The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis

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Objective. To study the effect of tobacco smoking and rheumatoid factor (RF) isotypes on disease activity and joint damage in early rheumatoid arthritis (RA).

Methods. One hundred early RA patients were followed prospectively for 2 yr. They were evaluated at recruitment and at 6 and 24 months. Sociodemographic information included smoking history, and radiographs of hands and feet were obtained. RF was monitored by IgM- and IgA-specific RF enzyme-linked immunosorbent assay and by agglutination, and serial measurements were also obtained for C-reactive protein. The influence of tobacco smoking and RF positivity on disease outcome was evaluated using multivariate analysis. Covariates for the regression analysis included sex, age, coffee consumption and IgA-RF positivity.

Results. A gradient of increase in disease activity was observed from never smokers to former smokers to current smokers during the 2 yr of observation, defined by number of swollen joints (SJC), tender joints (TJC) and visual analogue scale for pain (P<0.001, P=0.02 and P=0.005, respectively), but smoking status did not influence radiological progression. Ever smokers were more often IgA RF positive (P<0.05). IgA RF-positive patients had more active disease (SJC P=0.002, TJC P=0.01) and showed more radiological progression (P<0.0001) compared with IgA RF-negative patients. Of the RF-positive patients 22% had elevated IgM RF without IgA RF and these patients showed similar disease activity and radiological joint progression to the RF-negative patients. None of these associations were explained by possible confounders.

Conclusion. Tobacco smoking has an adverse effect on patients with early RA and this is possibly immunologically mediated. IgM RF does not predict poorer prognosis in RA unless it is associated with a concomitant elevation of IgA RF.

KEY WORDS: Early rheumatoid arthritis, Smoking, Rheumatoid factor isotypes, Disease activity, Joint damage.

Rheumatoid arthritis (RA) has a very heterogeneous course, ranging from a mild transient disease to a destructive arthritis with persistent inflammation, but the underlying pathogenic mechanisms are largely unknown. Tobacco smoking is the environmental factor that has most consistently been identified to have adverse effects on RA [1–3]. As previous studies have, with one exception, either been retrospective or cross-sectional, it remains to be established whether tobacco smoke has a direct effect on the immunopathogenic mechanisms of RA or whether the association is secondary to smoking-associated lifestyle factors [4, 5], hormonal balance [6] or the direct toxic effect of tobacco [7–9]. The only prospective study published to date suggested that smoking does not increase the severity of early inflammatory polyarthritis. However, the patient population was heterogeneous with regard to arthritis diagnosis as only 48% of the patients fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA [10].

Although it has been difficult to find links between environmental factors and prognosis in RA, there are well-documented associations between RA prognosis and immunological factors. Numerous studies have shown that rheumatoid factor (RF) [11, 12] and, more recently, antibodies to cyclic citrullinated peptide [13] are predictive of more severe disease. Seventy to eighty-five per cent of RA patients are RF positive, but the mechanisms of RF production and its pathogenic role in RA are largely unknown. However, studies have shown that smokers in the general population have an increased frequency of raised RF [14, 15] and that long-term smoking by RA patients is associated with increased prevalence of positive RF [1–3].

RF seropositivity is most commonly determined by agglutination tests, which preferentially detect IgM RF, but several studies indicate that IgA RF may be a better prognostic indicator in RA patients [11, 16, 17]. Interestingly, we observed in a retrospective study in RA a preferential association between IgA RF and tobacco smoking [1].

In this study we attempted to analyse the effect and interrelationship of tobacco smoking and RF isotypes on disease activity and severity in patients with very early RA that were followed prospectively for 2yr.

