The Effect of Cigarette Smoking on Rheumatoid Arthritis

Sigaranın Romatoid Artrit Üzerine Etkileri

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ABSTRACT

Purpose: To investigate the effect of smoking on rheumatoid arthritis as a causative factor, sero-positivity and activity.

Materials and Methods: This case control study which is carried out in the rheumatology division of Sulaimaniya teaching hospital & clinic from 15th August 2009 to 15th June 2010, Ninety-two patients 73(79%) females and 19(21%) males who fulfilled the American College of Rheumatology diagnostic criteria for diagnosis of adult rheumatoid arthritis were included compared to 92 controls. Detail history of smoking taken and disease activity assessed according to DAS28j(Disease activity score of 28 joints).

Results: All forty-six smoker patients had active disease, 38(82.6%) had highly active disease according to DAS28j, these results are statistically significant (P-value =0.04), and 42(91.3%) of them had rheumatoid factor which means the positive relation between smoking and seropositivity also (P-value =0.000).

Conclusion: Majority of smokers demonstrated highly active disease according to DAS28j measurement for disease activity, and the relation of smoking with seropositivity found to be positive.

Key Words: Smoking, activity, RF, rheumatoid arthritis.

ÖZET

Amaç: Romatoid Artrit sebebi olan faktörlerden biri olan ve hastalığın seyrini ve sero-positivitesini etkileyen sigara kullanımının Romatoidartrit gelişimi üzerine etkilerinin incelenmesi.


Bulgular: Sigara kullanan 46 hastada ilerleyen bir romatoid arit olduğu ve 38 hastada (%82.6) DAS28J’ye göre değerlendirildiğinde, hastalığın seyrinin oldukça ilerlemiş olduğu tesbit edildi (p<0.04). 42 (%91.3) Sigara kullanımı ve seropozitivite arasında da pozitif bir ilişki olduğu belirlendi (p<0.000).


AnahtarKelimeler: Sigara kullanımı, hastalıkk aktivitesi, RF, romatoid artrit.
INTRODUCTION

Rheumatoid arthritis (RA) is chronic autoimmune inflammatory disease affecting joints and several organs, like lungs, serosa, heart, and the peripheral nervous system. The disease is of unknown etiology but several factors are clearly implicated in its etiology and pathogenesis which include: genetic predisposition, hormonal factors, environmental exposure such as tobacco smoking or infectious agents (Epstein-Barr virus).

So far, serological support in the diagnosis of RA was mainly based on the presence of rheumatoid factors (RF) and Anti-CCP antibodies which are autoantibodies directed against the amino acids formed by the posttranslational modification of arginine.

RA is characterized, in part, by increased production of the inflammatory cytokines IL-1, IL-6, IL-8, IL-18 and TNF-alpha, seems to be a key mediator in the disease process.

Many authors looked at the effect of smoking as a predictor for development of the rheumatoid arthritis through the RF production and enhancing the risk of developing anti-CCP positive RA in patients with the shared epitope.

