) for 1 hour at room temperature before probing for 2 h with antibody against IL-15Rα (0.5 μg/mL) (AF247, R&D System). After incubation with horseradish-peroxidase- (HRP-) conjugated secondary antibodies (rabbit anti-goat HRP, 1 : 1,000 dilution) (A8919, Sigma, USA) in 5% in TBS (pH 8) for 1 h at room temperature, bound antibodies were visualized using enhanced chemiluminescence (Amersham Pharmacia Biotech, Little Chalfont, UK).

2.5. Flow Cytometry. Freshly isolated cells collected by centrifugation from synovial fluid were washed with PBS, 2% fetal calf serum (FCS), and incubated on ice for 1 h with an anti-IL-15 mAb (MAB2471; R&D System), or an irrelevant IgG1 isotype control mAb (MAB002; R&D System), anti-CD3 (sc1239; Santa Cruz Biotechnology), or anti-CD8 (sc 7970; Santa Cruz Biotechnology). Cells were then washed and incubated on ice for 30 minutes with anti-mouse-FITC (F2772, Sigma, USA). After washing once with PBS 2% FCS and once with PBS, cells were resuspended in 1%

paraformaldehyde and analyzed in a PAS-III flow cytometer using FloMax software (Partec, Germany).

For acid treatment, cells were incubated in ice-cold glycine buffer (25 mM glycine and 150 mM NaCl [pH 3.0]) for 10 min previously incubated with specific antibodies.

2.6. Cell Stimulation with IL-15Rα. Cells were incubated in 24-well plates at 10^6 cells per well either with or without sIL-15Rα at 250 ng/mL as duplicates in two independent experiments. After 72-hour incubation, supernatants were collected and stored at −70°C until further evaluation. IL-6 concentration was determined by ELISA (D6050, R&D Systems, Minneapolis, MN, USA).

2.7. Statistics. The nonparametric Mann-Whitney *U* test was used for group comparisons of IL-6 and IL-15R alpha serum levels. The correlation coefficient was obtained by the nonparametric Spearman's rank correlation test.

3. Results

3.1. Increased SIL-15Rα Levels in Synovial Fluid from Patients with RA. An indirect ELISA assay was performed to measure IL-15Rα concentration using P8 peptide as capture. Therefore, we detected IL-15Rα using an anti-IL-15Rα antibody (AF247, R&D) as a detection antibody as previously described [21]. Human sIL-15Rα-Fc fusion protein (R&D) was used as standard with a detection limit of 0.25 nM. Next, we measured the IL-15Rα level in synovial fluid from patients with RA or OA. The sIL-15Rα was detected in 18 of 18 RA patients (100%) versus 14 of 17 patients of OA (82.3%). A significant increase in concentrations of sIL-15Rα was observed in synovial fluid collected from RA patients compared to those from OA patients (Figure 1).

To confirm IL-15Rα protein in synovial fluids, we used P8 peptide synthesized on TentaGel-S pearls to capture IL-15Rα. Proteins bound to TentaGel-P8 peptide were eluted and analyzed by immunoblotting assay using a specific anti-IL-15Rα antibody (AF247, R&D). A band was detected between 29 and 66 kDa (Figure 2), corresponding to previously described size around 55 kDa [9].

3.2. Synovial Cells Express Membrane IL-15. To study the presence of membrane-bound IL-15, we analyzed the expression of membrane IL-15 by FACS in cells present in the synovial fluid. As shown in Figure 3(a), there is a different cell population in synovial fluids, but we only detected the expression of membrane IL-15 in R1 region (Figure 3(b)). The mIL-15 detected varied among patients, and interestingly, we found that the cell population in R1 region also expresses CD3 (Figure 3(c)) and CD8 markers (Figure 3(d)).