Patients and methods

Patients and clinical data collection

Patients with recent onset of symmetric inflammatory polyarthritis were consecutively recruited from private clinics and university

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hospital out-patient rheumatology clinics during the years 1997–2000. The study was carried out at Landspitali University Hospital in Reykjavik. All patients were of European Causcasoid origin and of 177 consecutively recruited patients 100 eventually fulfilled the 1987 ACR criteria for RA. The 77 non-RA patients were diagnosed with various other rheumatological disorders (34 undifferentiated arthritis, 13 psoriatic arthritis, 5 connective tissue disease, 1 polymyalgia rheumatica, 2 inflammatory bowel disease, 7 reactive arthritis, 3 ankylosing spondylitis, 12 other diagnoses). Follow-up data were obtained at 6 and 24 months thereafter for 89 and 85 patients, respectively. The reasons for lack of follow-up at 24 months were: death (three patients), psychiatric illness or dementia (four patients), relocation (two patients), and refusal to participate further (two patients). Four patients were lost to follow-up and could not be accounted for. At each visit patients had a detailed clinical evaluation, including a structured questionnaire and physical examination by two rheumatologists (AV and AJG) and one specially trained medical resident (VFM). Disease activity was determined by the 38 swollen joint count (SJC) score and tender joint count (TJC) score [18], and by a visual analogue scale (VAS) of 0–10 for joint pain. Information was obtained on numerous demographic, lifestyle and psychosocial parameters, including smoking history, caffeine consumption, education, body mass index (BMI) and self-reported symptoms of anxiety and depression. The extent of tobacco smoking was quantified as numbers of pack-years, one pack-year being equivalent to 20 cigarettes or 8 cigars daily for 1 yr. Caffeine consumption was determined by estimating the number of cups of coffee or tea, or the number of bottles of caffeinated soft drink consumed daily. Caffeine consumption in Iceland is largely based on coffee (88% of total caffeine consumption) rather than caffeinated tea or soft drinks (J. Kristinsson, personal communication). The quantity of caffeine consumed was extrapolated from an Icelandic database in which the caffeine content of coffee at restaurants and other public places had been determined. To increase the reliability of estimated tobacco and caffeine consumption the current and past consumption was reviewed at each visit. Educational status was classified as low (compulsory school only), medium (vocational school or junior college) or high (university).

Blood tests and radiological studies
At each visit blood cell counts and levels of C-reactive protein (CRP) were obtained, and RF was measured with an agglutination kit (Serodia-RA, product no. 220689, Fujirebio Inc., Tokyo, Japan) and by an isotype-specific enzyme-linked immunosorbent assay (ELISA) as previously described [19]. The agglutination test has similar sensitivity and specificity for RF as the classical Rose-Waaler test. Radiographs of the hands and feet were obtained at each visit and scored according to the modified van der Heijde method [20] by a radiologist who was blinded to the clinical information and the RF status.

Statistical analysis
Analysis of variance (ANOVA) was used to detect differences in disease activity/radiological score between the groups defined by smoking or RF status over time (multifactorial ANOVA) and at each time point (one-way ANOVA). Detected differences were further analysed by post hoc multiple comparison with Bonferroni adjustment of significance levels. The Fisher exact test was employed to compare groups defined by smoking status with respect to RF positivity. For correlation we used Spearman’s rank test.

Ordinary least squares regression (OLSR) was performed to estimate the independent association of selected predictor variables with disease activity. Disease activity was assessed as the number of swollen joints at 6 months and as radiological score after 24 months of follow-up. Two sets of models were constructed, one for each outcome measure. The candidate predictor variables were selected based on their correlation with each outcome in bivariate analyses. Backwards elimination was employed to remove those variables that did not exhibit an independent statistical association with the outcome. The level of significance was set at 5%. Programs used for statistical analysis were SigmaStat version 6.0 and NCSS version 6.0.

Results
Characteristics of the subjects
The main baseline characteristics of the patients are shown in Table 1. The average age of the patients was 53 yr and 57% were females. The median interval between first arthritic symptoms and the recruitment into the study was 3 months. At study entry, the RA patients had on average 13.5 (s.d.±9.7) swollen joints, 17.0 (s.d.±8.8) tender joints and scored 6.3 (s.d.±2.5) by VAS for joint pain. At the time of the first evaluation, 18% of the patients had recently started on disease-modifying anti-rheumatic drugs (DMARDs) or corticosteroids, 57% were only taking non-steroidal anti-inflammatory drugs (NSAIDs), but 25% was not taking any medication for arthritis. None of the patients received anti-tumour necrosis factor alpha (TNFα) therapy during the study period. At 6 months’ follow-up, 83% of the patients were receiving DMARDs, mostly methotrexate, and/or corticosteroids.

