Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients?

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Abstract

Objective

To investigate the association of cigarette smoking with clinical expression, disease activity and severity in a cohort of Greek patients with early rheumatoid arthritis (RA).

Methods

From January 1993 until December 2002, 293 patients with early RA were diagnosed and followed up in our rheumatology clinic. All patients fulfilled the American College of Rheumatology criteria for RA, had disease duration of less than one year, without prior treatment of disease modifying anti-rheumatic drugs (DMARDs) or steroids. The patients were treated with at least one DMARD, and 287 of them had a last follow up during the year 2004. The demographic, personal, clinical, laboratory, radiological and therapeutic features were compared at entry and at the last follow-up, according to their smoking habits at entry.

Results

Among the 293 patients, 6 were lost to follow-up, thus 287 patients were evaluated. There were 200 females (67.7%) and 87 males (30.3%). Eighty-two (28.6%) were current smokers, 21 (7.3%) ex-smokers and 184 (64.1%) non-smokers at presentation. RA smoker patients displayed the disease at a younger age than the non-smokers. Additionally, the smokers presented at disease onset more prominent features of articular involvement as was evaluated by the higher number of total joint count with tenderness and swelling and by the higher disease activity for 28 joint indices score (DAS-28). Smokers also presented a higher Larsen's score and higher frequency of IgM and IgA rheumatoid factors as compared to non-smokers. At the end of the study, the smoker patients presented more active and severe disease as evaluated by the higher total number of tender and swelling joint count, the higher DAS-28, and higher Larsen's score as compared to non-smokers. Furthermore, the smokers more frequently had rheumatoid nodules than the ex-smokers and non-smokers. The association of smoking with disease activity and severity was independent of sex, age, educational level, alcohol consumption, and follow-up duration. Finally, no significant differences were observed concerning the therapeutic procedure among the three groups.

Conclusions

In our early RA patients, cigarette smoking was associated with increased disease activity, and severity, independently of several other possible confounders and despite the early disease treatment.

Key words

Early rheumatoid arthritis, cigarette smoking, DAS-28, Larsen's score, activity, severity.

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Introduction

Cigarette smoking has been suggested as a possible cause of rheumatoid arthritis (RA) and other autoimmune diseases (1-3). Several epidemiological studies have provided strong indications that cigarette smoking is a risk factor for developing RA particularly in men (1, 2, 4-7). The impact of smoking on disease activity, severity and outcome remains uncertain, although some recent studies suggest that smoking habits may be related to RA severity (8-10). On the other hand, disease severity may influence smoking habits, which may lead to a false lack of association between smoking and disease severity in cross sectional studies. Thus a more accurate picture would be gained by studying the effect of smoking on disease outcome among the patients followed prospectively, with an ascertainment of their smoking status close to disease onset. It would also be interesting to compare the effect of other confounders and the response to disease modifying anti-rheumatic drugs (DMARDs) in smokers and non-smokers, both of which may influence the disease outcome. A number of psychosocial and personal factors could act as confounders when studying the association of smoking with RA severity (11-14). Thus, smokers are more likely to be male and younger in age than non-smokers. Some life style and socioeconomic characteristics could also be related to smoking, as well as to RA severity. These factors include alcohol consumption, education level, socioeconomic status, diet and others (11-14). As a consequence, it is important to study the possible association of smoking with RA severity and outcome, independently of those possible confounders.

In addition, most of the studies published on this field were based on patients with established RA, in whom the association of smoking with disease severity was assessed cross-sectionally (8-10). Those studies are subject to several potential biases, such as misclassification of exposure to smoking, or under representation of very mild or very severe disease. Therefore, it is important to investigate this association in patients who presented with early RA.

Another important issue is related to the fact that smokers are known to present a higher frequency of positive rheumatoid factor (RF) than non-smokers. As a consequence, differences in disease activity and severity observed between smoking and non-smoking patients, may be explained by this association. Therefore, it would be of interest to examine disease activity and severity separately for seropositive and seronegative patients.

In this report we investigate the association of smoking with disease expression, activity and severity in a cohort of patients with early RA with respect to possible confounders, which could influence the association studied. In our analysis we consider as main indicators of disease severity and activity, the DAS-28 score and Larsen's score at baseline, and DAS-28 score, Larsen's score and presence of rheumatoid nodules at the last follow-up.

