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COMORBIDITIES IN SMOKING AND NONSMOKING MALE SAUDI PATIENTS WITH RHEUMATOID ARTHRITIS

Abdulsalam A. Noorwali

Department of Internal Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.
Email: aanoorwali@uqu.edu.sa

ABSTRACT

There are a variety of comorbidities with rheumatoid arthritis (RA). Smoking has been associated with the disease activity in patients having RA, and it was found that smoking can promote the risk of RA. Hence, the present case control study was planned for studying the effect of smoking and comorbidities in male Saudi patients with rheumatoid arthritis (N: 410; age range: 40-70 years; smoking RA patients: 230; nonsmoking RA patients: 180), that might help understanding the pathophysiological mechanisms explaining relationship between smoking and RA. The comorbidities in smoking RA vs. nonsmoking RA patients showed significantly increased level ($p < 0.05$) of hypertension, diabetes, coronary artery disease, stroke and other cerebrovascular diseases, chronic obstructive pulmonary disease (COPD) and lung and other respiratory diseases. The current study emphasizes to carry out further studies in large population data.

Key words: Rheumatoid arthritis, smoking, disease activity, comorbidities, disease duration

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic autoimmune disorder (Smolen *et al*., 2018; Deane and Holers, 2021; Gianfrancesco and Crowson, 2021; Yip and Navarro-Millán, 2021; Heluany *et al*., 2022; Nasef *et al*., 2022; Karlsson *et al*., 2023; Kramer *et al*., 2023). Smoking and even passive smoking has been associated with the disease activity in patients having rheumatoid arthritis (RA), and it was found that a major environmental factor, cigarette smoking can promote the risk of RA (Kim and Choe, 2017; Deane and Holers, 2021). Smoking has been found to be associated with factors increasing the risk for the occurrence of rheumatic arthritis (RA) (Deane and Holers, 2021).

There are a variety of investigations including disease activity, disease severity, and complicated outcomes confirmed to be associated with smoking (Papadopoulos *et al*., 2005; Costenbader *et al*., 2006; Di Giuseppe *et al*., 2013; Smolen *et al*., 2018; Deane and Holers, 2021). Even second-hand smoke for those who never smoked might be a potential risk factor associated with the disease activity (Söderlin *et al*., 2013; Gianfrancesco and Crowson, 2021).

Increased characteristics of inflammation were found in dendritic cells in patients with RA, and an association was revealed between smoking and maturation of dendritic cells in RA patients, though with the ethnicity as a major key factor in autoimmune diseases (Prado *et al*., 2018; Yip and Navarro-Millán, 2021). Polymorphisms of genes related to immunity/ inflammation or inflammatory cytokines are found to be related to ethnicity (Kim *et al*., 2014; Nasef *et al*., 2022).

Some of the studies emphasizing on tobacco smoke as a risk factor for RA have demonstrated citrullination as main source of autoantibodies involved in RA (Boissier *et al*., 2012; Kramer *et al*., 2023), DCs (dendritic cells) that may induce Th1/Th17 directed response in RA (Kazantseva *et al*., 2012, and the role of nicotine in enhancing the activation of NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) and hence rising the pro-inflammatory activity of antigen-presenting cells (Heluany *et al*., 2022)

Effect of intense smoking on disease activity in RA patients was investigated and it was revealed that it causes quite a chronic, inflammatory rheumatic disorder that may lead to significant disability (Roelsgaard *et al*., 2017). The Prevalence of RA in general is around 1% (Symmons *et al*., 2002) and the disease course improves with the use of anti-rheumatic drugs for disease modification (Hewlett *et al*., 2012). A report shows that 30 % of RA patients are daily smokers (Loppenthin *et al*., 2015).

Cardiovascular consequences in RA are higher risk of cardiovascular disease (CVD) (John *et al*., 2011), myocardial infarction (Semb *et al*., 2001), ischemic stroke and inflammatory disorders associated with heightened risk of CVD (Liao *et al*., 2009). Other reports indicate the association of smoking with

chronic persistent RA (Svendsen *et al*., 2017), extent of pain, fatigue, fast radiographic progression and other factors related to disease activity (Sokolove *et al*., 2016).