Regarding the relation of smoking and TNF-alpha production, found that TNF-alpha production by peripheral blood mononuclear cells is elevated in smokers, furthermore Giorgos S. Metsios et al. claiming that Smoking has also been linked to imbalances in the production of TNF-alpha and soluble TNF receptors, leading to a relative excess of TNF-alpha. This may be one of the mechanisms leading to the increased hypermetabolism specifically in RA smokers. Jouni JK Jaakkola et al. reporting maternal smoking results in fetal exposure to tobacco and thus effects of tobacco products on immune system could begin during the fetal period this increases the risk of polyarthritis including Juvenile rheumatoid arthritis in childhood. Padyukov L et al. looked at an interaction between smoking and carriage of the HLA-DRB1 shared epitope claiming that this sharing increases the risk of developing RF positive RA. According to P Stolt1,2 et al. Smokers of both sexes have an increased risk of developing seropositive, but not seronegative, RA, furthermore Zsuzsanna Baka et al. concluding that smoking is considered to play a major role in the pathogenesis of autoimmune diseases and it has long been known that there is a connection between it and rheumatoid factor-positive rheumatoid arthritis and Hutchison et al. claiming heavy cigarette smoking is strongly associated with RA, particularly in patients without a family history of RA. Cigarette smoking appears to be one of the environmental factors in rheumatoid arthritis, the effect of smoking extends to extraarticular features according to Shirley A et al. Tobacco smoking has an adverse effect on patients with early RA and this is possibly immunologically mediated according to V. F. Manfredsdottir et al. The effect of smoking on RA looked at by Harrison and Beverley found that cigarette smoking is a well-known risk factor for rheumatoid arthritis and has a number of important effects on the immune system and sex hormones that may influence disease pathogenesis, Diane Feskanich et al. going further claiming that past and current cigarette smoking were related to the development of RA, in particular seropositive RA, a similar conclusion is also made by Zsuzsanna Baka et al. who claiming that It has long been known that there is a connection between rheumatoid factor-positive rheumatoid arthritis and cigarette smoking and Söderlin MK et al. concluding that RA patients who smoke have a more active disease, Lindsey A Criswell and coworker looked at the effect of smoking on postmenopausal RA patients their results suggest that abstinence from smoking may reduce the risk of rheumatoid arthritis among them. Regarding the effect of treatment Abhishek A et al. found that RA patients who
smoke are less likely to respond to an anti-TNF-alpha agent and according to Scott Baltic\(^9\) sustained RA remission can be achieved without biologic Drugs.

**MATERIALS and METHODS**

This study was carried at the division of Rheumatology of Sulaimania –Iraq between 15th August 2009 and 15th June 2010. Ninety two patients with adult rheumatoid arthritis(RA) 46 smokers and 46 nonsmokers enrolled whose consent obtained, diagnosis made by consultant rheumatologist according to 1987 American College of rheumatology revised criteria for of rheumatoid arthritis(RA) and disease activity assessed according 28 to swollen and tender joints DAS28) ,with erythrocytic sedimentation rate(ESR) and visual analogue scale(VSA). (Values >5.1 regarded as high active disease , <3.2 as low low active less than 2.6 to be in remission. Patients collected randomly when attended for the ordinary follow up.

Clinical examination included also age , sex duration of the disease and physical examination. Regarding smoking history , patients were asked whether smoked in past , currently or never smoked. Smoker asked about duration of smoking and number of cigarettes smoked in a day. The DAS28 is calculated using the results of the 28 tender joint counts (TJC28), the 28 swollen joint count (SJC28) ESR (mm/hr) and (VSA).

**Statistical Analysis:**

Data, concerning different variables for analysis, were analyzed by entering data into Excel office and analysis was done by (SPSS version 14), P-value of or <0.05 accepted to be significant.

**RESULTS**

The sample comprised of 92 rheumatoid patients 46 smokers and 46 were non-smokers , 73 (79%) were females 28 of them were smokers while other 45 were non smokers, meanwhile 18 of 19(21%) males were smokers which indicate that smoking is more among males.

**Table (1) smoking status among gender.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Smoker</th>
<th>Non Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female(73 )</td>
<td>28(38.4)</td>
<td>45(61.6)</td>
</tr>
<tr>
<td>Male (19)</td>
<td>18(94.7)</td>
<td>1(5.3)</td>
</tr>
</tbody>
</table>

Eighteen of nineteen mal patients (94.7%) were seropositive, while 47(64.4%) of 73(79%) females had rheumatoid serum factor which means a highly significant association of seropositivity and sex.

**Table(2)Relation between gender and seropositivity**

<table>
<thead>
<tr>
<th>Sex</th>
<th>RF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Female</td>
<td>26(35.6)</td>
<td>47(64.4)</td>
</tr>
<tr>
<td>Male</td>
<td>1(5.3)</td>
<td>18(94.7)</td>
</tr>
</tbody>
</table>
Regarding the relation between smoking and sex, 28(38.4%) of 73(79%) females were smokers compared to 18(94.7%) of 19(21%) of male patients were smokers, the association was highly significant p-value (0.000) (table 3).

