Reumatol Clin. 21 (2025) 501948

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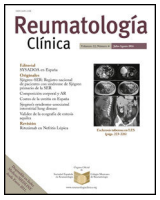

Brief report

Association between hypothyroidism and elderly-onset rheumatoid arthritis: A cross-sectional study at national hospital in Peru

Paul J. Tejada-Llacsa,[a,*] Vidia Lumbe Diaz,[b] Carlos Diaz-Arocutipa[c]

[a] *Clínica Jesús del Norte, Lima, Peru*
[b] *Servicio de Reumatología, Hospital Nacional Adolfo Guevara Velasco, EsSalud, Cusco, Peru*
[c] *Unidad de Revisiones Sistemáticas y Meta-análisis (URSIGET), Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru*

ARTICLE INFO

Article history:
Received 30 January 2025
Accepted 22 July 2025

Keywords:
Hypothyroidism
Elderly-onset rheumatoid arthritis
Peru
Rheumatoid arthritis
Cross-sectional study

ABSTRACT

Objective: To determine the association between hypothyroidism and elderly-onset rheumatoid arthritis (EORA).
Methods: A cross-sectional study was performed including patients with rheumatoid arthritis at the Adolfo Guevara Velasco National Hospital, Cusco, Peru in 2024. The outcome was EORA, defined as disease onset after 60 years old. The exposure was a history of hypothyroidism, and the following covariates were considered: sex, smoking, family history of autoimmune disease in first-degree relatives, rheumatoid factor and anti-CCP levels. The association between hypothyroidism and EORA was assessed using prevalence ratios (PR) with their 95% confidence interval (CI), estimated by generalized linear models with a Poisson family, log link, and robust variance. A p-value <0.05 was considered statistically significant.
Results: A total of 133 patients were included, 14 (10.5%) of whom had EORA. The mean age was 55 ± 12.6 years and 90% were female. Only 8.3% of patients reported a history of hypothyroidism. Hypothyroidism was significantly associated with EORA (adjusted PR 9.03, 95% CI 3.17–26.68). Other factors associated with EORA were disease duration, smoking, the history of autoimmune disease in a first-degree relative, and rheumatoid factor.
Conclusions: A history of hypothyroidism was independently associated with EORA in patients with rheumatoid arthritis from Peru. Screening for hypothyroidism in EORA patients may enhance management and address autoimmune comorbidities.

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Asociación entre hipotiroidismo y artritis reumatoide de inicio tardío: un estudio transversal en un hospital nacional de Perú

Palabras clave:
Hipotiroidismo
Artritis reumatoide de inicio tardío
Perú
Artritis reumatoide
Estudio transversal

RESUMEN

Objetivo: Determinar la asociación entre hipotiroidismo y artritis reumatoide de inicio tardío (ARIT).
Métodos: Estudio transversal en pacientes con artritis reumatoide en el Hospital Nacional Adolfo Guevara Velasco (Cuzco, Perú), en 2024. La ARIT se definió como inicio de la enfermedad después de los 60 años. La exposición fue el antecedente de hipotiroidismo, con covariables como sexo, tabaquismo, antecedente familiar de enfermedad autoinmune, factor reumatoide y anti-CCP. Se estimaron razones de prevalencia con IC 95% mediante regresión de Poisson con varianza robusta. Se consideró significativo p < 0,05.
Resultados: Se incluyeron 133 pacientes, 14 (10,5%) con ARIT. La edad media fue 55 ± 12,6 años, el 90% eran mujeres. El 8,3% tenía hipotiroidismo, el cual se asoció con ARIT (razones de prevalencia ajustada 9,03; IC 95%: 3,17-26,68). Otros factores asociados fueron la duración de la enfermedad, el tabaquismo, el antecedente autoinmune familiar y el factor reumatoide.

* Corresponding author.
E-mail address: paultejada24@gmail.com (P.J. Tejada-Llacsa).

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Conclusión: El hipotiroidismo se asoció independientemente con ARIT. Su detección podría mejorar el manejo y abordar comorbilidades autoinmunes.