Characteristics of the subjects according to smoking status
Patients were divided according to smoking status into current, former and never smokers (Table 1). Compared with never or current smokers, former smokers were older (P<0.01) and more often males (P<0.01). Former smokers also had higher BMI than current smokers (P<0.05). Current smokers had significantly higher caffe ine intake than never smokers (P<0.01).

Current and former smokers were more often RF seropositive than were never smokers and this difference reached statistical significance for IgA RF (P<0.05). There was no correlation between the number of pack-years and the levels of RF, either for IgM RF or IgA RF (data not shown).

At entry into the study, there was no significant difference between the three smoking groups in disease duration, the use of NSAIDs or DMARDs/corticosteroids, CRP, radiological score, self-reported symptoms of anxiety and depression or educational status.

Disease activity and smoking
Overall, during the 24-month observation period, the current smokers had the highest and the never smokers the lowest disease activity determined by the SJC and TJC scores (multifactorial ANOVA, P<0.001 and P=0.02, respectively) (Fig. 1). Additionally, comparison between the three groups at each time point showed that the current smokers had the highest and the never smokers the lowest scores for SJC at entry and at 6 months (P=0.03, P=0.02, respectively) and for TJC at entry (P=0.04). The difference between the groups decreased with time and at 24 months’ follow-up it was only evident for the SJC score, although it did not reach statistical significance at that stage.
Table 1. Characteristics of the RA study subjects at entry (n=100)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All RA patients (n=100)</th>
<th>Current smokers (n=34)</th>
<th>Former smokers (n=38)</th>
<th>Never smokers (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
<td>57</td>
<td>68</td>
<td>34</td>
<td>75</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Age (yr) (mean±s.d.)</td>
<td>53.4±17.9</td>
<td>48.8</td>
<td>61.7</td>
<td>47.6</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>RA duration (months) [median (range)]</td>
<td>3.0 (0.3–36.0)</td>
<td>3.0</td>
<td>3.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Smoking (pack-years) [median (range)]</td>
<td>25 (0–80)b</td>
<td>21</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drug therapy (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs only</td>
<td>57</td>
<td>62</td>
<td>55</td>
<td>54</td>
<td></td>
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<tr>
<td>DMARDs and/or corticosteroids</td>
<td>18</td>
<td>15</td>
<td>24</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>25</td>
<td>23</td>
<td>21</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor positivity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>47</td>
<td>56</td>
<td>47</td>
<td>36</td>
<td></td>
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<tr>
<td>Agglutination</td>
<td>44</td>
<td>50</td>
<td>45</td>
<td>36</td>
<td></td>
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<tr>
<td>IgA RF±IgM RF (ELISA)</td>
<td>35</td>
<td>44</td>
<td>40</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Isolated IgM RF (ELISA)</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l) [median (range)]</td>
<td>20 (2.0–299.0)</td>
<td>16.0</td>
<td>24.0</td>
<td>22.0</td>
<td></td>
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<tr>
<td>Radiological score [median (range)]</td>
<td>2.0 (0–20.0)</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Caffeine (mg/day) [median (range)]</td>
<td>342.5 (0–1425)</td>
<td>342.5</td>
<td>342.5</td>
<td>200.0</td>
<td>&lt;0.01d</td>
</tr>
<tr>
<td>BMI (kg/m^2) (mean±S.D.)</td>
<td>25.9±4.4</td>
<td>24.8</td>
<td>27.0</td>
<td>25.6</td>
<td>&lt;0.05e</td>
</tr>
<tr>
<td>Symptoms of anxiety (%)</td>
<td>29</td>
<td>35</td>
<td>24</td>
<td>29</td>
<td></td>
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<tr>
<td>Symptoms of depression (%)</td>
<td>23</td>
<td>29</td>
<td>18</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Educational level (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>41</td>
<td>52</td>
<td>40</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>46</td>
<td>38</td>
<td>49</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>13</td>
<td>10</td>
<td>11</td>
<td>18</td>
<td></td>
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</tbody>
</table>

(P=0.08). Although the overall VAS pain score for the three groups showed statistically significant differences (P=0.005), further analysis at each time point revealed that never smokers had significantly lower VAS pain score only at entry (P=0.04). The differences in SJC, TJC and VAS pain score could not be explained by difference between the groups in doses of methotrexate, other DMARDs or corticosteroids (data not shown). No association was observed between disease activity and the number of pack-years of tobacco smoking (data not shown).