Materials and methods

From January 1993 until December 2002, 293 patients with early RA were diagnosed and followed up in the outpatient rheumatology clinic of the University Hospital of Ioannina. All patients fulfilled the American College of Rheumatology criteria for RA at entry (15), and had a disease duration of less than one year without prior treatment of DMARDs or steroids. Patients were treated with at least one DMARD, and 287 of them had a last follow-up during the year 2004.

The demographic and personal parameters considered at baseline included: age at the time of diagnosis, age at disease onset, gender, disease duration, educational level, smoking habits and alcohol consumption. Data on smoking and alcohol consumption were collected through a standard questionnaire applied to all patients in our clinic since 1992. Patients' smoking habits were evaluated at presentation. We considered as ex-smokers all patients who had stopped smoking at least one year before the first examination. Information about pack-years of smoking was collected for current and ex-smokers.

The clinical, laboratory and radiologi-

cal features were compared at entry, and at the last follow-up. The clinical variables included the total joint count for tenderness and swelling. To assess disease activity, the disease activity for 28 joint indices score (DAS-28) was calculated for each patient (16). The following extra-articular manifestations were considered: anemia of chronic disease (17), secondary Sjögren's syndrome (18), skin vasculitis, Raynaud's phenomenon, subcutaneous nodules. No patients in our study cohort had Felty's syndrome.

Laboratory variables included: the erythrocyte sedimentation rate (ESR) (Westergren method), C-reactive protein (CRP) (nephelometric method), IgM RF (Latex agglutination test, positive if patients had titers > 1/40) and IgA RF determined by an enzyme linked immunoabsorbent assay (positive if patient had > 20 IU).

The radiological findings were evaluated by the Larsen score method measuring the radiological damage on hands and wrists x-rays (19).

All data concerning the clinical, laboratory, therapeutic, demographic and personal characteristics have been extracted from medical records of our Rheumatology clinic, by two specialized rheumatologists, according to a precise research protocol. All the above parameters were compared between smokers, ex-smokers and never smokers, at baseline and at the last follow-up.

Statistical analysis

Statistical comparisons among the groups were conducted using the $\chi 2$ test for categorical parameters, or analysis of variance for continuous parameters. Logistic regression analysis was conducted to examine the independent association of smoking status with disease activity and severity. The analysis was done adjusting for age, sex, years of education, and alcohol consumption at presentation, and adjusting for age, sex, DAS-28 score at baseline, Larsen's score at baseline, RF IgM, RF IgA and follow-up duration at the end of the study. Smoking status at presentation was classified as current smokers and never smokers. Ex-smokers were not included in the analysis because of the small number of patients in this group. Smokers were also classified according to number of pack-years into three groups (0-9, 10-19, ≥20). Regression analysis was conducted using the DAS-28 score and the Larsen score as outcome measures, at presentation and at the end of the study. These outcomes were measured as continuous parameters, and ordinal regression techniques were used, by dividing these parameters into three categories by tertiles. At the end of the study, rheumatoid nodules were also used as an outcome measure, and binary regression analysis was conducted for this dichotomous parameter.

Results

Among the 293 early RA patients, 6 were lost to follow-up, thus 287 patients were evaluated. No deaths were noted during the study. There were 200 females (69.7%) and 87 males (30.3%). Eighty-two (28.6%) were current smokers at presentation, 21 (7.3%) were ex-smokers and 184 (64.1%) were never smokers. Current treatment consisted of: 210 patients were on methotrexate (MTX) (12.5-20.0 mg/week) plus prednisone (< 7.5 mg/day); 32 patients were on MTX (12.5-15.0 mg/week) plus cyclosporine A (2.5-3.0 mg/kgr/day) plus prednisone (<7.5 mg/day); 30 patients were on leflunomide (20 mg/day) plus prednisone (<7.5 mg/day). Finally, 15 patients were on MTX (12.5-17.5 mg/ week) plus infliximab (3 mg/kgr at week 0, 2, 6 and every 8 weeks thereafter).

Among current smokers, 12 smoked less than 20 cigarettes per day, 60 smoked between 20-40 and 10 patients smoked over 40 cigarettes per day. The majority of current smokers was male and seemed to develop RA at a younger age. There were statistically significant differences among current smokers, never smokers and ex-smokers concerning the level of education and alcohol consumption (Table I).

