

## The Association of Smoking with the Extra-Articular Manifestations in Rheumatoid Arthritis Patients

Mohammed Hadi Al-Osami<sup>\*</sup>, Ali Abdul Majid Allawi<sup>\*\*</sup>,  
Tahir Hussein Al-Saadawi<sup>\*\*\*</sup>

### ABSTRACT:

#### BACKGROUND:

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affect all ethnic groups throughout the world, the main characteristic symptom is persistent synovitis of diarthroidal joints often symmetrical resulting in pain, stiffness, and limitation of movement. Smoking is the most established environmental risk factor for development, severity, and extra-articular manifestation of RA.

#### OBJECTIVE:

To assess the association between smoking and appearance of extra-articular manifestation.

#### PATIENTS AND METHODS:

A cross sectional study was conducted on 244 patients with RA meeting the American College of Rheumatology Criteria for the classification of RA. Patients data were obtained via face - to- face interview performed by rheumatologist. RA disease-related data, such as disease duration, drug use (all anti-rheumatic drugs , glucocorticoid use and NSAID's), history of smoking which is classified into current smoker, former Smoker ( patient discontinue smoking for at least three months ), and never smoker , also number of cigarette per day were also recorded. Extra-articular manifestation of RA were assessed in all patient by thorough physical examination, and the patient send for appropriate investigation to confirm the diagnosis.

#### RESULTS:

Among 244 patients with RA, 76.2% were women and 23.8% were men, the females were significantly predominate the study samples ( $P < 0.001$ ). The mean (SD) age are  $46.9 \pm 11.4$ , the age varies with smoking history ( $P = 0.043$ ). It is significant to find that two third of patients (69.3%) not have smoking history ( $P < 0.001$ ) because majority of patients were female. Smoking is significantly increase rheumatoid factor positivity ( $P = 0.013$ ), Smoking is significantly associated with rheumatoid nodules ( $P < 0.001$ ), secondary Sjögren syndrome ( $P < 0.001$ ), and eye involvement ( $P = 0.002$ ), while there is no significant association with other extra-articular manifestations.

#### CONCLUSION:

There is significant association between smoking and RA extra-articular manifestations.

**KEY WORDS :** rheumatoid arthritis, extraarticular manifestation, smokingrh.

### INTRODUCTION:

Rheumatoid arthritis

Definition

RA is a chronic systemic autoimmune

Rheumatoid arthritis is a chronic systemic autoimmune inflammatory disease that affect all ethnic groups throughout the world.<sup>(1)</sup>

The main characteristic symptoms is persistent synovitis of diarthroidal joint, often symmetrical in distribution, resulting in pain, stiffness, and loss of function.<sup>(2)</sup>The

disease process is not only restricted to the joints and associated structures but also associated with development of extra-articular features.<sup>(3)</sup>

Epidemiology

The overall prevalence of RA is 0.5% - 1% and may reach to more than 5 % in some population.<sup>(4)</sup> Definite RA was observed in 1% of population samples in Iraq.<sup>(5)</sup> The prevalence is lowest in black Africans and Chinese, and highest in pima Indian of Arizona.<sup>(6)</sup>

\* Baghdad Teaching Hospital.

\*\*Baghdad College of Medicine, Baghdad Teaching Hospital.

\*\*\* Baghdad College of Medicine.

### Etiology and risk factors

1-Genetics: genetics background contribute disease susceptibility in RA, the concordance rate is highly remarkable in monozygotic twins than dizygotic twins.<sup>(7)</sup>

The strongest gene association considered to be the one of the human leukocyte antigens(HLA) region, particularly HLA-DRB1 gene accounting for about two third of the genetics of RA.<sup>(8)</sup>

The shared epitope is glutamine-leucine-arginine-alanine-alanine, and presence of shared epitope is associated with increase susceptibility and severity of RA.<sup>(9)</sup>

Another significant association is with polymorphism of protein tyrosine phosphatase non receptor 22 (PTPN 22) gene.<sup>(10)</sup>

### 2-Non genetic risk factors

-Female sex: The highest incidence of RA in women occur after menopause when the level of sex hormones decreases, estrogen and progesterone seem to have a suppressive effect on RA disease mechanism.<sup>(11)</sup>