VAS pain score. Notably, isolated elevation of IgM RF did not predict increased disease activity at 6 or 24 months’ follow-up. Patients with a positive RF agglutination test had lower SJC, TJC and VAS pain scores at all time points compared to IgA RF-positive patients (data not shown).

Smoking, RF seropositivity and radiological progression

At entry into the study the radiological scores for the hands and feet ranged from 0 to 20 (median 2) (Table 2). At 24 months’ follow-up the scores ranged from 0 to 41 (median 4).

IgA RF-positive patients had significantly worse radiological outcome (median radiological score) than both the RF-negative patients and those patients who had isolated elevation of IgM RF (multifactorial ANOVA, P=0.01) (Table 2). Importantly, progression of radiological changes was similar in patients with isolated IgM RF and RF-negative patients. By classifying patients with isolated IgM RF as RF negative, the prognostic significance of IgA RF positivity for joint damage became more statistically significant (P<0.0001, data not shown). At study entry there was already a trend towards more radiological damage in the IgA RF-positive patients (P=0.06) and this difference became more apparent with time (P<0.01 at 24 months). In addition to showing significantly higher median radiological score, a markedly higher percentage of the IgA RF-positive patients progressed radiologically over the 24-month study period (76% of IgA RF-positive patients vs 48% of RF-negative and isolated IgM RF-positive patients, P=0.02).

Smoking status did not significantly influence radiological progression over the study period. All three smoking groups had a median radiological score of 4 after 24 months and no correlation was observed between number of pack-years of tobacco smoking and radiological score (data not shown).

CRP value at entry and at 6 months did not predict radiological score at 24 months’ follow-up (data not shown). However, CRP
FIG. 1. Disease activity (SJC score, TJC score and VAS pain score) at entry and after 6 and 24 months relative to smoking status; current smokers (black), former smokers (hatched), and never smokers (white). *P values were determined by multi-factorial ANOVA and denote the overall significance of difference in each disease activity parameter between the three smoking groups and over time. †P values derived from one-way ANOVA and denote difference in disease activity between the groups at each evaluation.

FIG. 2. Disease activity (SJC score, TJC score and VAS pain score) at entry and after 6 and 24 months relative to RF status at entry; RF negative (white), isolated IgM RF (hatched), and IgA RF ± IgM RF (black). *P values were determined by multifactorial ANOVA and denote the overall significance of difference in each disease activity parameter between groups and over time. RF negative patients and patients with isolated elevation of IgM RF were analysed as one group and compared with IgA RF-positive patients. †P values were determined by one-way ANOVA at each evaluation.
value obtained at 24 months’ follow-up correlated significantly with radiological score at 24 months ($r=0.303, P<0.01$).

**Regression statistics**

Tables 3 and 4 show the regression results obtained by fitting an OLSR model to the outcome number of swollen joints at 6 months and radiological score at 24 months’ follow-up, respectively.

In the saturated model of the number of swollen joints at 6 months, none of the predictor variables (age, gender, smoking status, IgA RF status and caffeine consumption) exhibited statistical significance at the 0.05 level, although IgA RF positivity and current smoking were quite close (Table 3). Stepwise elimination of one variable at a time from the model, including caffeine consumption, did not significantly alter the coefficients of the remaining variables. Current smoking reached strong statistical significance ($P=0.006$); when non-significant predictors were eliminated, its estimated effect on the outcome was 3.28 or more than three additional swollen joints on average at 6 months. However, elimination did not yield statistical significance for IgA RF positivity ($P=0.08$) (data not shown).