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Introduction

Elderly-onset rheumatoid arthritis (EORA) is recognized as a distinct subset of rheumatoid arthritis (RA) typically defined by an age of onset at or after 60 years, although some literature suggests a threshold of 65 years.[1] The incidence of RA among individuals over 65 years increased significantly in recent decades.[2] Clinically, EORA often presents with a more abrupt onset, frequently accompanied by myalgias and predominant involvement of large joints, distinguishing it from typical-onset RA.[3]

In addition to its clinical implications, the potential association between hypothyroidism and RA has attracted considerable attention. A Mendelian randomization study found that hypothyroidism was linked to a 23% increased risk of developing RA.[4] Similarly, an increased incidence of RA has been described in patients with autoimmune thyroid disease (AITD), and vice versa. Additionally, there is an increased risk of AITD in patients with a recent RA diagnosis.[5]

In the context of aging, notable immune system changes occur, including diminished T cell proliferation and increased production of inflammatory cytokines. This age-related shift leads to and enhanced immune response to self-antigens.[6] Consequently, the interaction between hypothyroidism and EORA may be more pronounced in the elderly population. Although studies specifically evaluating this relationship are scarce, there are those find similar prevalence of hypothyroidism in both EORA and typical-onset RA cases[7,8] or more frequent of hypothyroidism in EORA in comparison to typical-onset RA.[9] Therefore, this study aimed to evaluate the association between hypothyroidism and EORA in an Andean population from Peru.

Methods

Design

A cross-sectional study was conducted involving patients diagnosed with RA who were treated at the Adolfo Guevara Velasco National Hospital of EsSalud – Cusco, Peru from January to June 2024.

Study population

The study included adult patients (aged ≥18 years) with a confirmed diagnosis of RA according to the ACR/EULAR 2010 classification criteria, and provided complete data on age at disease onset and hypothyroidism history.

Variable

The outcome variable was EORA, defined as disease onset at or after the age of 60. The exposure variable was a history of hypothyroidism. Covariates included sex, age, marital status, education level, disease duration (years), smoking, alcohol use, family history of autoimmune disease in first-degree relatives, corticosteroid use, use of disease-modifying antirheumatic drugs (DMARDs), disease activity measured by the RAPID-3, and functional status assessed using the modified Health Assessment Questionnaire (mHAQ). Additionally, serum levels of rheumatoid factor (normal value <14 UI/ml), anti-cyclic citrullinated peptide (anti-CCP) (normal value <20 UI/ml), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were evaluated.

Data collection

Patients attending the rheumatology outpatient clinics at AGVNH during the study period were enrolled. Rheumatologists conducted data collection through in-person clinical evaluations, while laboratory data were extracted from electronic medical records.

Statistical analysis

Descriptive statistics were presented using mean ± standard deviation or median (p25–p75) for continuous variables, while categorical variables were summarized using absolute frequencies and percentages. Bivariate analysis included the chi-square test for categorical variables and the Student's *t*-test for continuous variables. To evaluate the association between a history of hypothyroidism and EORA, prevalence ratio (PR) with its 95% confidence interval (CI) was estimated using generalized linear models, Poisson family, log link, and robust variance. A p-value <0.05 was considered statistically significant. With 133 participants (11 with hypothyroidism and 122 without), the study had approximately 98% power ($\alpha = 0.05$, two-sided) to detect the observed difference in EORA prevalence (45.5% vs 7.4%), calculated post hoc.

Ethics

The protocol for this study was approved by the ethics committee of HNAGV. Informed consent was obtained from all enrolled patients. Confidentiality of the collected information was ensured, and only the researchers had access to the participants' data.

Results

A total of 133 patients were included, the mean age was 55 ± 12.6 years, 90.7% (117/129) were female, 10.5% met the criteria for EORA, 24.8% reported a first-degree family history of autoimmune disease, and 8.3% had a history of hypothyroidism (Table 1). In relation to antibodies, 97.4% had rheumatoid factor (RF) positivity and 91.4% had anti-CCP positivity. Regarding treatment, 68.4% of patients receiving corticosteroids, 96.2% were on synthetic DMARDs, and 6.1% (8/132) were on biological DMARDs. The median RAPID-3 score was 9.85 (5.7–14.4), and the median mHAQ score was 0.38 (0.13–0.38).

Patients with EORA showed a higher proportion of comorbidities, with statistically significant differences compared to those with typical-onset RA. Among the EORA group, 100% were female, 42.9% had a first-degree family history of autoimmune disease, and the levels of rheumatoid factor and anti-CCP were elevated compared to the typical-onset RA group, although these differences did not reach statistical significance. Furthermore, the proportions of RF and anti-CCP positivity were similar between patients with typical-onset RA and those with EORA. RF positivity was observed in 100% of EORA cases compared to 97.1% in typical-onset RA, while anti-CCP positivity was 92.3% in EORA and 91.3% in typical-onset RA. Additional characteristics are detailed in Table 1.

Table 1
Characteristics of patients with elderly-onset arthritis in patients at national hospital in Peru.