-The use of oral contraceptive pills is associated with decrease incidence of RA, this effect is strongest with pills that have high estrogen content.<sup>(12)</sup>

-Bacteria and viruses: The theory that bacterial or viral infection is etiologically related to RA is tenaciously held despite many false leads and absence of firm confirmatory evidence.<sup>(13)</sup>

-Smoking is considered to have a crucial role in the pathogenesis of many diseases, cigarette smoke represent a mixture of 4000 toxic substances including nicotine, carcinogens, organic compounds, solvents, gas substances, and free radicals.<sup>(14)</sup>

Many data suggest that smoking has modulator role in the immune system contributing to a shift from T-helper 1 to T-helper 2 immune system(Appendix 2), exposure to cigarette smoke result in depression of phagocytic and antibacterial activity of alveolar macrophages.<sup>(15)</sup>

Smoking has been associated with a significant increase in the risk of developing RA, this association has been particularly strong in men and in those with rheumatoid factor positive disease.<sup>(16)</sup>

Smoking is most established environmental risk factors for development of RA.<sup>(17)</sup> One hypothesis on the effect of smoking is that smoking causes citrullination of peptides and in context of RA less than 0.05 considered significant.

study sample ( $P < 0.001$ ). The mean (SD) age are  $46.9 \pm 11.4$ , the age significantly varies with

susceptibility gene contribute to the elicitation of immunity to these citrullinated proteins/peptide and eventually onset of RA.<sup>(18)</sup>

### AIM OF THE STUDY:

To assess the association between smoking and extra - articular manifestation in patients with RA.

### PATIENTS AND METHODS:

#### Study population

A cross sectional study was conducted on 244 patients with RA meeting the American College of Rheumatology Criteria for the classification of RA (Appendix1). All patients were seen in the Department of Rheumatology in Baghdad Teaching Hospital , a tertiary referral center in Iraq between September 2010 and June 2011.

The study was granted full ethical approval from the local ethics committee and all patients gave their informed written consent prior to commencement of the study.

#### Rheumatoid arthritis disease characteristics:

Patients data were obtained via face - to- face interview performed by rheumatologist. RA disease-related data, such as disease duration, rheumatoid factor positivity, drug use (all anti-rheumatic drugs , glucocorticoid use and NSAID's), history of smoking which is classified into current smoker, former smoker (patient discontinue smoking for at least three months), and never smoker , also number of cigarette per day were also recorded.

Extra-articular manifestation of RA were assessed in all patient by thorough physical examination, and the patient send for appropriate investigation to confirm the diagnosis.

#### Statistical Analysis

Statistical Package for Social Sciences version 18 (SPSS 18) was used for data input and analysis. Discrete variables presented as numbers and percentages. Continuous variables presented as mean and standard deviation (SD). Chi square test for goodness of fit used to test the significance of observed distributions. Chi square test for independence used to test the significance of association between two discrete variables. To test the significance of difference in mean for more than one sample; ANOVA test used for normally distributed variables and Kruskal-Willis test used when the distribution was in question. P value used for all tests was asymptotic and two sided. Findings with P value

### RESULTS:

smoking history ( $P=0.043$ ). It is significant to find that two third of patient (69.3%) have no

## EXTRA-ARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS

Descriptive characteristics of study population: Among 244 patients with rheumatoid arthritis, 186(76.2%) were women and 58(23.8%) were men, female significantly predominate

**Distribution of extra-articular manifestations of rheumatoid arthritis according to smoking history.** Rheumatoid nodules show significant association with current smoker 19(35.8%) and with former smoker 9(40.9%), the (P<0.001).

smoking history (P<0.001). (Body mass index show no significant difference among smoking history subgroups, also current and former

Also secondary sjögren's syndrome show significant association especially with current smoker 10(18.9%), (P<0.001) and former smoker 6(27.3%), (P<0.001) also eye problems show significant association with current and former smoker were (P=0.002)

**Table1: Demographic Distribution and clinical characteristics of samples studied.**

	All RA patients	Current Smokers	Former Smokers	Never Smokers	
	N= 244	N= 53	N= 22	N= 169	P
Totals ; %	100.0	21.7	9.0	69.3	<0.001
Age (yr)(M ± SD)	46.9 ± 11.4	50.2 ± 10.7	48.0 ± 10.5	45.7 ± 11.6	0.043

