Original Article

Clinical Characteristics, Comorbidities, and Sex-related Differences Among Smoking and Non-smoking Patients with Rheumatoid Arthritis: A Matched Case–control Study

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Abstract

Background: Smoking may increase levels of pro-inflammatory cytokines, which is an important contributor to rheumatoid arthritis (RA) pathogenesis.

Objectives: The aim of this study was to describe the characteristics of RA patients who were smokers compared with non-smokers.

Methods: A total of 849 RA patients who were smokers out of a large RA cohort of 10,364 patients (8.2%) were compared to 924 age-, sex-, and body mass index-matched RA patients who were non-smokers. Patients were subjected to full history-taking and clinical examination. Laboratory tests such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were measured. The disease activity score 28 (DAS28) and the health assessment questionnaire (HAQ) score were assessed.

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Results: The mean age among smokers was 46.4 ± 11.3 years, the male–female ratio was 3:1, and the mean disease duration was 6.4 ± 6.2 years. There was a significantly higher frequency of diabetes mellitus, hypertension, and metabolic syndrome in smokers compared to non-smokers (13.7%, 17.1%, and 9.2% vs. 8.4%, 12.9%, and 3.5%; $P < 0.0001$, $P = 0.01$, $P < 0.0001$, respectively), while hypothyroidism was more common in non-smokers ($P = 0.03$). Rheumatoid nodules ($P = 0.03$), oral ulcers ($P = 0.002$), keratoconjunctivitis sicca ($P = 0.043$), and neurological manifestations ($P = 0.002$) were significantly more common in smokers, but the DAS28 was lower (4.2 ± 1.5 vs. 4.8 ± 2.5; $P < 0.0001$). RA-related changes were significantly more common in female smokers than in males. On regression analysis, none of the differences found in the comparison between smokers and non-smokers remained significant.

Conclusions: Smoking in RA patients was found to be associated with a higher frequency of traditional comorbidities, rheumatoid nodules, oral ulcers, sicca complex, and neurological manifestations, but a lower disease activity. There is an obvious sex-driven pattern, with clinical alterations occurring more frequently in female smokers. Higher RF, anti-CCP, and double seropositivity are more observable in males and positive antinuclear antibody in females.

Keywords: Anti-CCP, DAS28, Egypt, rheumatoid arthritis, rheumatoid factor, sex, smoking

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease caused by a combination of environmental and genetic factors. It is more common in females, with a two to three times greater incidence compared with males. However, the onset of RA is highest among those in their sixties, regardless of sex.[1] Anti-cyclic citrullinated peptide (anti-CCP) autoantibodies are found in about 70% of RA patients.[2] A link between smoking and anti-CCP positivity in RA has been reported.[3]

It is important to note that smoking, irrespective of the presence of the anti-CCP antibody, increases the disease susceptibility in individuals with a genetic predisposition.[4] It is well established that smoking raises levels of pro-inflammatory cytokines and interleukin-17 (IL-17), both of which are significant contributors to the pathophysiology of RA.[5] It was stated that smoking could potentially exacerbate disease activity.[6] Current smoking has been deemed a substantial independent risk factor for disease development in early RA, with an increase in the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[7] Furthermore, smoking has long been associated with the existence of rheumatoid factor (RF), even in the absence of RA.[8] In a study of first-degree relatives of patients with RA, smoking was associated with joint tenderness and swelling, even in the absence of RA-related autoantibodies. This finding raises the possibility that smoking may have an early direct joint effect that may be related to the potential upcoming development of RA.[9] This may raise the question of whether smoking duration and/or intensity increase the risk for RA.[10,11]

The aim of this study was to describe the characteristics of patients with RA who were smokers compared with non-smokers, focusing on comorbidities, clinical features, and sex-driven differences in disease presentation and severity.

METHODS

Study design, setting, and participants

This case–control study was conducted from September 2018 to December 2021 and included adult patients with RA (smokers and non-smokers) from multiple university hospitals across Egypt. Patients who were included fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria.[12] Initially, from a large cohort of RA patients ($N = 10,364$), all those who smoked were included in the current study.[13] Then, in a 1:1 ratio, age-, sex-, and body mass index (BMI)-matched non-smoker RA patients were also included from the same cohort.