The clinical and laboratory parameters at disease presentation and at the last follow-up are presented for current smokers, ex-smokers and never smokers in Table II. All parameters studied differ significantly among the three groups, and current smokers present more active and severe disease than ex-smokers, and never smokers as evaluated by tender and swollen joint count, DAS-28, CRP, ESR, Larsen's score, and seropositivity. In addition, the ex-smokers presented higher levels than the never smokers for all these parameters. At the last follow-up the picture was similar, with the exception of ESR, which did not differ significantly between the groups.

Concerning the extra-articular manifestations at presentation, the current smokers presented more frequently rheu-

Table I. Baseline demographic, personal and clinical data in relation to smoking status among 287 patients with early RA.

	Current smokers n = 82	Never smokers n = 184	Ex-smokers n = 21	p value
Age at disease onset (years) (mean ± SD)	52.0 (13.3)	56.6 (17.0)	59.6 (13.0)	< 0.05
Disease duration (months) (mean ± SD)	0.7 (0.4)	0.8 (0.3)	0.7 (0.3)	NS*
Female/male	0.5	10.5	6	< 0.001
Follow up duration	46.8 (37.9)	45.1 (33.6)	40.8 (30.0)	NS
Level of education				
< 6 years	23 (28.0)	95 (51.6)	7 (33.3)	
≥ 6 years	59 (71.9)	89 (48.4)	14 (66.7)	< 0.05
Frequency of drinking				
< 1 glass daily	50 (61.0)	176 (95.7)	17 (81.0)	
≥ 1 glass daily	32 (39.0)	8 (4.3)	4 (19.0)	< 0.05

*Not statistically significant.

Table II. Clinical and laboratory findings in patients with early RA at presentation and at the last follow-up.

	Current smokers n = 82	Never smokers n = 184	Ex-smokers n = 21	p values
At presentation				
Tender joint count (mean ± SD)	17.09 (6.2)	9.38 (4.31)	12.05 (7.13)	< 0.001
Swollen joint count (mean ± SD)	12.13 (4.58)	6.10 (3.16)	7.38 (5.16)	< 0.001
DAS-28 (mean ± SD)	6.82 (0.74)	5.42 (0.74)	5.97 (0.96)	< 0.001
ESR (mm/1st hour) (mean ± SD)	61.22 (25.37)	48.16 (26.87)	56.76 (32.42)	< 0.001
CRP (mg/l) (mean ± SD)	43.23 (22.09)	26.46 (23.94)	38.57 (29.93)	< 0.001
Larsen's score (mean ± SD)	23.63 (10.84)	13.06 (10.42)	14.33 (10.59)	< 0.001
IgM RF (%)	69 (84.1)	60 (32.6)	12 (57.1)	< 0.001
IgA RF (%)	70 (85.4)	34 (18.5)	6 (28.6)	< 0.001
Last follow up				
Tender joint count (mean ± SD)	4.79 (4.46)	2.94 (3.54)	3.71 (3.54)	< 0.001
Swollen joint count (mean ± SD)	2.76 (2.77)	1.14 (1.99)	1.81 (2.58)	< 0.001
DAS-28 (mean ± SD)	4.37 (1.13)	3.46 (1.13)	3.64 (1.41)	< 0.001
ESR (mm/1st hour) (mean ± SD)	37.61 (29.08)	32.10 (20.93)	29.38 (18.00)	NS*
CRP (mg/l) (mean ± SD)	24.6 (20.74)	10.34 (14.37)	14.57 (14.29)	< 0.001
Larsen's score (mean ± SD)	32.37 (18.96)	17.11 (12.50)	19.10 (11.23)	< 0.001

*Not statistically significant.

Table III. Smoking and extraarticular manifestations in patients with early RA.

Extraarticular manifestations	Current smokers n = 82	Never smokers n = 184	Ex-smokers n = 21	p values
Rheumatoid nodules	33 (40.2)	9 (4.9)	1 (4.8)	< 0.001
Anemia of chronic disease	29 (35.4)	72 (39.1)	8 (38.1)	NS*
Raynaud's phenomenon	11 (13.4)	26 (14.1)	2 (9.5)	NS
Sjögren's syndrome	9 (11)	29 (15.8)	0	0.09
Skin vasculitis	5 (6.1)	3 (1.6)	0	NS
Any manifestation	56 (68.3)	110 (59.8)	9 (42.9)	0.09

*Not statistically significant.

matoid nodules, than the ex- and never smokers (Table III).