## EXTRA-ARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS

Sex (female); n (%)	186 (76.2)	27 (50.9)	16 (72.7)	143 (84.6)	<0.001
BMI (kg/m <sup>2</sup> ) (M ± SD)	27.3 ± 4.9	27.7 ± 4.8	27.5 ± 5.1	27.1 ± 5.0	0.728
RA Duration (month) (M ± SD)	8.1 ± 7.5	7.7 ± 7.3	7.6 ± 5.4	8.4 ± 7.8	0.891
Cigarettes Packs per day (M ± SD)	1.4 ± 0.7	1.6 ± 0.7	---	---	0.290
Drug Therapy; n (%)					
NSAIDs only	26 (10.7)	7 (13.2)	1 (4.5)	18 (10.7)	0.542
DMARD &/or Corticosteroids	218 (89.3)	46 (86.8)	21 (95.5)	151 (89.3)	
DMARD; n (%)					
Methotrexate	180 (73.7)	42 (79.2)	16 (72.8)	132 (72.2)	0.361
Sulfasalazine	24 (9.8)	8 (15.1)	2 (9.1)	14 (8.3)	0.364
Hydroxychloroquine	39 (16.0)	13 (24.5)	3 (13.6)	23 (13.6)	0.159
Immuran	22 (9.0)	1 (1.9)	3 (13.6)	18 (10.7)	0.110
Corticosteroids; n (%)	110 (45.1)	18 (34.0)	12 (54.5)	80 (47.3)	0.227
N; number, P; P value, %; percent, M; Mean, SD; standard deviation.,					

smoker don't significantly differ in number **148** tra-articular manifestations and smoking cigarette smoked per day as shown in table 1 (P>0.05) as shown in table 2. There is no significant association between other

**Table 2: Distribution of extra-articular manifestations of RA according to smoking history.**

Extra-articular Manifestations	Smoker N=53 (100%)	Former Smoker N=22 (100%)	Nonsmoker N=169 (100%)	P
Rheumatoid nodules	19 (35.8)	9 (40.9)	6 (3.6)	<0.001
Secondary Sjögren's syndrome	10 (18.9)	6 (27.3)	9 (5.3)	<0.001
Eye problem	11 (20.8)	6 (27.3)	12 (7.1)	0.002
Cutaneous Vasculitis	1 (1.9)	0 (0.0)	2 (1.2)	0.539
Felty's syndrome	1 (1.9)	0 (0.0)	1 (1.9)	0.388
Interstitial lung disease, and/or pulmonary fibrosis	0 (0.0)	0 (0.0)	2 (1.2)	1.000

## EXTRA-ARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS

Pericarditis	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Pleuritis and pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	1.000
N; number, %; percent, P; P value, Eye Problem; Scleritis, Episcleritis&/or Keratoconjunctivitis sicca.				

### Distribution of studied samples according to smoking history and rheumatoid factor.

The results shows that the probabilities to have

positive rheumatoid factor significantly increases with smoking history (P=0.013) as shown in table 2.

**Table 3: Distribution of studied sample according to smoking history and rheumatoid factor.**

	Rheumatoid Factor			P
	Positive	Negative	Total	
Smoking History	N (%)	N (%)	N (%)	
Smoker	45 (84.9)	8 (15.1)	53 (100.0)	
Former Smoker	16 (72.7)	6 (27.3)	22 (100.0)	0.013
Nonsmoker	108 (63.7)	61 (36.3)	169 (100.0)	
Total	169 (69.1)	75 (30.9)	244 (100.0)	

### DISCUSSION:

In this study cigarette smoking have been significantly associated with increased risk of rheumatoid factor positive RA compared to non smokers, this finding were similar to other authors<sup>(33,34,35)</sup> findings.

Two-thirds of our patients had had no smoking history, the possible explanation is that the majority of our patients were females, and it is our traditions that the majority of females are non smokers in our population.

Number of cigarette smoking per day may affect intensity of RA but it did not reach statistical significance which is differs from other studies done by Karlson et al<sup>(36)</sup>, and Hutchinson et al<sup>(37)</sup>.