With respect to the outcome of radiological score at 24 months’ follow-up, a statistically significant estimate was only obtained for the regression coefficient of IgA RF status (Table 4). A positive IgA RF status was on average accompanied by close to six additional points on the radiological score at 24 months’ follow-up ($P=0.001$), whereas RF seropositivity determined by an agglutination test added only 3.6 points on average to the radiological score at 24 months’ follow-up (data not shown).

**Discussion**

This is to our knowledge the first prospective study analysing the effects of tobacco smoking on disease activity in patients with very early RA. It shows that tobacco smokers have higher disease activity during the first 24 months of arthritis. This effect is most evident during the first 6 months and is not limited to current smokers but is also observed in former smokers, albeit to a lesser degree.

The only previously published prospective study on the effects of tobacco smoking on disease activity in early polyarthritis did not reveal such association [10]. However, the inclusion criterion for that study was inflammatory polyarthritis with only 48% of the patients fulfilling the 1987 ACR criteria for RA. The number of swollen joints in that patient population was quite low at 3 yr (median SJC score close to 1), which is different from most published series on early RA [21, 22], possibly reflecting the heterogeneity of the patients. It should be noted in this context that in our study only those patients who fulfilled the 1987 ACR criteria for RA were included in the analysis. We and others have previously reported increased joint damage and/or decreased functional status in tobacco smokers with long-standing RA [1–3]. These studies have been either cross-sectional or retrospective and therefore lacking reliable information on important confounders known to be associated with tobacco smoking including anxiety, depression, educational level, body mass index, caffeine consumption and use of anti-rheumatic medications. In our study none of these confounding factors were found to be associated with disease activity and, importantly, none of them explained the association of tobacco smoking with disease activity. Thus, our findings suggest that the observed effects of tobacco smoking on disease activity in early RA are immunologically mediated.

There have been speculations about the potentially adverse effect of caffeine on the efficacy of methotrexate. Studies suggest that the anti-inflammatory effect of the drug is at least in part mediated through adenosine [23, 24] and that caffeine could counteract its effects on the adenosine receptors [25]. Although the current smokers in our study had significantly higher caffeine intake than never smokers, we did not find a significant association between caffeine consumption and disease activity in our regression models (Table 3). Smoking induces cytochrome-P450 activity and smokers may therefore require a caffeine intake four times higher to obtain the same plasma caffeine level as non-smokers [26]. This biological interaction between smoking and plasma caffeine levels might mask a relationship between caffeine consumption and disease activity. Due to our limited sample size, we were not able to assess this possibility in our multivariate analyses.

The gradient of increase in joint inflammation from non-smokers to former smokers to current smokers suggests that tobacco smoking may have both short- and long-term effects on immune responses in the joint. We have observed a marked tobacco-associated increase in acute and chronic joint swelling in an antigen-induced arthritis model in Lewis rats [27]. Studies
have shown that smoking increases the number of peripheral blood lymphocytes [28, 29] and that this change persists after smoking ceases [30]. In our study the prevalence of elevated IgA RF was similar in current and former smokers and significantly higher than in never smokers (Table 1), which suggests that smoking induces a permanent increase in IgA RF production. Although our study showed clinically increased disease activity in current smokers during the first 2 yr of disease, radiological joint damage was not increased in smokers. This is contrary to previous cross-sectional studies on long-standing RA, which showed increased radiological joint damage in smokers [1–3]. This lack of association in the current study may be due to the relatively small group of patients with very early RA that were followed for only 2 yr, suggesting that a longer observational period is needed to demonstrate the association of smoking and joint damage. Alternatively the earlier and more aggressive DMARD therapy our patients received compared with the cohorts in earlier studies may reduce or prevent subsequent joint damage [31]. Tobacco smoking increases the prevalence of RF positivity in the general population [14, 15] as well as in RA patients [1–3, 32], and RF titres correlate with the duration of smoking [3]. Smoking has mostly been correlated with IgM RF, but in the current study we observed a stronger correlation between tobacco smoking and IgA RF. This is in accordance with previous cross-sectional studies in patients with long-standing RA [1, 32].