The study was approved by the Institutional Research Board of the Faculty of Medicine at Mansoura University, Egypt. All participants were informed of the objectives and scope of the research and their rights. Informed written consent was obtained from all participants.

Examinations and definitions

Patients were subjected to full history-taking and clinical examination. The presence of extraarticular manifestations, comorbidities and medications received was recorded. Extraarticular manifestations and comorbidities were defined as follows: rheumatoid nodules were identified as subcutaneous nodules confirmed by clinical examination; oral ulcers as recurrent mucosal ulcers observed clinically;

keratoconjunctivitis sicca/Sjögren's syndrome (KCS/SS) was diagnosed based on dry eyes/mouth, positive Schirmer's test, or anti-SSA/SSB antibodies; neurological involvement included peripheral neuropathy, carpal tunnel syndrome, or cervical myelopathy confirmed clinically or electrophysiologically; gastrointestinal involvement encompassed symptoms confirmed by clinical evaluation or endoscopy; cardiovascular involvement included pericarditis, myocarditis, or vasculitis confirmed clinically or by imaging; chest involvement referred to interstitial lung disease or pleuritis confirmed by imaging; fibromyalgia syndrome (FMS) was diagnosed based on ACR criteria; and renal involvement included glomerulonephritis or amyloidosis confirmed by laboratory tests or biopsy. Comorbidities were defined as diabetes mellitus (fasting glucose ≥126 mg/dL, HbA1c ≥6.5%, or antidiabetic medication use); hypertension (systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or antihypertensive medication use); metabolic syndrome (MetS) (IDF criteria: central obesity plus two of elevated triglycerides, reduced high-density lipoprotein (HDL), elevated BP, or elevated fasting glucose); osteoporosis (T-score ≤-2.5 on DEXA or fragility fractures); hepatitis C virus (HCV) infection (positive HCV RNA or serology); asthma (clinical history and spirometry findings); and hypothyroidism (elevated TSH with or without low free T4, or thyroid hormone replacement use).

Oral ulcers may overlap with other autoimmune conditions, such as SS or lupus, which can coexist with RA or present with similar clinical features. By evaluating oral ulcers, we aimed to capture a broader spectrum of disease manifestations and better understand the systemic impact of RA in smokers versus non-smokers. HCV infection was included due to its association with chronic inflammation and its potential impact on RA progression and treatment outcomes. Asthma was included as a representative respiratory comorbidity, given the well-documented link between smoking and respiratory diseases. These conditions were chosen to provide a comprehensive evaluation of the health profile of smoking versus non-smoking RA patients.

The laboratory investigations performed included complete blood count, ESR, CRP, liver and kidney function tests, HDL, serum uric acid (SUA), RF, anti-CCP, antinuclear antibody (ANA), and anti-double-stranded DNA (anti-dsDNA). In addition, Disease Activity Score (DAS28)[14] and Health Assessment Questionnaire (HAQ) score[15] were assessed.

Statistical analysis

Data were collected on a standardized data sheet and stored in an electronic database. All analyses were carried out using SPSS version 25. Variables were presented as frequencies and percentages or mean and standard deviation. The Mann-Whitney *U*-Test was used to compare two groups, especially for ordinal or non-normally distributed data, while the Chi-square test was used to assess whether there is a significant difference between categorical variables. Logistic regression analysis was considered to verify if any of the significant differences are related to smoking. A P value <0.05 was considered significant.

RESULTS

The study included 1773 RA patients: 849 smokers (636 males and 213 females; male: female 3:1) and 924 matched non-smokers. Eleven patients in both groups had a juvenile-onset RA. The mean duration of RA disease at the time of study participation was 6.3 years. Tables 1 and 2 present the characteristics of the smokers and non-smokers. Most of the neurological manifestations were in the form of carpal tunnel syndrome. Smokers had a higher prevalence of diabetes mellitus ($P < 0.0001$), hypertension ($P = 0.01$), and MetS ($P < 0.0001$) compared to non-smokers. Additionally, certain disease manifestations, such as rheumatoid nodules ($P = 0.03$), oral ulcers ($P = 0.002$), and neurological complications ($P = 0.002$), were significantly more frequent among smokers. Laboratory findings revealed that smokers had significantly lower ESR ($P < 0.0001$) and higher CRP levels ($P < 0.0001$) than non-smokers. Regarding treatment, smokers were less likely to receive hydroxychloroquine ($P < 0.0001$), leflunomide ($P = 0.01$), and biologic therapies ($P = 0.007$).