In addition, we tested whether IL-15 was expressed as membrane-IL-15 anchored through IL-15Rα or as IL-15R-independent membrane-bound IL-15. To accomplish this, we performed acidic treatment to remove membrane-IL-15 anchored through IL-15Rα as reported by Dubois et al. [7]. This result showed a slight decrease in the amount of cell-surface-bound IL15 after acidic treatment which suggests

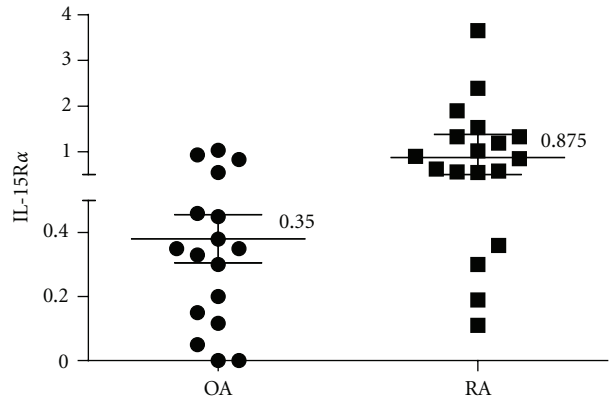

Figure 1: Increased sIL-15Rα levels in RA synovial fluids. The graphic represents median and interquartile range. Mann-Whitney test shows a significant difference, $P = 0.0025$, between OA and RA groups.

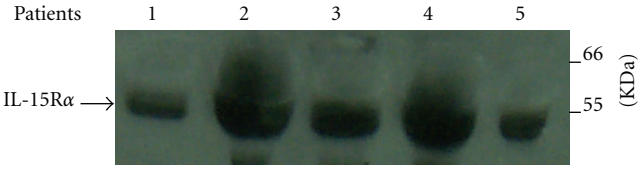

Figure 2: Western blot analysis of IL-15Rα in synovial fluids from RA patients. Proteins from synovial fluids from different patients (lanes 1–5) were separated on 12.5% SDS-PAGE and transfer to nitrocellulose for western blotting. The western blot was probed with anti-IL-15Rα antibody and development with anti-goat-HRP. Representative western blot is shown.

that part of the protein could be associated to IL-15Rα in the membrane, but most of IL-15 is expressed as a membrane-anchored protein (Figure 3(e)).

3.3. Relationship between IL-6 and IL-15Rα in Rheumatoid Arthritis. IL-6 levels were measured by ELISA in synovial fluids in both groups of patients, and we found that a high percent of RA patients (80%) expressed high levels of IL-6 (>700 pg/mL) versus 35% of OA patients as shown in Figure 4. This result in our patients is in agreement with previous reports but interestingly, in RA but not in OA, synovial IL-6 levels were positively correlated with high levels of sIL-15Ra ($P = 0.006$). The result is showed in Figure 5.

In order to study the induction of IL-6 by IL-15Rα in cells from synovial fluid, we performed an experiment to incubate cells from synovial fluid of RA patient with IL-15Rα and in Figure 6 show a strong activation of IL-6 secretion determined by ELISA after 72 h of treatment.

4. Discussion

IL-15Rα is a private receptor for IL-15 that plays an important role in the biology of this cytokine. It has been described as a membrane and soluble receptor in serum from mice and humans [9]. This recent study confirms the