Characteristics	Elderly-onset arthritis				*p*-Value
	Yes		No		
	N	%	*N*	%	
Sex[b] *(n = 129)*					
Male	0	0	12	10.4	
Female	14	100	103	89.6	
Age mean (SD)	69.9 (4.0)		53.3 (11.9)		<0.001[a]
Disease duration (years), mean (SD)	5.0 (4.4)		13.4 (11.4)		0.007
Education[b] *(n = 131)*					
Yes	8	57.1	58	49.6	0.592*
No	6	42.9	59	50.6	
Marital status single[b] *(n = 130)*					
Yes	12	85.7	88	75.8	0.409*
No	2	14.3	28	24.2	
Smoking[b] *(n = 131)*					
Yes	2	15.4	6	5	0.141*
No	11	84.6	112	95	
Alcohol					
Yes	0	0	16	13.4	0.144*
No	14	100	103	86.6	
Number of comorbidities					
≥1	12	85.7	41	37.6	0.001*
None	2	14.3	68	62.4	
Hypothyroidism					
Yes	5	35.7	6	5	<0.001*
No	9	64.3	113	95	
History of autoimmune disease in first-degree relative					
Yes	6	42.9	27	22.7	0.098*
No	8	57.1	92	77.3	
NSAID					
Yes	8	57.1	74	62.2	0.714*
No	6	42.9	45	37.8	
Corticosteroid					
Yes	9	64.3	82	68.9	0.725*
No	5	35.7	37	31.1	
Synthetic DMARD					
Yes	14	100	114	95.8	
No	0		5	4.2	
Biological DMARD[b] *(n = 132)*					
Yes	1	7.1	7	5.9	0.858*
No	13	92.9	111	94.1	
Bone erosions[b] *(n = 130)*					
Yes	3	23.1	15	12.8	0.310*
No	10	76.1	102	87.2	
RAPID-3 mean (SD)	9.89 (6.15)		10.48(6.14)		0.733[a]
HAQ mean (SD)	0.63 (0.61)		0.5 (0.49)		0.389[a]
CPR mean (SD)	0.72 (1.19)		1.18 (2.61)		0.548[a]
ESR mean (SD)	25.17 (12.63)		24.17 (10.63)		0.721[a]
Rheumatoid factor	356.88 (74.73)		257.00 (240.37)		0.166[a]
Anti-CCP	755.69 (363.25)		638.79 (387.48)		0.304[a]

[a] Student's *t*-test.
[b] Valid *N* shown in parentheses; denominators vary because of occasional missing data.
* Chi square.

Hypothyroidism was significantly associated with EORA in both bivariate (crude PR 6.16, 95% CI 2.49–15.24) and multivariable analysis (adjusted PR 9.03, 95% CI 3.17–26.68) (Table 2). Other factors associated with EORA were disease duration (adjusted PR 0.87, 95% CI 0.82–0.93), smoking (adjusted PR 4.44, 95% CI 1.37–14.43), history of autoimmune disease in a first-degree relative (adjusted PR 4.80, 95% CI 1.90–12.12), and rheumatoid factor (adjusted PR 1.004, 95% CI 1.002–1.005).

Discussion

Our study identified an independent association between a history of hypothyroidism and the presence of EORA, adjusting for smoking, first-degree family history of autoimmune disease, and levels of rheumatoid factor and anti-CCP. While risk of hypothyroidism has been estimated with OR 2.25 in patients with RA,[4] the underlying mechanisms remain poorly understood. Both

Table 2
Association between hypothyroidism and elderly-onset arthritis in patients at national hospital in Peru.

Characteristics	Bivariate analysis			Multivariable analysis		
	PR	95% CI	*p*	PR	95% CI	*p*
Disease duration (years)	0.90	0.85–0.95	<0.001	0.87	0.82–0.93	<0.001
Smoking						
Yes	2.79	0.73–10.58	0.13	4.44	1.37–14.43	0.013
No	Ref.			Ref.		
History of autoimmune disease in first-degree relative						
Yes	2.27	0.85–6.01	0.103	4.80	1.90–12.12	0.001
No	Ref.			Ref.		
Rheumatoid factor	1.00	0.99–1.00	0.154	1.004	1.002–1.005	<0.001
Anti-CCP	1.00	0.99–1.002	0.330	1.00	1.00–1.003	0.616
Hypothyroidism						
Yes	6.16	2.49–15.24	<0.001	9.03	3.17–26.68	<0.001
No	Ref.			Ref.		

conditions share an autoimmunity basis, with common genetic predispositions.[10] Although age is commonly considered a shared risk factor, Bagherzadeh-Fard et al. did not find an association between age and thyroid dysfunction. In contrast, they reported that rheumatoid arthritis remained independently associated with thyroid dysfunction after adjusting for age and sex, suggesting that factors beyond aging may be involved.[11]

Several Mendelian randomization studies have explored the relationship between thyroid function and RA.[12–14] First, most of these studies were conducted in individuals of European ancestry, which limits generalizability to other populations. Second, one study reported a bidirectional relationship between hypothyroidism and RA.[13] Furthermore, there is a study where found some genes that can be involve in the genetic architecture of hypothyroidism and RA (TYK2, IL2RA and IRF5),[14] suggesting that autoimmunity could be a possible explanation for this relationship.