Sex-based comparison

When comparing male and female smokers, a first-degree family history of RA and a history of HCV infection were observed exclusively in five males. Diabetes and hypertension were significantly more frequent in female smokers compared to males (diabetes: 19.7% vs. 11.6%, $P = 0.003$; hypertension: 24.9% vs. 14.5%, $P = 0.001$). Rheumatoid nodules, oral ulcers, and keratoconjunctivitis sicca were significantly higher in females (11.3%, 5.6%, and 8.9%) compared to males (4.4%, 1.1%, and 7.2%; $P < 0.0001$, $P < 0.0001$, and $P = 0.04$, respectively). Compared to males, in females, DAS28 was higher (4.6 ± 1.3 vs. 4.1 ± 1.5; $P = 0.001$) and hemoglobin level was lower (11.4 ± 1.5 g/dl vs. 12.3 ± 1.7 g/dl; $P < 0.0001$). The HDL was significantly lower in male smokers (55.2 ± 30.5 mg/dl vs. 91.1 ± 48.3 mg/dl; $P = 0.001$), while SUA was higher in female smokers (5.9 ± 1.4 vs. 5.0 ± 1.1; $P = 0.003$). RF, anti-CCP, and double seropositivity were significantly more frequent in male smokers (84.2%, 78.6%, and 70.6%) compared to female smokers (61.1%, 29.9%, and

Table 1: Demographic and clinical characteristics, comorbidities, and disease activity of the rheumatoid arthritis smokers and nonsmokers

Parameter	All RA patients (*N*=1773), *n* (%)	Smoking		*P*
		Yes (*n*=849), *n* (%)	No (*n*=924), *n* (%)	
Age (years), mean±SD	46.4±11.8	46.4±11.3	46.3±12.2	0.84
Sex (male: female)	1330:443	636:213	694:230	0.92
Disease duration (years), mean±SD	6.3±6.3	6.4±6.2	6.3±6.3	0.65
Age at onset (years), mean±SD	40.04±12	40.04±11.7	40.1±12.2	0.99
BMI (kg/m^2), mean±SD	28.7±5.2	29±5	28.5±5.4	0.35
Family history of RA	18 (1.02)	5 (0.59)	13 (1.4)	0.08
Comorbidities				
Diabetes mellitus	194 (10.9)	116 (13.7)	78 (8.4)	**<0.0001**
Hypertension	264 (15)	145 (17.1)	119 (12.9)	**0.01**
Metabolic syndrome	110 (6.2)	78 (9.2)	32 (3.5)	**<0.0001**
Osteoporosis	15 (0.85)	5 (0.59)	10 (1.1)	0.25
HCV infection	12 (0.68)	5 (0.59)	7 (0.76)	0.66
Asthma	6 (0.34)	2 (0.24)	4 (0.43)	0.47
Hypothyroidism	12 (0.68)	2 (0.24)	10 (1.1)	**0.03**
Clinical manifestations				
Rheumatoid nodules	96 (5.4)	52 (6.1)	44 (4.8)	**0.03**
Oral ulcers	23 (1.3)	19 (2.2)	4 (0.43)	**0.002**
KCS/SS	133 (7.5)	65 (7.7)	68 (7.4)	**0.043**
Neurological	136 (7.7)	102 (12)	34 (3.7)	**0.002**
Gastrointestinal	169 (9.5)	91 (10.7)	78 (8.4)	0.08
Cardiovascular	133 (7.5)	71 (8.4)	62 (6.7)	0.09
Chest	95 (5.4)	46 (5.4)	49 (5.3)	0.25
FMS	69 (3.9)	25 (2.9)	44 (4.8)	0.55
Renal	50 (2.8)	17 (2)	33 (3.6)	0.16
DAS28	4.5±2.1	4.2±1.5	4.8±2.5	**<0.0001**
HAQ score	1.1±1.2	0.91±0.66	1.12±1.35	0.074