Logistic regression analysis adjusted for sex, age, education level, and alcohol consumption, showed an independent and statistically significant association of current smoking with DAS-28 score and Larsen's score at presentation. Patients presented with 20 or more pack years of smoking showed the strongest association (Table IV). This association was observed in both seropositive and seronegative patients for DAS-28, but only for IgM seropositive patients for Larsen score. There was no independent association of alcohol consumption or educational level with outcome measures. Thus, the respective odds ratios are not shown.

Table V presents the results of regression analysis at the end of the study, after adjustment for age, sex, follow up duration, DAS-28 and Larsen's score at baseline and presence of rheumatoid factor. No independent significant association with smoking status was observed.

Discussion

A significant number of studies have suggested that smoking is a risk factor in the susceptibility to RA (1, 2, 4-7). However, there have been a few investigators who have provided evidence of the impact of smoking on disease outcome. Recent studies have suggested that heavy smoking may influence overall RA severity (8-10). Smoking is known to have important effects on the immune system and on the sex hormones that may influence disease activity in RA. However, these effects are complex and may differ under different circumstances (1, 20).

The results of previous studies investigating the possible association between smoking and articular disease in RA are controversial. Studies carried out among individuals without RA, as well as among RA patients have shown that smokers have an increased probability to be RF positive. The association between smoking and joint inflammation remains uncertain. Concerning the extraarticular manifestations of the disease, previous studies suggest that smokers are more likely to develop rheumatoid nodules, as well as rheumatoid vasculitis and interstitial lung disease (9, 21).

Several confounding factors can be implicated in the study of the role of smoking in RA severity. Smokers are more likely to be male or to belong to a younger age group. On the other hand, age and sex have been suggested to influence the disease expression independently (22, 23). This is also the case for some socioeconomic factors and lifestyle characteristics, which could be related to smoking and also to RA severity. Those factors include alcohol consumption, diet, physical activity, educational level, and social class (11-14).

It has been suggested that the association between smoking and RA severity could be different in early RA than in established disease. In established RA, smoking could interact with immunologic, hormonal, psychosocial, comorbid and therapeutic factors in a different way compared to early disease, having a significant influence on disease outcome. (21).

The results of the present study suggest that cigarette smoking was associated with disease activity and with higher radiological damage, in a cohort of patients with early RA. This association was independent of possible confounders like gender, age, level of education, and alcohol consumption. Our results are similar to those reported by Saag, Wolfe and Masdottir who noted that smokers had higher levels of radiological damage (8-10) and differ somewhat from those of Harrison's, who reported a trend towards lower radiological damage in long-standing smokers (21). However, the studies published on this

Table IV. Association of smoking status with clinical outcomes in 287 patients with early RA at presentation (adjusted for sex, age, education, and alcohol consumption).

	DAS-28 score OR (95% CI)			Larsen score OR (95% CI)		
Smoking status	RF IgM positive	RF IgM negative	All patients	RF IgM positive	RF IgM negative	All patients
Never smokers	1	1	1	1	1	1
Current smokers	2.7 (1.6-3.8)	4.7 (2.9-6.4)	3.5 (2.6-4.4)	2.1 (1.1-3.1)	1.4 (0.1-2.7)	2.2 (1.5-3.0)
1-9 pack years	2.3 (1.0-3.6)	3.0 (1.3-4.7)	2.7 (1.7-3.7)	1.3 (0.1-2.5)	0.7 (0.1-2.6)	1.1 (0.3-2.0)
10-19 pack years	1.8 (0.5-3.1)	5.0 (2.5-7.5)	2.7 (1.6-3.7)	1.7 (0.5-2.9)	3.0 (1.1-5.0)	2.1 (1.1-3.1)
≥ 20 pack years	3.5 (2.1-4.9)	4.8 (2.2-7.4)	4.0 (2.9-5.1)	2.7 (1.4-4.0)	0.9 (0.1-2.3)	2.5 (1.6-3.5)
	DAS-28 score OR (95% CI)			Larsen score OR (95% CI)		
Smoking status	RF IgA positive	RF IgA negative	All patients	RF IgA positive	RF IgA negative	All patients
Never smokers	1	1	1	1	1	1
Current smokers	2.2 (1.0-3.5)	3.4 (1.9-4.9)	3.5 (2.6-4.4)	1.9 (0.7-3.1)	0.8 (0.1-2.0)	2.2 (1.5-3.0)
1-9 pack years	2.4 (0.8-3.9)	2.5 (1.1-3.9)	2.7 (1.7-3.7)	1.3 (0.1-2.7)	0.9 (0.1-2.1)	1.1 (0.3-2.0)
10-19 pack years	1.8 (0.4-3.2)	2.9 (0.8-4.9)	2.7 (1.6-3.7)	1.6 (0.3-2.9)	1.8 (0.1-3.6)	2.1 (1.1-3.1)
≥ 20 pack years	2.6 (1.1-4.1)	4.3 (1.5-7.0)	4.0 (2.9-5.1)	2.2 (0.8-3.6)	0.2 (0.1-2.1)	2.5 (1.6-3.5)