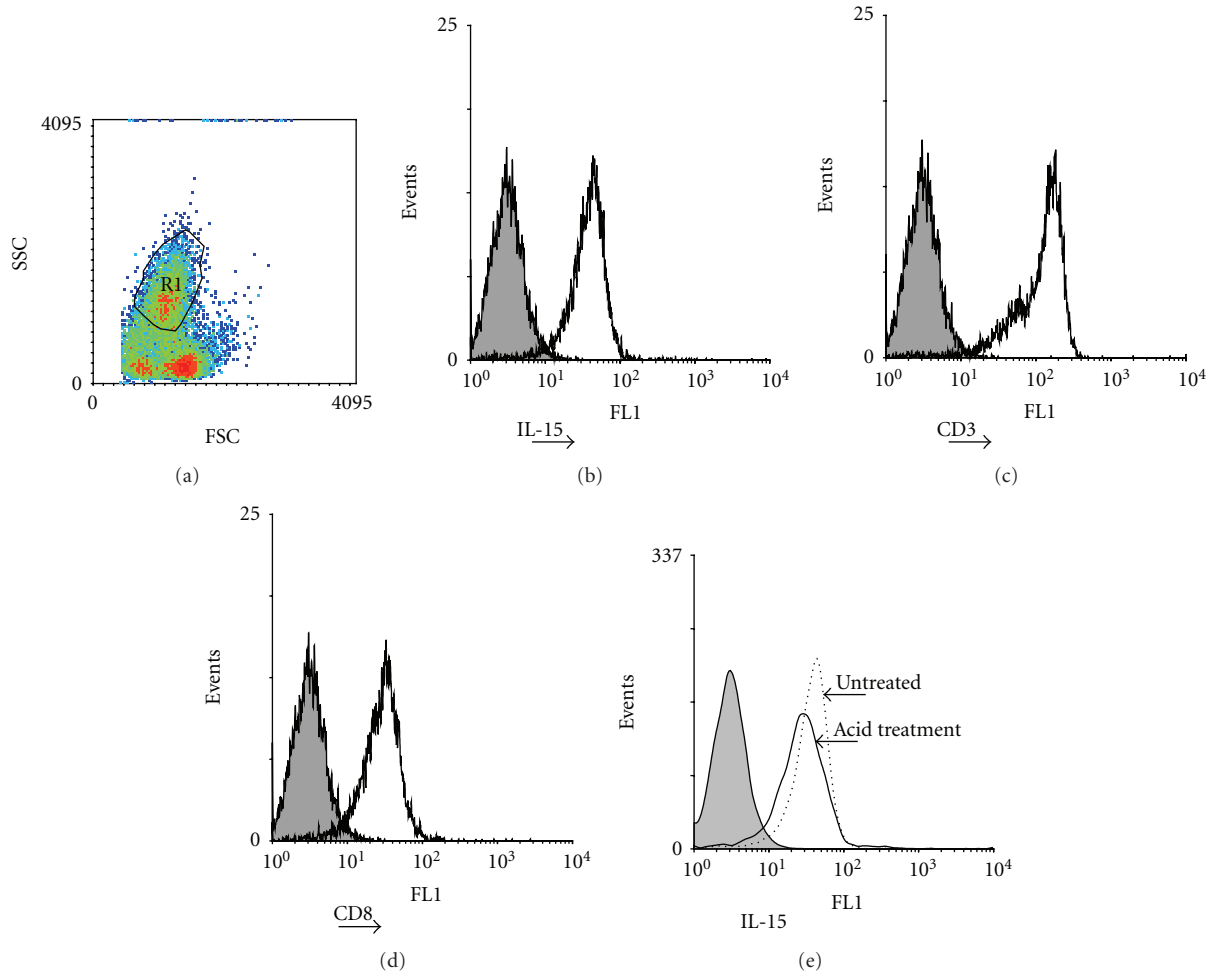

Figure 3: Flow cytometric analysis of a cell population positive for membrane-bound IL-15 (R1 region). Density plot had shown different population of cells in synovial fluid (a). Fluorescence intensity in R1 region is represented by white histograms, using a specific antibody MAB 2471(b); specific antibodies to detect CD3 (c) or CD8 (d) and gray histograms refer to the background staining. Acid treatment with acid buffer (pH 3.0) before incubation with MAB 2471 produced a slight decrease in fluorescence intensity (bold gray line) in comparison to incubation with MAB 2471 in PBS (dotted line) (e).

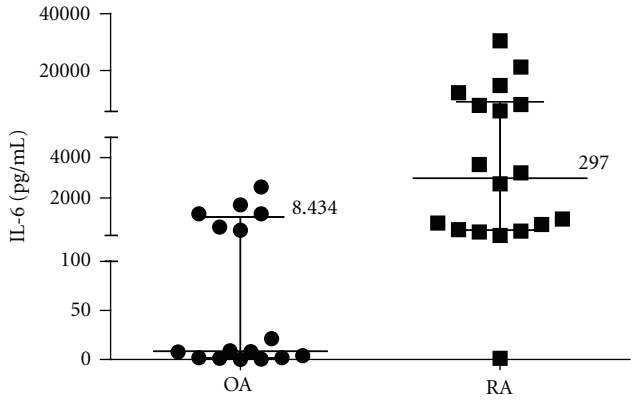

Figure 4: Increased IL-6 levels in RA synovial fluids. The graphic represents median and interquartile range. Mann-Whitney test has shown significant difference $P = 0.0011$, between OA and RA groups.