Bold values are significant at $P<0.05$. BMI – Body mass index; HAQ – Health Assessment Questionnaire; HCV – Hepatitis C virus; KCS – Keratoconjunctivitis sicca; SD – Standard deviation; SS – Sjögren's syndrome; FMS – Fibromyalgia syndrome; DAS28 – Disease activity score; RA – Rheumatoid arthritis

Table 2: Laboratory parameters and medications received by patients with rheumatoid arthritis according to smoking status

Parameter	All RA patients (*N*=1773), mean±SD	Smoking		*P*
		Yes (*n*=849), mean±SD	No (*n*=924), mean±SD	
Hemoglobin (g/dL)	12.1±1.7	12±1.71	12.1±1.67	0.33
TLC (×10^3/mm^3)	7.4±2.5	7.3±2.5	7.5±2.5	0.21
Platelets (×10^3/mm^3)	292.2±98.3	287.2±93.4	294.7±100.5	0.26
ESR (mm/1st h)	45.7±28	41.6±26.1	48.8±28.9	**<0.0001**
CRP (mg/dL)	22.7±37.8	29.4±53.5	18.5±22.3	**<0.0001**
ALT (IU/L)	24.7±14.6	24.8±12.6	24.6±15.5	0.87
Creatinine (mg/dL)	0.86±0.33	0.87±0.38	0.86±0.3	0.54
Cholesterol (mg/dL)	227.2±82.3	234.4±80.3	213±84.8	0.053
Triglycerides (mg/dL)	135.9±60.7	139.1±61.9	132.2±59.7	0.56
HDL (mg/dL)	63.6±38.1	69.7±42.3	55.2±30.02	0.02
LDL (mg/dL)	100.02±39.8	95.5±37.2	105.6±42.6	**0.2**
SUA (mg/dL)	5.2±1.3	5.2±1.2	5.1±1.4	0.8
RF (*N*=1189), *n* (%)	908 (76.4)	368/478 (77)	540/711 (75.9)	0.06
Anti-CCP (*n*=889), *n* (%)	603 (67.8)	248/406 (61.1)	355/483 (73.5)	0.36
DSP (*n*=885), *n* (%)	500 (56.5)	219/406 (53.9)	281/479 (58.7)	0.31
ANA (*n*=466), *n* (%)	57 (12.2)	34/283 (12)	23/183 (12.6)	0.86
Anti-dsDNA (*n*=295), *n* (%)	3 (1)	3/212 (1.4)	0/83 (0)	-
Medications, *n* (%)				
Steroids	789 (44.5)	285 (33.6)	504 (54.5)	0.94
Methotrexate	1193 (67.3)	546 (64.3)	647 (70)	0.4
Hydroxychloroquine	717 (40.4)	299 (35.2)	418 (45.2)	**<0.0001**
Leflunomide	523 (29.5)	178 (21)	345 (37.3)	**0.01**
Sulfasalazine	34 (1.9)	9 (1.1)	25 (2.7)	0.39
Azathioprine	12 (0.68)	4 (0.47)	8 (0.87)	0.4
Biologics	103 (5.8)	29 (3.4)	74 (8)	**0.007**

Bold values indicate statistical significance at $P<0.05$. TLC – Total leucocytic count; ESR – Erythrocyte sedimentation rate; CRP – C-reactive protein; ALT – Alanine transaminase; HDL – High-density lipoprotein; LDL – Low-density lipoprotein; SUA – Serum uric acid; RF – Rheumatoid factor; Anti-CCP – Anti-cyclic citrullinated peptide; DSP – Double seropositivity; ANA – Anti-nuclear antibody; SD – Standard deviation; RA – Rheumatoid arthritis

23.6%; $P < 0.0001$ for all). ANA was frequently more positive in female smokers (18.9% vs. 6.4%; $P = 0.002$). A positive anti-dsDNA was present only in three males. Other parameters were comparable. Demographic, clinical characteristics, disease manifestations, laboratory data, and medications use stratified by sex are presented in Tables 3 and 4.

On regression analysis, none of the differences found in the comparison between smokers and non-smokers remained significant.

