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ORIGINAL ARTICLE

An Association between Rheumatoid Arthritis and Scabies Infection: A Population-based Study in Taiwan

Ren-Jun Hsu[1,2,3]*, Jui-Ming Liu[1,4,5]*, Her-Young Su[6], Cheng-Ping Yu[2], Mu-Hsien Yu[6], Jih-Chin Lee[7], Fung-Wei Chang[6]

[1]National Defense Medical Center, Graduate Institute of Life Sciences, [2]Department of Pathology, National Defense Medical Center, Graduate Institute of Pathology and Parasitology, The Tri-Service General Hospital, [3]National Defense Medical Center, Biobank Management Center of the Tri-Service General Hospital, [4]Department of Surgery, Division of Urology, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, [6]Department of Obstetrics and Gynecology, National Defense Medical Center, Tri-Service General Hospital, [5]Faculty of Medicine, National Yang-Ming University, [7]Department of Otolaryngology, Head and Neck Surgery, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan, Republic of China

**These authors contributed equally to this work.*

Background: Scabies is an infectious inflammatory skin disease, and rheumatoid arthritis (RA) is also an immune-medicated inflammatory disease. Immune-mediated inflammatory processes result in the pathophysiologic mechanism in both diseases. Only a few studies have investigated the possible association between scabies and RA. **Methods:** This nationwide population-based study included 5135 patients with scabies as the study group; 19,115 people chosen from the National Health Insurance Research Database of Taiwan formed a control group. We tracked patients in both groups for 7 years to identify newly diagnosed cases of RA. Demographic characteristics and comorbidities were analyzed. Cox proportional hazards regressions were performed to calculate the hazard ratio (HR) of RA during the 7-year follow-up period. **Results:** Of the 24,250 patients enrolled in this study, 217 (0.9%) were diagnosed with RA during the 7-year follow-up period; 61 (1.2%) were from the scabies group and 156 (0.8%) were from the control group. The data showed that patients with scabies had a higher risk of subsequent RA, with an HR of 1.46 (95% confidence interval = 1.09–1.96). **Conclusions:** The results indicated an increased risk for RA among the patients with scabies infections. The data also showed that the assessment of RA symptoms should be included in the long-term follow-up of patients with scabies.

Key words: Rheumatoid arthritis, scabies, National Health Insurance Research Database

INTRODUCTION

Scabies is a pruritic disease caused by a parasitic skin infection. Scabies is easily spread by contact with the mite *Sarcoptes scabiei*.[1-3] About 300 million people worldwide are infected with scabies each year.[4] Those with a lower quality of life have a greater chance of having intensely itchy skin lesions caused by scabies infection. In developing countries, the prevalence rate is high among preschool children, adolescents, and the elderly.[5] However, scabies infection is also more common among nursing home residents, institutionalized patients, and immunocompromised persons.[6-8] The pathophysiology of scabies infection is generated by hypersensitivity-like reactions, followed by immune responses.[9]

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily involves cartilage and bone. It can also affect other organs, including the kidneys, blood vessels, and the lungs. RA affects approximately 0.5%–1.0% of the world's

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Corresponding Author: Dr. Fung-Wei Chang, Department of Obstetrics and Gynecology, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan, Republic of China. Tel: (886)-2-87923311#16738; Fax: (886)-2-6600-0309. E-mail: doc30666@gmail.com

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population.[10] RA patients suffer from fatigue, chronic pain, and functional disability, which leads to a tremendous mental and physical burden.[11,12]

However, a few studies have assessed an association between RA and scabies.[13,14] Our aim during our 14-year study has been to investigate the possible relationship between scabies and RA.