Our Andean cohort adds evidence for an independent association between hypothyroidism and EORA.[9] The coexistence of hypothyroidism and rheumatoid arthritis in elderly patients has been noted decades ago.[15] Aging may play a significant role in this association, as accelerated biological aging and the presence of certain risk factors have linked to an increased susceptibility to RA.[16] Moreover, while not assessed in our study, it is plausible that this finding differs from other studies due to genetic factors such as Amerindian ancestry, which may influence susceptibility.[17] Additionally, some studies have suggested that levothyroxine use could be a potential risk factor for the development of RA, warranting further investigation.[18]

We did not find differences in acute phase reactants, rheumatoid factor, or anti-CCP levels between patients with and without EORA. Previous research has shown mixed results, with some studies indicating higher levels of acute phase reactants and a higher proportion of seronegative results for rheumatoid factor or anti-CCP in patients with EORA.[8] For example, Cho et al. found higher rheumatoid factor and anti-CCP positivity in patients aged 40–59 years compared to those <40 years and >60 years.[7] On the other hand, other markers of inflammation are proposed, such as ESR and CRP, may be influenced by age-related comorbidities, underscoring the need to consider alternative markers like the platelet-to-lymphocyte ratio.[19]

The association between hypothyroidism and EORA has important clinical implications, as it underscores the potential value of routine thyroid function screening in patients with EORA. Early detection of hypothyroidism could enable timely intervention, optimizing the management of autoimmune comorbidities and improving patient outcomes. Furthermore, the observed relationship between hypothyroidism and EORA aligns with the concept of aging-related immune dysregulation, which may enhance susceptibility to autoimmunity in older populations. However, the absence of data on the temporal sequence between the diagnosis of hypothyroidism and the onset of EORA limits our ability to draw causal inferences. Longitudinal studies are needed to confirm these findings, investigate underlying mechanisms, and explore whether thyroid hormone replacement therapy could influence the clinical course of EORA.

This study has some limitations. First, selection bias is possible as the study included patients from a referral hospital in Cusco, which may have a higher concentration of elderly patients with significant comorbidities requiring specialized care. Although no a priori sample-size calculation was performed, a post hoc power analysis showed that the study had sufficient power to detect the observed association; however, more modest associations may have gone undetected. Second, we were unable to determine the temporal relationship between the diagnosis of hypothyroidism and RA, introducing the possibility of reverse causality. Third, the definition of EORA remains somewhat arbitrary, with 60 years being the most commonly used cutoff. Notably, Uchiyama et al. suggested that and optimal cutoff age for defining EORA might vary; in their Japanese cohorts, this age was 73 years in one cohort and 68 years in another. Their definition of EORA included characteristics such as abrupt onset, anti-CCP negativity, and elevated ESR.[20] Fourth, the etiology of hypothyroidism was not documented, which limits to explore the autoimmune aspects of our findings. However, given that Hashimoto's thyroiditis is the most common cause of hypothyroidism,[21] it is reasonable to infer that autoimmunity may play a significant role. Defining the etiology of hypothyroidism in future studies will be essential to better understand its relationship with EORA. Finally, some covariates contained missing data; although valid denominators are reported, residual information bias may persist.

Conclusion

Our results suggest that a history of hypothyroidism is independently associated with EORA in an Andean population with RA from Peru. These findings underscore the potential value of screening thyroid function in patients with EORA, which could facilitate early detection and integrated care strategies. Recognizing and managing this comorbidity may contribute to more comprehensive treatment approaches and improved outcomes for patients with RA.

CRediT authorship contribution statement

Ideation of manuscript was done by PJTLL; drafting of manuscript was done by PJTLL, CDA. Critical revisions were done by all authors. Final approval of version was done by all the authors.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained.

Funding

This study was funded by the "Red Asistencial Essalud Cusco" under the program "Fomento de Desarrollo de Investigación en salud 2023".

Conflict of interest

None declared.

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