DISCUSSION

The association between smoking and RA is widely recognized.[16] Research indicates that long-term smoking increases the risk of RA.[17] Among the pathophysiological mechanisms that are involved are oxidative stress, apoptosis, a state of proinflammatory inflammation, the formation of autoantibodies, and the interplay between genetic factors.[16]

In the present study, RA patients who were smokers had a significantly higher frequency of diabetes mellitus, hypertension, and MetS. An elevated risk of cardiovascular events was observed in smokers in comparison to non-smokers.[18,19] A potential correlation between smoking and MetS and its risk factors, such as central obesity, decreased HDL cholesterol, elevated triglycerides, blood pressure, and fasting plasma glucose, has been suggested.[20] Smoking is not only a significant cardiovascular risk factor, but it also exacerbates or promotes thyroid, digestive, renal, and bone diseases.[3] Hypothyroidism was significantly increased in the current non-smoking RA patients. The relationship between thyroid function and smoking is not well understood. Smokers have reduced thyrotropin levels and elevated thyroid hormone levels, suggesting that smoking is associated with an increased likelihood of developing hyperthyroidism.[21] Indeed, it has been noticed that smoking may have a protective effect on thyroid carcinoma.[3]

Smoking in this study was associated with a higher frequency of rheumatoid nodules, mouth ulcers, KCS/SS, and neurological manifestations. However, these associations became less significant when regression analysis was performed. Smoking has a negative impact on several rheumatic disease-specific outcomes.[19] The association between smoking and extra-articular manifestations is unclear.[19,22] New evidence shows that up to 40% of RA cases are due to exposure to potentially modifiable factors. Among the evidence-based recommendations is to cease smoking.[23] Patients who smoked at the outset of the disease were more severely affected, particularly for rheumatoid nodules.[24] Tobacco smoking is the

Table 3: Demographic and clinical characteristics, comorbidities and disease activity of the rheumatoid arthritis smokers stratified by sex (*N*=849)

Parameter	Smoking		*P*
	Female (*n*=213), *n* (%)	Male (*n*=636), *n* (%)	
Age (years), mean±SD	42.6±11.6	47.7±10.9	**<0.0001**
Disease duration (years) mean±SD	6.7±5.9	6.3±6.4	0.43
Age at onset (years), mean±SD	35.9±11.3	41.4±11.5	**<0.0001**
BMI (kg/m^2), mean±SD	29.5±4.8	28.8±5.0	0.37
Family history of RA	0	5 (0.79)	0.19
Comorbidities			
Diabetes mellitus	42 (19.7)	74 (11.6)	**0.003**
Hypertension	53 (24.9)	93 (14.5)	**0.001**
Metabolic syndrome	17 (40.5)	61 (27.8)	0.10
Osteoporosis	1 (0.47)	4 (0.63)	0.79
HCV infection	0	5 (0.79)	-
Asthma	1 (0.47)	1 (0.16)	0.42
Hypothyroidism	1 (0.47)	1 (0.16)	0.42
Clinical manifestations			
Rheumatoid nodules	24 (11.3)	28 (4.4)	**<0.0001**
Oral ulcers	12 (5.6)	7 (1.1)	**<0001**
KCS/SS	16 (8.9)	52 (7.2)	**0.04**
Neurological	25 (22.1)	77 (15.6)	0.09
Gastrointestinal	10 (9.3)	81 (16.9)	0.05
Cardiovascular	16 (8.3)	55 (10.8)	0.33
Chest	11 (18.3)	35 (13.9)	0.39
FMS	10 (25.0)	15 (10.9)	**0.02**
Renal	6 (10.2)	11 (4.5)	0.08
DAS28	4.6±1.3	4.1±1.5	**0.001**
HAQ score	1.0±0.37	0.88±0.69	0.43

Bold values are significant at $P<0.05$. BMI – Body mass index; HAQ – Health Assessment Questionnaire; HCV – Hepatitis C virus; KCS – Keratoconjunctivitis sicca; SD – Standard deviation; SS – Sjögren's syndrome; FMS – Fibromyalgia syndrome; DAS28 – Disease activity score

Table 4: Laboratory parameters and medications received by patients with rheumatoid arthritis who were smokers stratified by sex (*n*=849)