METHODS

Data collection

This nationwide population-based study was authorized by the Institutional Review Board of the Tri-Service General Hospital in Taiwan (approval number: TSGHIRB NO. B-105-06). The data were collected from the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance (NHI) is a special health and medical insurance system program that provides broad health-care coverage to residents of Taiwan. The NHI program was begun in 1995, and covered 99.9% of the 23 million residents until the end of 2013.[15] The NHIRD includes the data of people who have sought medical help; these data include, for example, medical records, prescription records, demographic data, and medical procedures. We randomly selected one million people from the Longitudinal Health Insurance Database 2000 (LHID2000), which is a sub-dataset of the NHIRD.

Study sample

The study population was selected from the LHID2000 from January 2000 to December 2013. All newly diagnosed patients with scabies infection (The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 133.0)[16] from January 2001 to December 2006 were enrolled in the study, and the clinical diagnoses were based on the ICD-9-CM [Figure 1]. Those younger than 20 years of age ($n = 1348$), those with incomplete medical records ($n = 67$), those with a previous history of scabies or RA ($n = 62$), and subjects diagnosed with scabies before January 1, 2001 ($n = 345$) were excluded from the study.

There were 24,250 subjects enrolled in this study, who were assigned to one of two groups, a study group or a control group. A total of 5135 patients with scabies infections were enrolled in the scabies group. The 19,115 nonscabies control subjects were randomized with a ratio of 1:4 by matching them to the subjects with scabies. The nonscabies control subjects were matched to those in the scabies group by gender, age, insured region, and urbanization.

We tracked each subject for 7 years, starting with his or her index date, to identify and evaluate those diagnosed with

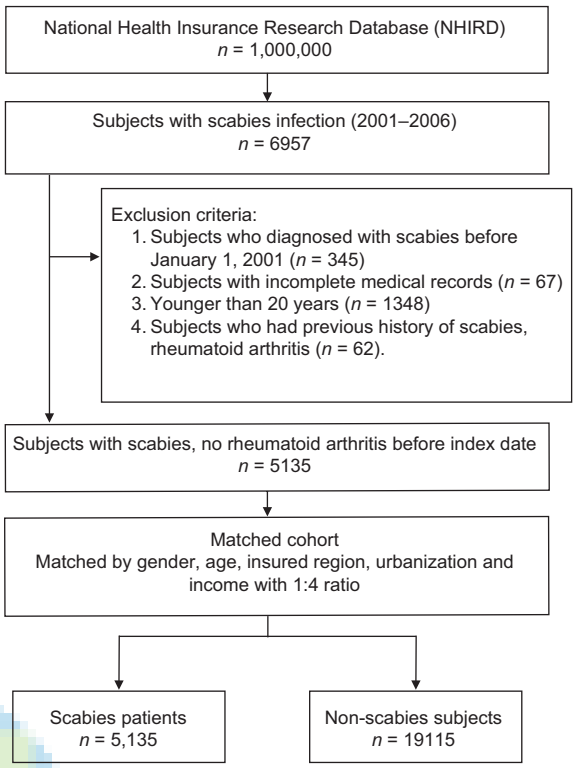

Figure 1: Flowchart of recruitment of subjects from the 1-million random sample of the National Health Insurance Research Database from 2001 to 2006 in Taiwan

RA (ICD-9-CM: 714.0). The diagnosis of RA and scabies was determined by physicians according to the results of the patient history and physical examination. We identified RA patients according to (ICD-9-CM) Code 714.0 and included only patients with RA who had received a catastrophic illness certificate, to ensure that RA diagnoses were valid. Several studies have been published that have examined the epidemiology of systemic autoimmune diseases, particularly RA, by using data from the NHIRD.[17,18] Typical symptoms of scabies, such as inflammatory pruritic papules, severe pruritus, especially at night, burrows, nodules or generalized itching sparing the face, were required for the clinical diagnoses of scabies.[1]