presence of soluble IL-15Rα in synovial fluids from RA and OA patients, although it was undetected in 3 patients of OA. First, we established an ELISA using as a capture a previously described peptide which specifically binds to IL-15Rα and displaces IL-15/IL-15Rα binding in a dose-dependent manner [21]. Therefore, we considered that detected IL-15Rα is not forming complexes with endogenous IL-15. Measured levels of IL-15Rα were significantly increased in RA compared with OA (a rheumatic nonautoimmune disease) suggesting a proinflammatory role in this disease. To determine the molecular weight of IL-15Rα in synovial fluids, we captured it with a P8 peptide synthesized on TentaGel-S pearls. A band about 42 kDa was recognized in a western blot using an anti-IL-15Rα antibody. The observed size corresponded to the previous report for soluble IL-15Rα released from positive cells by a shedding process involving matrix metalloproteinases [9]. Presence of IL-15Rα in the synovial fluids is a requisite to induce reverse signaling through membrane-bound IL-15. A mechanism

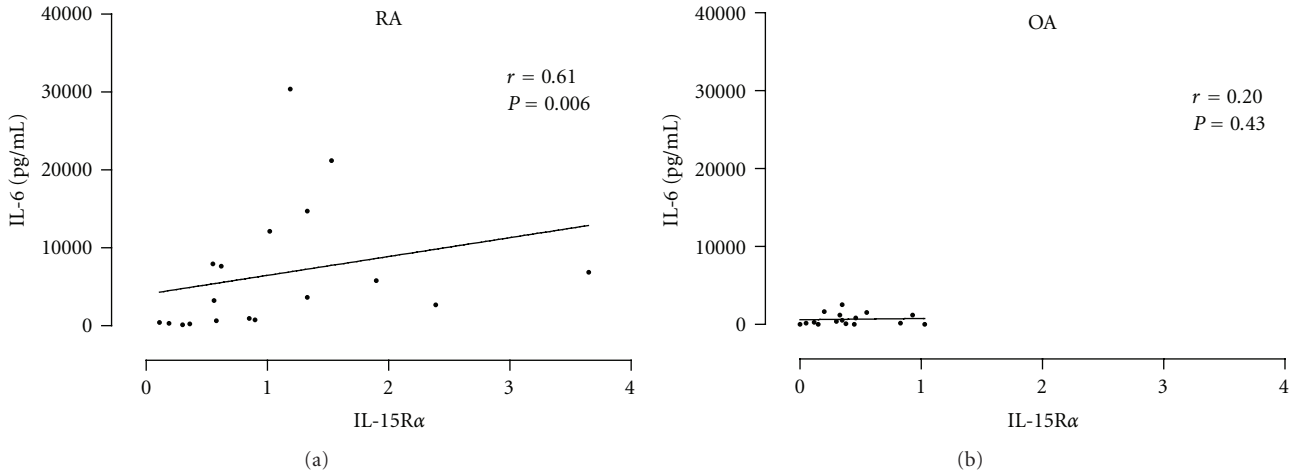

Figure 5: Correlation between IL-6 and sIL-15Ra levels in synovial fluid. Positive correlation was observed in RA ($r = 0.61$).

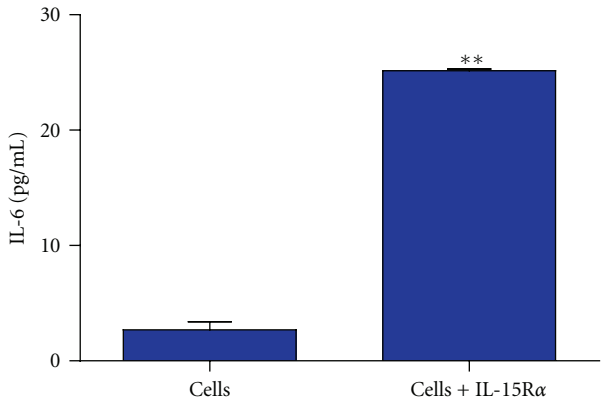

Figure 6: Effect of IL-15Rα on IL-6 secretion in synovial cells. Treatment with 250 ng/mL of IL-15Rα significantly upregulated IL-6 expression. Each bar represents the mean and SD of two determinations. ** = $P < 0.001$.