Parameter	Smoking		*P*
	Female (*n*=213), mean±SD	Male (*n*=636), mean±SD	
Hemoglobin (g/dL)	11.4±1.5	12.3±1.7	**<0.0001**
TLC (×10³/mm³)	6.9±2.5	7.4±2.5	0.12
Platelets (×10³/mm³)	277.0±102.7	291.4±89.2	0.22
ESR (mm/1st h)	40.2±25.8	41.9±26.2	0.48
CRP (mg/dL)	25.4±5	18.5±22.3	**<0.0001**
ALT (IU/L)	24.8±11.5	24.6±12.9	0.67
Creatinine (mg/dL)	0.77±0.29	0.89±0.38	0.08
Cholesterol (mg/dL)	224.9±59.6	236.9±85.1	0.41
Triglycerides (mg/dL)	149.4±61.9	130.6±61.5	0.24
HDL (mg/dL)	91.1±48.3	55.2±30.5	**0.001**
LDL (mg/dL)	100.5±34.4	91.0±39.6	0.32
SUA (mg/dL)	5.9±1.4	5.0±1.1	**0.003**
RF (*n*=478), *n* (%)	91 (61.1)	277 (84.2)	**<0.0001**
Anti-CCP (*n*=406), *n* (%)	43 (29.9)	206 (78.6)	**<0.0001**
DSP (*n*=406), *n* (%)	34 (23.6)	185 (70.6)	**<0.0001**
ANA (*n*=283), *n* (%)	24 (18.9)	10 (6.4)	**0.002**
Anti-dsDNA (*n*=212), *n* (%)	0	3 (2.6)	-
Medications, *n* (%)			
Steroids	50 (68.5)	235 (75.3)	0.23
Methotrexate	83 (74.8)	463 (78.1)	0.44
Hydroxychloroquine	62 (86.1)	237 (82.0)	0.41
Leflunomide	36 (62.1)	142 (48.5)	0.05
Sulfasalazine	1 (33.3)	8 (44.4)	0.72
Azathioprine	0	4 (1.7)	-
Biologics	5 (13.9)	24 (10.4)	0.54

Bold values indicate statistical significance at $P<0.05$. TLC – Total leucocytic count; ESR – Erythrocyte sedimentation rate; CRP – C-reactive protein; ALT – Alanine transaminase; HDL – High-density lipoprotein; LDL – Low-density lipoprotein; SUA – Serum uric acid; RF – Rheumatoid factor; Anti-CCP – Anti-cyclic citrullinated peptide; DSP – Double seropositivity; ANA – Anti-nuclear antibody; SD – Standard deviation

most significant preventable risk factor for periodontitis.[25] In addition to being linked to dryness of the eyes, smoking has a detrimental impact on the precorneal tear film.[26] Former smoking was related to a higher risk of subsequent SS than never smoking.[27] Cigarette smoking is a well-known risk factor for various autoimmune diseases, but its role in SS is uncertain.[28] However, a negative relationship between current smoking and the occurrence of SS among RA patients has been established, as tobacco may decrease the focus score in salivary gland biopsies and perhaps negatively influence the presence of anti-SSA/Ro and/or anti-SSB/La antibodies.[29] A link between smoking and an increased occurrence of carpal tunnel syndrome is also reported,[30] as it impacts the oxygen supply to the median nerve.

Currently, smokers with RA have a higher tendency toward positive RF but not for anti-CCP. Tobacco exposure increases the risk factor for anti-CCP antibodies only in shared epitope-positive patients with RA. The gene–environment interaction between smoking and shared epitope leading to autoantibodies is specific for RA.[31] The association between RF-positive RA and cigarette smoking is well-known. Smoking is associated with a notable risk of causing positive anti-CCP and cytokine balance alterations, which can potentially contribute to the onset of RA in its early stages.[32] Regardless of whether smoking was discontinued after RA diagnosis, active smoking at the onset of RA appears to have a detrimental impact on the progression of the disease and to exacerbate the production of RF.[24] Smoking increases the risk of developing anti-CCP at an early stage, whereas human leukocyte antigen-shared epitope (HLA-SE) alleles mediate symptoms and inflammatory arthritis later on.[33] Additionally, pulmonary lesions associated with RA are associated with elevated anti-CCP levels.[34] The current patients had a long mean disease duration and a low frequency of chest manifestations. The HLA-SE, exposure to tobacco smoke, and the presence of anti-CCP antibodies represent 3 pieces of a pathogenetic puzzle in RA that remain disconnected.[35] Interestingly, anti-dsDNA positivity was present only in smokers. A strong and specific association between smoking and anti-dsDNA positivity has been established.[36]