Outcome measures

The results of this study were evaluated by the occurrence and severity of newly diagnosed RA. We analyzed all the medical procedures, medical diagnoses, and prescriptions each subject had received during the 7 years. The diagnosis of RA (ICD-9-CM: 714.0) was made by dermatologists when a patient was admitted to the hospital at least once or if at least two consistent diagnoses of RA had been made in the outpatient department. Covariates such as

age, monthly income, urbanization, and comorbidities were analyzed in both groups. Comorbidities selected in this study included diabetes mellitus (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), hypertension (ICD-9-CM: 401-405), chronic liver disease (ICD-9-CM: 456, 571, 572), chronic obstructive pulmonary disease (ICD-9-CM: 491, 492, 496), cerebrovascular accident (ICD-9-CM: 430-438), chronic kidney disease (ICD-9-CM: 585,586,588), and coronary heart disease (ICD-9-CM: 410-414). Age was categorized in a 10-year interval into 6 groups, as mentioned before. The monthly income, in New Taiwan Dollars (NTD), was divided into four categories: <NTD $20,000; NTD $20,000 through NTD $39,999; NTD $40,000 through NTD $59,999; and >NTD $60,000. Urbanization in Taiwan was classified into four groups. The geographic residential areas of Taiwan were divided into four regions, Northern region, Central region, Southern region, and "other" regions (eastern and outlying islands).

Statistical analysis

The Chi-square test and Student's *t*-test were used to analyze categorical descriptive data, including income, age, demographic characteristics, geography, comorbidities between the scabies patients and nonscabies control subjects, and level of urbanization. The Cox proportional hazards regression model was performed to obtain the effects of potential confounders on the hazard ratios (HRs) of the incidence of RA during the 7-year follow-up period between both study groups. We listed HR accompanying with 95% confidence intervals (CIs). A two-sided $P < 0.05$ was determined to be statistically significant. We used SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis and Microsoft® SQL Server® 2008 software for data management.

RESULTS

A total of 24,250 people were enrolled in this study from January 2001 to December 2006. A total of 5135 patients with scabies infection formed the study group, and 19,115 subjects were controls, in a 1:4 ratio matched with members of the study group. The demographic characteristics of all subjects are illustrated in Table 1. There were 2195 female patients and 2940 male patients with scabies infections. There is no significant difference in gender in this study. The two peak incidences occurred in the age group who were older than 70 years of age, and in the 20–29-year age group. Most patients with scabies infections had low incomes, and those who lived in northern Taiwan and urbanized areas had a higher proportion of scabies infections. The most common comorbidities in patients with scabies were chronic obstructive pulmonary disease, diabetes mellitus, cerebrovascular accident, and hypertension.

There were 217 newly diagnosed cases of RA among the 24,250 study subjects during the 7-year study. Of these, 61 (1.2%) occurred in scabies group and 156 (0.8%) in the control group [Table 2]. The incidence of RA was significantly higher among those in the scabies infection group than among those in the control group. Moreover, the results also indicated that an increased risk of RA in scabies infection was noted with HR 1.46 (95% CI = 1.09–1.96) [Table 3]. After adjusting for gender, age, income, geography, urbanization, and comorbidities, the adjusted HR (aHR) of scabies was 1.09 (95% CI = 1.02–1.47). Male patients (aHR: 0.49; 95% CI = 0.37–0.65) had a lower aHR than female patients. Hypertension (aHR: 1.68; 95% CI = 1.16–2.24), coronary heart disease (aHR: 1.75; 95% CI = 1.27–2.4), chronic liver disease (aHR: 1.71; 95% CI = 1.27–2.4), and chronic obstructive pulmonary disease (aHR: 1.46; 95% CI = 1.07–1.99) were significantly all associated with RA [Table 3].

DISCUSSION

This is the first study to investigate the relationship between RA and scabies. There were 5135 subjects with scabies and 19,115 controls studied for 7 years, with a 7-year follow-up. We found that patients with scabies infections had a 46% increased risk of developing RA.