field present several methodological differences, as concerning the data collection, the parameters studied, the selection of RA patients, and the statistical analysis. As a consequence it is difficult to interpret and compare the available data.

The mechanism by which smoking could influence RA activity and severity is unclear at present. However, smoking may have direct effects on the disease process by inducing and/or increasing the production of RF or by activating the immune system (20). In fact, in population studies of individuals without RA, smoking was associated with RF production (24, 25). Similarly, studies of RA patients have shown that smokers are significantly more likely to be RF positive (7-9). This association appears strongest for the IgA RF isotype (10, 26). On the other hand, several studies have shown that RF is the major predicting factor for increasing the severity of radiographic erosions in RA patients (27-31). In our patients the frequency of RF was significantly higher among smokers, as expected. However, DAS-28 score was significantly associated with smoking status for both seropositive and seronegative patients at presentation. This finding could be related to the fact that smoking is an important contributor for immune dysfunction with abnormalities in T-lymphocytes (32), a reduction in natural killer cells (33), and alterations in cell-mediated immunity (34).

In this study we used data concerning the clinical, laboratory, demographic and personal characteristics which have been extracted from medical records of our Rheumatology clinic. The patients were seen according to their need for visits in the clinic. For this reason we analyzed data available only at baseline and at the end of the study. These methodological issues put some limitations on the interpretation of our results. However, all patients included in the analysis had a last visit with a complete examination during 2004, considered as the last follow-up. Only six patients were lost to this last follow-up. In addition, all the patients attending our clinic had a relatively complete examination following a standard protocol at presentation. As a consequence, we consider that the data extracted from the medical records are valid enough.

Another methodological issue is related to the definition of the smoking status, which is based on a questionnaire administer to each patient. We do not know to what extent this information is exact. In addition, we do not have information about changes in smoking habits during the follow-up period. However, we consider that our approach to smoking habits gives a relatively valid picture of the smoking status for each patient up to presentation.

Our results suggest that in early RA patients, cigarette smoking is associated with increased disease activity and radiological damage, independently of several possible confounders and despite the early disease treatment. We are keen to examine whether this association persists at longer follow-up times in our cohort. Further prospective studies in early RA are needed to confirm this association and more work is needed on the influence of cigarette smoking on the immune system.

Table V. Association of smoking status with clinical outcomes in 287 patients at last follow up (adjusted for sex, age, DAS-28 at baseline, Larsen score at baseline, RF IgM, RF IgA, and follow up duration).

Smoking status	DAS-28 score OR (95% CI)	Larsen score OR (95% CI)	Nodules OR (95% CI)
Never smokers	1	1	1
Current smokers	1.1 (0.2-1.9)	1.4 (0.3-2.4)	0.9 (0.4-1.9)
1-9 pack years	0.9 (0.2-1.8)	0.5 (0.1-1.6)	0.4 (0.6-2.0)
10-19 pack years	0.5 (0.1-1.5)	1.0 (0.2-2.3)	1.0 (0.2-4.9)
≥ 20 pack years	1.3 (0.3-2.3)	2.1 (0.8-3.4)	1.1 (0.2-6.1)

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