which has been recently described in THP1 monocytic cells, PC-3 prostate carcinoma cells and in patients with head and neck cancer. There it is proposed that IL-15 anchored in plasma membranes acts as a receptor being capable to bind soluble IL-15R alpha then inducing MAPK and IL-6. MAPKs (ERK and p38) are a family of highly conserved serine/threonine kinases that have been described to play key regulatory roles in downstream signaling events leading to joint inflammation, and joint destruction including production of proinflammatory cytokines such as IL-6 [22]. Expression of IL-6 is increased in the synovium of patients with RA, and serum levels of IL-6 have been shown to correlate with clinical and laboratory markers of disease activity, and IL-6 has recently been validated as a target in RA [23]. Therefore, it is important to know if this signaling pathway induced by interaction between membrane IL-15 and IL-15Rα takes place in RA to induce IL-6.

Although membrane IL-15 had been detected in synovial tissues from RA patients [18, 24], it has not been studied whether membrane IL-15 is bound to IL-15Rα or exists as a membrane-anchored protein. In membrane IL-15 bound to IL-15Rα, IL-15 is retained on the cell surface, and it is transpresented to IL-2R/15Rβ-γc on nearby effector NK and T cells by the formation of an immunological synapse [25, 26]. Thus, IL-15/IL-15Rα activates the JAK1/JAK3 and STAT3/STAT5 pathways to induce proliferation of T and NK cells, and this mechanism could limit exposure to circulating IL-15, that contributeS to the risk of autoimmunity [7]. In contrast, IL-15 R-independent membrane-bound IL-15 could act as a receptor inducing reverse signaling. In this current study, we found that after acid treatment most of IL-15 is present as a membrane-anchored protein, and a certain number of IL-15 molecules are bound to membrane IL-15 Rα confirming the expression of membrane-anchored IL-15 on cells from synovial fluids.

Chronic joint inflammation is related to leukocytes infiltration in synovial compartment. The synovium of patients with established RA is expanded and contains large numbers of fibroblasts, macrophages, and highly differentiated T cells [27]. We observed at least three cell populations with different SSC/FCS characteristics by flow cytometry (Figure 3(a)). We could not perform double staining, but interestingly, IL-15 positive cells were present in the R1 region, and 95% of this population was CD3 positive and 83.8% were CD8 positive, suggesting, they were IL-15-positive T cells. This finding is in agreement of previous results by Miranda-Carús et al., who detected IL-15 on rheumatoid arthritis T cells [18].

To explore the production of the proinflammatory cytokine IL-6 in these patients, we quantified IL-6 levels in synovial fluids from RA and OA patients. Higher and significant concentrations of IL-6 were found in RA when compared with OA patients. This result is in agreement with a previous paper [28], but interestingly, we found a positive correlation ($r = 0.61$; $P = 0.006$) between high levels of IL-6 and high levels of IL-15Rα in RA but not in OA. This data suggested that IL-15Rα present in synovial fluids could be possibly inducing IL-6 through a reverse signaling pathway and then contributing to a proinflammatory medium in RA.

To demonstrate that cells from synovial fluid could secrete IL-6 in response to IL-15Rα, we performed an experiment in which cells from synovial fluid were incubated with or without IL-15Rα. A significant increase of IL-6 was observed in the supernatant culture of cells treatment with IL-15Rα.

This result reveals a possible proinflammatory role of soluble IL-15Rα through reverse signaling. The presence of soluble IL-15 in synovial fluids from RA patients and its role in inducing migration of T cells and induction of TNF alpha is already known [8]. Possibly, both soluble and membrane IL-15 are implicated in the proinflammatory process through different pathways. Therefore, this finding might imply that different approaches would be necessary for an effective inhibition of IL-15 signaling in RA. Now, we will perform experiments to assess antagonist properties of the P8 peptide in this context.

In conclusion, we have detected soluble IL-15 alpha in synovial fluids, which is increased in RA in comparison to OA. In addition, it is positively correlated to IL-6 specifically in RA. These results suggested that IL-15R alpha could induce IL-6 in RA through its binding to membrane IL-15.

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