This study found that there is significant association between smoking (current and former) and extra-articular manifestation mainly rheumatoid nodules, secondary Sjögren's syndrome, and eye problem (scleritis, episcleritis, and keratoconjunctivitis sicca) which may show increase number and size of rheumatoid nodules and increase prevalence of secondary Sjögren's syndrome and eye problems among smokers than non smokers, this finding is in agreement with study done by Mikuls et al.<sup>(38)</sup>

Other studies done by Struthers et al<sup>(39)</sup>, and Turrenson et al.<sup>(40)</sup> found that the smoking to be a predictor of vasculitis which is in contrast with our finding were vasculitis not significantly associated with smoking and this is probably due

to decrease prevalence of vasculitis among RA in Iraqi patients<sup>(41)</sup>

The main limitation of our study was the small size of studied sample and being cross-sectional study has limited the correlation regarding the cause and effect relationship between smoking and disease severity.

### CONCLUSION:

There is significant associations between smoking and extra-articular manifestation mainly with rheumatoid nodules, secondary Sjögren's syndrome, and eye problems.

### REFERENCES:

1. Drosos A. Epidemiology of rheumatoid arthritis. *Autoimmune Rev* 2004; 3(suppl. 1):20-22.
2. Stenger A A M E, Van Leeman M A, Houtman M A, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *British J rheum* 1998;37:1157-63.
3. Turesson C, Matteson E L. Extra-articular features of rheumatoid arthritis and systemic involvement. In Hochberg M C, Silman A J, Smolen J C, Weinblatt M E, Weismann M H, eds, *Rheumatology*, 4<sup>th</sup>edn, Mosby Elsevier 2007:773-83.
4. Gabriel S E. The epidemiology to rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:269-81.
5. Al-Rawi Z S, Alazzawi A J, Al-Ajilli F M, et al. Rheumatoid arthritis in population

- 
- samples in Iraq. *Ann rheum Dis* 1978;37:73-75.
6. Doherty M, Lanyon P, Ralston S **150**  
Musculoskeletal disorders. Nicholas A. Boon, Nicki R. Colledge, Brian R. Walker, John A.A. Hunter. *Davidson's Principles and Practice of Medicine*. 20th Edn. Elsevier's Health Sciences Rights Department, 2008;25:1065-44.
  7. Waldenburger J M, Firestein G S. Rheumatoid arthritis, In Klippel J H, Stone J H, Crofford L J, and White P H, eds, *Primer on rheumatic diseases*, 13<sup>th</sup>, New York, USA, Springer science and business media, 2008:122-32.
  8. Bowes J, Barton A. Recent advances in the genetics of rheumatoid rthritis susceptibility. *Rheumatology(oxford)* 2008;47:399-402.
  9. Gregerson P K, Silver J, Winchester R J. The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205- 13.
  10. Gregerson P K. Pathway to gene identification in rheumatoid arthritis: PTPN22 and beyond. *Immunol Rev* 2005;204:74-86.
  11. Rockner Olsson A, Skogh T, Wingren G. Comorbidity and lifestyles, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001;60:934-39.
  12. Symmons D P M. Looking back: Rheumatoid arthritis etiology, occurrence, and mortality. *Rheumatology* 2005;44(suppl. 4):14-17.
  13. MackAY J M K, SIM A K, McCORMIK. Etiology of rheumatoid arthritis: an attempt to transmit infective agents from patients with rheumatoid arthritis to baboons. *Ann Rheum Dis* 1983;42:443-47.
  14. Costenbader K H, karlson E W. Cigarette smoking and autoimmune diseases: what we can learn from epidemiology? *Lupus* 2006;15:737- 45.
  15. Ortega E, Barriga C, Rodriguez A B. Decline in the phagocytic function of alveolar macrophage from mice exposed to cigarette smoke. *Comp ImmunolMicrobiol Infect Dis* 1994;17:77-84.
  16. ZsuzsannaBaka, Edit Buzas, Gyorgy Nagy. Rheumatoid arthritis and smoking: putting the pieces together. *Arthritis and Research Therapy* 2009;11:238.
  17. Klareskog L, Padyukov L, Lorentzan J, et al. Mechanism of disease: genetic susceptibility and environmental triggers in the development of rheumatoid arthritis. *Nat ClinPracRheumatol* 2006;2:425-33.
  18. Karlson E W, Chang S C, Cui J, et al. Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. *Ann Rheum Dis* 2010;69:54- 60.
  19. Hochberg M C, Johnson S S, John A K. The incidence and prevalence of extra-articular and systemic manifestation in a cohort of newly diagnosed patient with rheumatoid arthritis between 1999-2006. *Curr Med Res Opin* 2008; 24:469-80.
  20. Carmana L, Gonzalez-Alvaro I, Balsa A, et al. Rheumatoid arthritis in spain: occurrence of extra-articular manifestation and estimate of disease severity. *Ann Rheum Dis* 2003;62:897-900.
  21. Al-Ghamdi A, Attar S M. Extre-articular manifestation of rheumatoid arthritis: A hospital based study. *Ann Saudi Med* 2009;29:189- 93.
  22. Matthey D L, Dawes P T, Fisher j, et al. Nodular disease in rheumatoid arthritis: association with cigarette smoking and HLA-DRB1/ TNF gene interaction, *J Rheumtol* 2002;29:2313-18.
  23. Ziff M. The rheumatoid nodule. *Arthritis Rheum* 1990;33:761-67.
  24. Voskuyl A E, Zwinderman A H, Westedt M L, et al. Factors associated with development of vasculitis in rheumatoid arthritis: a result of a case-control study. *Ann Rheum Dis* 1996;55:190-92.
  25. Hay E M, Thomas E, Pal B, et al. Weak association between subjective symptoms and /or objective testing for dry eyes and dry mouth: a result from population based study. *Ann Rheum Dis* 1998;57:20-24.
  26. Matsuo T, Kono R, Matsuo N, et al. Incidence of ocular complication of rheumatoid arthritis and the relation to kerato-conjunctivitis sicca to its activity. *Scand J Rheumatol* 1997;26:113-16.
-