RF status determined by agglutination did not reliably predict disease activity at first visit. However, we observed a statistically significant association between IgA RF at the first visit and SJC score at 6 and 24 months’ follow-up (Fig. 2). In the multivariate analysis positive IgA RF at entry accounted for 2.3 additional swollen joints at 6 months’ follow-up. However, this did not reach statistical significance (P = 0.09), perhaps due to the limited sample size.

Multivariate analyses of radiological scores showed IgA RF status to be a strong predictor of erosive disease at 24 months’ follow-up, accounting for 5.9 additional points in radiological score (Table 4). This effect was independent of age, gender and the number of swollen joints at entry. Although the association between IgA RF and joint damage has been reported in earlier studies [11, 16, 17], this has not previously been demonstrated by multivariate analyses.

RF is most commonly measured by agglutination tests that primarily detect IgM RF. Seventy-eight per cent of the RF-positive patients in our study had elevated IgA RF, usually with concomitant elevation of IgM RF, but 22% had isolated elevation of IgM RF. We observed no increase in disease activity in patients with isolated elevation of IgM RF. This has not been previously reported. Additionally, we observed no increase in joint damage in patients with isolated IgM RF which is in agreement with the study of Teitsson et al. [11]. It is generally accepted that autoantibodies of IgG and/or IgA isotype are more specific for autoimmune diseases [33, 34]. This may reflect that T-cell involvement in autoimmune diseases induces production of IgG and/or IgA antibodies. IgM RF per se may therefore not be involved in the pathogenesis of RA. Indeed, we have previously reported that isolated elevation of only one RF isotype is not associated with increased prevalence of RA in a population-based study in Iceland [35, 36]. Therefore, if IgA RF but not IgM RF preferentially predicts severe RA, agglutination tests for RF are less helpful in this regard and we suggest that the traditionally used RF agglutination tests should either be suspended or supplemented with isotype specific methods.

The relationship between tobacco smoke and RA appears to be multifactorial. Smoking increases joint inflammation in early disease but does not seem to directly induce early joint damage, at least in patients who are treated with DMARDs. Smoking is also associated with raised IgA RF in some patients and this association is strongly linked to subsequent joint damage. IgA RF seropositivity is as frequently observed in current and former smokers. This suggests that once IgA RF production has been triggered, it signals increased risk of erosive joint disease in that patient, irrespective of smoking status at that point. During the 24-month study period the synovitis in current smokers decreased towards the level of the non-smoking groups, but simultaneously the joint damage associated with IgA RF positivity increased. These observations are consistent with most previous reports, showing that the long-term effects of tobacco smoke on RA are primarily related to increased joint damage and decreased functional status but much less to increased joint inflammation [1–3].

The main weakness of our study is the low number of patients recruited over the study period, which is mainly due to the fact that the population of the Reykjavik metropolitan area is only 175,000. Our findings, therefore, need to be confirmed in studies with a larger cohort of early RA patients. However, most of the patients were recruited by two rheumatologists, ensuring homogeneous admission into the study and treatment approach. We believe that the profile of our patient population is similar to most other early RA patient populations [13, 21]. Importantly, the current smokers were quite similar to the never smokers for several important variables such as age, sex, BMI and use of anti-rheumatic medications. The former smokers on the other hand were older, more often males and had higher BMI.

In conclusion, our study suggests that tobacco smoking is strongly associated with increased disease activity and IgA RF production during the first 2 yr of early RA and that these effects may be immunologically mediated. We suggest that smoking-associated joint damage reported in patients with long-standing RA may in part be mediated by smoking-induced immunological changes including IgA RF production. Our study also confirms that isolated increase in IgM RF does not predict adverse prognosis in RA while IgA RF seropositivity with or without IgM RF may be an independent risk factor for more active disease and increased joint damage in early RA.

<table>
<thead>
<tr>
<th>Rheumatology</th>
<th>Key messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoking increases disease activity in early RA.</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking is associated with IgA RF production.</td>
<td></td>
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<tr>
<td>IgA RF seropositivity but not IgM RF seropositivity predicts poorer prognosis in early RA.</td>
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</tbody>
</table>

Acknowledgements

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The authors have declared no conflicts of interest.

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