There is a little information about the effect of smoking cessation for patients having RA (Aimer *et al*., 2017. However, it has been revealed that smoking cessation in patients with RA is achievable (Karlsson *et al*., 2023).

The mechanism involved in the process and progression of RA is still not clearly known though smoking is considered a risk factor for the development of RA-an autoimmune disorder with chronic inflammation of joints manifesting low level of soluble programmed death protein 1 (sPD-1) ligand (Wasén *et al*., 2018).

Though the etiology of RA is still uncertain, several risk factors of RA are associated with the combination of environmental and genetic causes (Firestein and Mcinnes, 2017). The environmental cause that has been studied much is cigarette smoking and it has been shown that smoking occurs due to direct stimulation of nicotine receptors (Wasén *et al*., 2017).

It is quite difficult to interpret pathogenesis of RA as it varies from subject to subject. It might, however, be helpful to assess serum autoantibodies rheumatoid factor and serum anti-citrullinated peptide antibodies (Catrina *et al*., 2016). If autoantibodies are positive, it will indicate the worse RA, though due to PD-1 blockade shows positivity for both types of these autoantibodies (Belkhir *et al*., 2017).

The present report was planned for studying the effect of smoking as an environmental factor and comorbidities in male Saudi patients with rheumatoid arthritis, that might help understanding the pathobiological mechanisms explaining relationship between smoking and RA.

METHODS AND MATERIALS

This case control study was carried out to determine the effects of smoking on disease activity in male patients with rheumatoid arthritis (RA). Among a total of 410 male patients with RA (age range: 40-70 years), 230 were smoking RA patients and 180 were nonsmoking RA patients. For the diagnostic purpose, the clinical response was assessed by disease- activity score-28 (DAS28) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (DAS28-ESR and DAS28-CRP) and also by the help of European League Against Rheumatism response criteria. Kit methods were used for measuring ESR and CRP levels. The RA-associated characteristics were assessed including seropositivity, rheumatoid factor-positive, anti-cyclic citrullinated peptide antibody (ACPA), chronic obstructive pulmonary disease (COPD), cutaneous vasculitis, scleritis, pleuritis, rheumatoid nodule, interstitial lung disease, glomerulonephritis and other related manifestations.

Medication for RA patients included synthetic disease modifying anti-rheumatic drug (DMADs), methotrexate, corticosteroids, leflunomide, sulfasalazine, dual DMARD therapy, triple DMARD therapy, quadruple DMARD therapy, biologic agents, tumor necrosis factor inhibitors, tacrolimus, hydroxychloroquine and other effective products.

In the pilot part of this study, the procedures for intervention and prevention were used for counselling sessions with a trained smoking cessation experts based on the principles of motivational counseling. Participants were provided standard care.

Characterization of smoking and nonsmoking male patients with rheumatoid arthritis was carried out and significance (unpaired t-test) was determined from the record of age (years) of the subjects, age at diagnosis of RA (years), and disease duration (years).

The main comorbidities in smoking and nonsmoking male patients with rheumatoid arthritis in number (n) and percentage (%) were compared employing p-value (Chi-Square) for hypertension, diabetes, chronic kidney disease, peptic ulcer/ GIT diseases, coronary artery disease, stroke and other cerebrovascular diseases, lung and other respiratory diseases, other cardiovascular diseases, psychiatric disorders, COPD, solid and metastatic tumors, and blood diseases.

RESULTS

The present study in male smoking and nonsmoking patients with RA showed no significant difference for age (years) and disease duration (years) (Table 1). However, the educational background of the subjects indicated an association with cigarette smoking. Duration of education (years) significantly differed for smoking RA vs. nonsmoking RA (p: 0.0001).

Table 1. General characterization of smoking and nonsmoking male patients with rheumatoid arthritis.