## EXTRA-ARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS

27. Wislowska M, Sypula S, Kowalik I. Echocardiographic finding and 24-hr electrocardiographic Holter monitoring in patient with nodular and non nodular rheumatoid arthritis. *Rheumatol Int* 1999;18:163-69.
28. Shannan T M, and Gale E. Non card 151 manifestation of rheumatoid arthritis in the thorax, *Journal of Thorax Imaging* 1992;7:19-29.
29. Boers M, Croneen A M, Dijkmans B A, et al. Renal finding in rheumatoid arthritis: Clinical aspects of 132 necropsies. *Ann Rheum Dis* 1987;46:658-63.
30. Kojima H, Uemura M, Sakurai S, et al. Clinical features of liver disturbance in rheumatic diseases: clinicopathological study with special reference to the cause of liver disturbance. *J gastroenterol* 2002;37:617-25.
31. Bowman S J, Haematological manifestation of rheumatoid arthritis. *Scand J Rheumatol* 2002;31:251-59.
32. Britt-Marie Nyhall-Wahlin, Ingemar F. Petersson, Jan-Ake Nilsson, et al. High disease activity disability burden and smoking predict severe extra-articular manifestation in early rheumatoid arthritis. *Rheumatology* 2009;48:416-20.
33. Kenneth G Saag, James R Cerhan, Sheela Kolluri. Cigarette smoking and rheumatoid arthritis severity. *Ann Rheum Dis* 1997;56:463-69.
34. Matthey D L , Dawes P T, Clarke S, et al. Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. *Arthritis Rheum* 2002;47:403-7.
35. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. *J Rheumatol* 2000;27:630-37.
36. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH: A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum* 1999;42:910-17.
37. Hutchinson D, Shepstone L, Moots R, et al. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001;60:223-27.
38. Mikuls T R, Hughes L B, Westfall A O, et al. Cigarette smoking, Disease severity and autoantibody expression in African American with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2008;67:1529-34.
39. Struthers G R, Scott D L, Delamere J P, et al. Smoking and rheumatoid vasculitis. *Rheumatol Int* 1981;1:145-46.
40. Turesson C, Schaid D J, Weyand C M, et al. Association of HLA-C3 and smoking with vasculitis in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:2776-83.
41. Al-Rawi Z S, Al-Saackarchi H A, Marjana N H, et al, Rheumatoid Arthritis in Iraq. *Rheumatol* 1977;16:128-32.