One of the possible reasons for this increased risk is chronic inflammation. Scabies is an infectious, inflammatory disease, and increasing evidence implicates inflammation as a critical mediator of RA. RA is a chronic immune disorder. The inflamed synovium is infiltrated with $CD4^+$ T-cells, and most of them express several activation markers.[19] RA is thought to be a kind of Th1 disease because peripheral blood or T-cell clones from synovium usually contain the Th1-like phenotype.[20] A Th1 cell generates interleukin 2 (IL-2) and interferon-*r* (IFN-*r*), which causes delayed-type hypersensitivity and activation of macrophages.[21] Scabies infection had also involved those inflammatory processes after infestation by *S. scabiei*.[22-25] Accordingly, it seems that elevations of IL-2 and IFN-*r* have been discovered both in patients with RA and in those with scabies in most studies.

The causal relationship between scabies and RA is still unknown. Pipitone *et al*. reported a case of crusted scabies in a 17-year-old female patient with juvenile RA who was treated with infliximab.[13] Baccouche *et al*. also had reported a case of an 80-year-old woman who had crusted scabies with RA and was treated with tocilizumab.[14] The use of immunomodulatory agents to treat RA may become a risk factor for severe scabies infection. Future studies will be needed to further evaluate the relationship between RA and scabies.

Table 1: Demographic scabies patients and control subjects

Variables	Scabies patients, *n* (%)	Nonscabies persons, *n* (%)	*P*
Total	5135 (100)	19,115 (100)	
Gender			
Female	2195 (42.7)	8131 (42.5)	0.788
Male	2940 (57.3)	10,984 (57.5)	
Age			
20-29	873 (17.0)	3388 (17.7)	0.664
30-39	628 (12.2)	2380 (12.4)	
40-49	705 (13.7)	2662 (13.9)	
50-59	631 (12.3)	2347 (12.3)	
60-69	575 (11.2)	2151 (11.3)	
≥70	1723 (33.6)	6187 (32.4)	
Insured region			
Northern Taiwan	2079 (40.5)	8084 (42.3)	<0.001*
Middle Taiwan	1075 (20.9)	3936 (20.6)	
Southern Taiwan	1769 (34.4)	6687 (35.0)	
Other (Eastern Taiwan and outlying Islands)	212 (4.1)	408 (2.1)	
Urbanization			
1 (highest)	1884 (36.7)	7203 (37.7)	0.193
2	1303 (25.4)	4855 (25.4)	
3	1235 (24.1)	4610 (24.1)	
4 (lowest)	713 (13.8)	2447 (12.8)	
Income NTD[a]			
<20,000	4265 (83.1)	16,184 (84.7)	<0.05*
20,000-39,999	547 (10.6)	1952 (10.2)	
40,000-59,999	242 (4.7)	750 (3.9)	
≥60,000	81 (1.6)	229 (1.2)	
Comorbidity			<0.001*
Diabetes mellitus	1553 (30.2)	3333 (17.4)	<0.001*
Hypertension	2550 (49.7)	6408 (33.5)	<0.001*
Hyperlipidemia	1251 (24.4)	4161 (21.8)	<0.001*
Coronary heart disease	1419 (27.6)	3300 (17.3)	<0.001*
Chronic kidney disease	591 (11.5)	1073 (5.6)	<0.001*
Chronic liver disease	1258 (24.5)	3159 (16.5)	<0.001*
Cerebral vascular accident	1711 (33.3)	2586 (13.5)	<0.001*
Chronic obstructive pulmonary disease	1901 (37)	3171 (16.6)	<0.001*

[a]NTD=New Taiwan dollars, of which 1 US $ = 32 NT$, *$P$<0.05

Limitation

One strength of our study is that it was a large, nationwide, population-based, longitudinal study of the association between scabies and RA. Despite this, there are several limitations. First, all the diagnoses in this study were made with an ICD-9 coding system that was sourced from an administrative database; thus, the database diagnoses may be less accurate than diagnoses made with standardized procedures. Second, we were unable to do further evaluation of inflammatory markers, and laboratory test results are not available in the NHIRD. Laboratory tests may provide more useful information to help researchers find the mechanism involved in the relationship of RA and scabies, although the diagnoses of RA and scabies are established based on the physician's clinical diagnosis under diagnostic criteria.