Patient characterization	**Smoking RA** (n: 230)	**Non- smoking RA** (n: 180)	**p-value**
Age (years)	62.52±3.43	62.8±4.33	0.4654
Disease duration (years)	7.84±6.67	7.78±6.58	0.9276
Years of education	11.52±7.84	15.30±6.95	0.0001

All values are mean ± SD, p-value was obtained using unpaired t-test, RA: rheumatoid arthritis

The comorbidities in smoking RA vs. nonsmoking RA patients showed significantly increased level ($p<0.05$) of hypertension, diabetes, coronary artery disease, stroke and other cerebrovascular diseases, chronic obstructive pulmonary disease (COPD) and lung and other respiratory diseases (Table 2). However, other conditions including chronic kidney disease, peptic ulcer/ GIT diseases, cardiovascular diseases except coronary artery disease and hypertension, psychiatric diseases, solid and metastatic tumors, and blood diseases did not manifest any significant variations in the number of subjects in smoking vs. nonsmoking RA patients. Some of the nonsmoking subjects with RA (43 of 180) did not show the obvious conditions/ comorbidities under observation.

Table 2. Comorbidities in smoking and nonsmoking male patients with rheumatoid arthritis.

Comorbidities	**Smoking RA** (n: 230)		**Non- smoking RA** (n: 180*)		**p-value**
	n	%	n	%	
Hypertension	72	31.30	40	22.22	0.0408
Diabetes	43	18.70	20	11.11	0.0347
Chronic kidney disease	19	8.26	20	11.11	0.3296
Peptic ulcer/ GIT diseases	18	7.83	16	8.89	0.6997
Coronary artery disease	17	7.39	4	2.22	0.0186
Stroke and other cerebrovascular diseases	16	6.96	4	2.22	0.0272
Lung and other respiratory diseases	13	5.65	3	1.67	0.0391
Other cardiovascular diseases	9	3.91	8	4.44	0.7895
Psychiatric disorders	9	3.91	10	5.56	0.4309
Chronic obstructive pulmonary disease	7	3.04	0	0.00	0.0184
Solid and metastatic tumors	5	2.17	8	4.44	0.1932
Blood diseases	2	0.87	4	2.22	0.2591

RA: rheumatoid arthritis, *43 of 180 nonsmoking RA did not show the mentioned comorbidities, p-value was obtained using Chi-Square.

DISCUSSION

The present study reveals that smoking might be a major factor at population/ community level responsible for higher disease activity in RA patients and people who never smoke might have good clinical response in RA and they get less severe manifestations and complications.

There are several limitations in our present study. The sample size might not be large enough to draw a clear conclusion. However, it is a case control attempt as done in several previous studies for understanding the impact of smoking in patients with RA (Kim and Choe, 2017; Roelsgaard *et al*., 2017; Gianfrancesco and Crowson, 2021; Karlsson *et al*., 2023). The questionnaire, though quite comprehensive contained mainly the self-reported information, and the required reliability was less.

For the improvement, both qualitative and quantitative parameters were studied including age at diagnosis, duration of disease, disease- activity score-28 (DAS28) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (DAS28-ESR and DAS28-CRP). This approach is quite similar to other reports (Papadopoulos *et al*., 2005; Costenbader *et al*., 2006; Di Giuseppe *et al*., 2013). Further work, however, with a larger sample size and more carefully developed questionnaire is required. As smoking is more prevalent in the general population, an interaction between disease activity in RA and smoking is further needed to be determined in a larger study population.

There are reports revealing association of smoking with RA (Sokolove *et al*., 2016; Svendsen *et al*., 2017; Gianfrancesco and Crowson, 2021; Karlsson *et al*., 2023) similar to the present study. The present approach of studying the role of smoking- a major environmental factor in RA has been emphasized in several studies (Firestein and Mcinnes, 2017; Gianfrancesco and Crowson, 2021; Karlsson *et al*., 2023), though it is quite difficult to interpret according to pathogenesis of RA as it varies from subject to subject, direct nicotine receptor stimulation has been implicated in smoking (Wasén *et al*., 2017; Heluany *et al*., 2022).

The current study emphasizes carrying out further case control studies in large enough population data for evaluating and understanding the pathobiological mechanisms explaining relationship between smoking and RA. Even the interactions of smoking with other toxic environmental factors may increase the risk of developing RA and more dangerous and hazardous consequences in general population.

The present hypothesis and suggestion for future management is that an intensive smoking cessation intervention be established that would contribute much for smoking cessation in patients with RA, and could then lead to a reduction in disease activity in RA.

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