In the current study, the disease activity and ESR were lower, and the CRP was higher among smokers. No association between the smoking status and the rate or the occurrence of remission has been reported. In the literature, findings are inconsistent, as some studies have found a significant association between smoking and disease activity,[22,37] while others have found no relation.[18,37,38] Similarly, findings in the literature are contradictory regarding the relationship between smoking and CRP.[19,37,39]

In the current study, the HAQ score was comparable between smokers and non-smokers, which is similar to the findings of a previous study that reported no significant correlation between smoking status and functional status.[19] However, studies have indicated the benefits of quitting smoking on RA-related outcomes.[40] In this study, smokers were less likely to receive hydroxychloroquine and biologics, and the significantly lower disease activity could partially explain this. Furthermore, smoking seems to inhibit the therapeutic efficacy of antimalarials,[41] and the response and drug survival to biologic therapy are poorer in heavy smokers.[42]

In general, RA is more common in females than males. This is also the case in the Arab world. A study from UAE reported that among 414 patients with RA, about 80% were females.[43] Similarly, another study that included 895 patients with RA from Jordan, Lebanon, Qatar, Saudi Arabia, and the United Arab Emirates, 85% of the patients were female.[44] In this study, patients were included from a large cohort of 10,364 Egyptian patients with RA, in which the ratio of male to female was 5.4:1. However, smoking was significantly more frequent in males (39.4%) compared to females (2.4%).[13]

Diabetes, hypertension, rheumatoid nodules, oral ulcers, KCS, anemia, and disease activity were significantly higher in female smokers. RF, anti-CCP, and double seropositivity were more frequent in male smokers. However, ANA was frequently more positive in female smokers. Female and male smokers have comparable frequencies of coexisting HCV and hypothyroidism conditions. The presence of KCS was higher in females compared to male smokers (16.4% vs. 8.9%, $P = 0.017$), which may explain the higher ANA frequency in that population. Smoking has several important effects on the immune system and sex hormones that may influence disease pathogenesis.[45] Smoking is a major risk factor for the incidence and severity of RA, especially in seropositive men.[45] However, in a previous study on Egyptian RA patients, secondhand smoking was linked to a higher disease activity in RA female patients.[46]

Limitations

This study cohort lacked sufficient detail to analyze certain confounding variables, such as smoking intensity, duration, and its timing relative to disease onset and prognosis. Additionally, the lower hemoglobin levels observed in smokers could not be fully attributed to common causes such as anemia of chronic disease or iron deficiency, highlighting another study limitation. A longitudinal study incorporating various aspects of smoking exposure is warranted to provide deeper insights into its impact on RA progression and outcomes.

CONCLUSIONS

Smoking was found to be associated with a higher frequency of traditional comorbidities, rheumatoid nodules, oral ulcers, sicca complex, and neurological manifestations, but a lower disease activity. There is an obvious sex-driven pattern, with clinical alterations being more common in female smokers. Lower HDL, higher RF, anti-CCP, and double seropositivity were more in males, while positive ANA was more in females.

Ethical considerations

The study was approved by the Institutional Research Board of the Faculty of Medicine at Mansoura University, Egypt (Approval No. R.24.06.2687). All study participants provided written consent before inclusion in the study. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

All data generated or analyzed during this study are included in this published article.

Author contributions

Conceptualization: H.M.F., S.T, K.E.H., Y.H.A., M.A.A., A.M.I., S.M.E., H.M.E., S.E., T.A.G.; Methodology, all authors; Data analysis: S.T., D.M., S.I.N., M.E.I., G.E., S.S.A., N.S., E.F.M., E.A.A., H.T., F.I., Z.I.S., N.M.G., A.E., O.H., N.H., R.H.M.; Writing–original draft preparation: T.A.G., N.H., S.T.; Writing—review and editing: all authors; Supervision: T.A.G., N.H., S.T.

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Conflicts of interest

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