Table 2: Individuals with and without scabies as predictors of rheumatoid arthritis identified by Cox regression

	Number of individuals	
	Scabies patients (*n*=5135)	Nonscabies control (*n*=19,115)
Rheumatoid arthritis (%)	61 (1.2)	156 (0.8)
Without rheumatoid arthritis (%)	5074 (98.8)	18959 (99.2)
Crude HR	1.46 (1.09-1.96)*	

*P<0.05. HR=Hazard ratio

Table 3: Cox regression analysis of independent predictors of rheumatoid arthritis among scabies patients

	HR (95% CI)
Scabies	1.46 (1.09-1.96)*
Gender	
Female	1
Male	0.48 (0.36-0.63)**
Age	
20-29	1
30-39	1.13 (0.53-2.42)
40-49	2.79 (1.52-5.14)*
50-59	4.03 (2.23-7.26)**
60-69	3.88 (2.13-7.06)**
≥70	2.81 (1.62-4.89)**
Insured region	
Northern Taiwan	1
Middle Taiwan	1.43 (0.98-2.07)
Southern Taiwan	1.65 (1.21-2.27)*
Other (Eastern Taiwan and outlying islands)	2.70 (1.43-5.12)*
Urbanization	
1 (highest)	1
2	1.60 (1.08-2.36)*
3	2.36 (1.65-3.39)**
4 (lowest)	2.42 (1.60-3.66)**
Insured amount NTD[a]	
<20,000	1
20,000-39,999	0.72 (0.44-1.18)
40,000-59,999	0.42 (0.16-1.14)
≥60,000	0.68 (0.17-2.73)
Comorbidity disease	
Diabetes mellitus	2.52 (1.92-3.31)**
Hypertension	3.39 (2.56-4.49)**
Hyperlipidemia	2.83 (2.16-3.70)**
Coronary heart disease	3.31 (2.53-4.33)**
Chronic kidney disease	1.94 (1.29-2.90)*
Chronic liver disease	2.59 (1.96-3.41)**
Cerebral vascular accident	2.08 (1.56-2.78)**
Chronic obstructive pulmonary disease	2.36 (1.79-3.10)**

[a]NTD=New Taiwan dollars, of which 1 US dollar=32 TWD, *P<0.05, **P<0.001. HR=Hazard ratio; CI=Confidence interval

Third, our study using NHIRD data were retrospective in nature; NHIRD data are available for approximately 99% of the 23 million residents currently living in Taiwan. Furthermore, the relationship between RA and scabies is not fully established, due to limitations of the population-based cohort study design. Further prospective studies are warranted to investigate the relationship between scabies and RA, and such studies are essential.

CONCLUSIONS

This nationwide population-based study demonstrated a possible relationship between RA and scabies. The risk of developing RA increased up to 46% among those with scabies infections. In addition, IFN-*r* and IL-2 were identified in both RA patients and those with scabies. In the past, the positive treatment of scabies may have decreased the subsequent risk of RA. In the future, long-term follow-up of patients with scabies will be needed to better assess their RA symptoms.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chosidow O. Clinical practices. Scabies. N Engl J Med 2006;354:1718-27.
2. Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: A systematic review. Lancet Infect Dis 2015;15:960-7.

3. Romani L, Koroivueta J, Steer AC, Kama M, Kaldor JM, Wand H, *et al*. Scabies and impetigo prevalence and risk factors in Fiji: A national survey. PLoS Negl Trop Dis 2015;9:e0003452.
4. Orkin M. Scabies: What's new? Curr Probl Dermatol 1995;22:105-11.
5. Hay RJ, Steer AC, Engelman D, Walton S. Scabies in the developing world – Its prevalence, complications, and management. Clin Microbiol Infect 2012;18:313-23.
6. Scheinfeld N. Controlling scabies in institutional settings: A review of medications, treatment models, and implementation. Am J Clin Dermatol 2004;5:31-7.
7. Downs AM, Harvey I, Kennedy CT. The epidemiology of head lice and scabies in the UK. Epidemiol Infect 1999;122:471-7.
8. Zafar AB, Beidas SO, Sylvester LK. Control of transmission of Norwegian scabies. Infect Control Hosp Epidemiol 2002;23:278-9.
9. Walton SF, Oprescu FI. Immunology of scabies and translational outcomes: Identifying the missing links. Curr Opin Infect Dis 2013;26:116-22.
10. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
11. Rezvani A, Aytüre L, Arslan M, Kurt E, Eroglu Demir S, Karacan I. Affective temperaments in patients with rheumatoid arthritis. Int J Rheum Dis 2014;17:34-8.
12. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, *et al.* The global burden of rheumatoid arthritis: Estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1316-22.
13. Pipitone MA, Adams B, Sheth A, Graham TB. Crusted scabies in a patient being treated with infliximab for juvenile rheumatoid arthritis. J Am Acad Dermatol 2005;52:719-20.
14. Baccouche K, Sellam J, Guegan S, Aractingi S, Berenbaum F. Crusted Norwegian scabies, an opportunistic infection, with tocilizumab in rheumatoid arthritis. Joint Bone Spine 2011;78:402-4.
15. Cheng TM. Reflections on the 20th anniversary of Taiwan's single-payer National Health Insurance System. Health Aff (Millwood) 2015;34:502-10.
16. ICD-9-CM coding and reporting official guidelines. American Hospital Association, American Medical Record Association, Health Care Financing Administration, National Center for Health Statistics. J Am Med Rec Assoc 1990;61 Suppl:1-17.
17. Lai NS, Tsai TY, Li CY, Koo M, Yu CL, Lu MC. Increased frequency and costs of ambulatory medical care utilization prior to the diagnosis of rheumatoid arthritis: A national population-based study. Arthritis Care Res (Hoboken) 2013;27:371-8.
18. Lai CH, Lai MS, Lai KL, Chen HH, Chiu YM. Nationwide population-based epidemiologic study of rheumatoid arthritis in Taiwan. Clin Exp Rheumatol 2012;30:358-63.
19. Panayi GS, Lanchbury JS, Kingsley GH. The importance of the T cell in initiating and maintaining the chronic synovitis of rheumatoid arthritis. Arthritis Rheum 1992;35:729-35.
20. Miltenburg AM, van Laar JM, de Kuiper R, Daha MR, Breedveld FC. T cells cloned from human rheumatoid synovial membrane functionally represent the Th1 subset. Scand J Immunol 1992;35:603-10.
21. Hilliquin P, Allanore Y, Coste J, Renoux M, Kahan A, Menkès CJ. Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case-control study. Rheumatology (Oxford) 2000;39:1020-6.
22. Abd El-Aal AA, Hassan MA, Gawdat HI, Ali MA, Barakat M. Immunomodulatory impression of anti and pro-inflammatory cytokines in relation to humoral immunity in human scabies. Int J Immunopathol Pharmacol 2016;29:188-94.
23. Liu X, Walton SF, Murray HC, King M, Kelly A, Holt DC, *et al.* Crusted scabies is associated with increased IL-17 secretion by skin T cells. Parasite Immunol 2014;36:594-604.
24. Mounsey KE, Murray HC, Bielefeldt-Ohmann H, Pasay C, Holt DC, Currie BJ, *et al.* Prospective study in a porcine model of *Sarcoptes scabiei* indicates the association of Th2 and Th17 pathways with the clinical severity of scabies. PLoS Negl Trop Dis 2015;9:e0003498.
25. Mullins JS, Arlian LG, Morgan MS. Extracts of *Sarcoptes scabiei* De Geer downmodulate secretion of IL-8 by skin keratinocytes and fibroblasts and of GM-CSF by fibroblasts in the presence of proinflammatory cytokines. J Med Entomol 2009;46:845-51.