**Table (3) Association of the gender with smoking.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Non smoker</th>
<th>Smoker</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45(61.6)</td>
<td>28(38.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Male</td>
<td>1(5.3)</td>
<td>18(94.7)</td>
<td></td>
</tr>
</tbody>
</table>

Forty two(91.3%) of forty six smokers had rheumatoid factor (RF) in their serum, while only half 23(50.0%) of nonsmokers were seropositive therefore the association between smoking with seropositivity for RF was highly significant P-value (0.000), the results indicate the effect of smoking on the production rheumatoid serum factors and its immunological effect.

**Table (4) Relation between smoking status and seropositivity for RF.**

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>RF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Non smoker</td>
<td>23(50.0)</td>
<td>23(50.0)</td>
</tr>
<tr>
<td>Smoke</td>
<td>4(8.7)</td>
<td>42(91.3)</td>
</tr>
</tbody>
</table>

Regarding the relation of smoking with disease activity found that all 46 smokers patients had active disease, 38(82.6%) had high active disease, 8(17.4%) had low active disease and non of them were in remission state compared to non smoker group whom 29(63.0%) had high active disease, 14(30.4%) low active disease and 3(6.5%) were in remission the results showing the association of smoking with activity of disease to be significant (p-value= 0.04).

According to the results found that majority 65 (70.7%) of seropositive patients 51(78.5%) had high active disease, the other 14(21.5%) had low active disease and non of them were in remission state, while 27(29.3%) sero-negatives, 16(59.3%) had high active disease, 8(29.6%) had low active disease and 3(11.1%) were in remission therefore the relation between sero-positivity and of disease activity was significant (p-value=0.010) table 5.
Table (5) shows the association of disease activity with smoking and seropositivity for RF.

<table>
<thead>
<tr>
<th>Variables</th>
<th>DAS28</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 2.6 remission</td>
<td>Less than 3.2 low active</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>History of smoking:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>3(11.1)</td>
<td>14(29.6)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0(0)</td>
<td>8(17.4)</td>
</tr>
<tr>
<td>Rheumatiod factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>3(11.1)</td>
<td>8(29.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>0(0)</td>
<td>14(21.5)</td>
</tr>
</tbody>
</table>

DISCUSSION

Rheumatoid arthritis is a chronic, systemic, inflammatory disease that causes articular and extraarticular symptoms and affects quality of life, identification of prognostic factors may be predictive for assessing the prognosis and determining the patients who need early aggressive treatment, among bad prognostic factors is smoking.20

Recently there is a growing interest in looking for the relation of tobacco smoking and RA patients, therefore we looked at 92 RA patients for the effect of smoking on the presence of RF and disease activity in which 46(50%) were smoker and 46(50%) were non-smokers.

Forty two(91.3%) of sixty five seropositive RA patients were smokers the figure indicate a statistically significant relation between tobacco smoking and presence of RF of IgM type (p-value 0.000), a similar conclusion made by Frederick Wolfe et al21, whose results showed that among RA patients, smokers are more often RF positive than non-smokers but claimed the relation to be stronger for women (p value=0.007) than men (P value=0.010), while we found a stronger relation between seropositivity and smoking in male patients with the association of statistically significant (p-value 0.006) level, this might be explained on the base that Iraqi male patients are smoking tobacco more than females, but in contrast to our results Eswar Krishnan22, looked at the relation of smoking with seropositivity for RF, found no statistically significant differences in the proportion of seropositivity for RF (67% versus 71%; p=0.29), between men and women with RA.

Controlling disease activity is a goal in RA, measures to achieve it is mandatory to be considered, according to our results we found that 67 (73%) of 92 patients had high active disease but high active disease was still higher among smokers when 38 (83%) of 46 smokers had it when measured by DAS28j score, this conclusion found to be close to results of Papadopoulos NG et al23, who reported that among 287 patients evaluated for disease expression and activity, 200 females and 87 males, 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 frequency of 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, compared to non-smokers.
We found that Majority of positive RF patients 51 (78.5%) had high disease activity with the association of statistically significant level (p-value 0.010) compared to nonsmokers, this outcome is close to the report of NyhallWahlin et al24, when found Patients who developed severe extra-articular features, having higher mean DAS28 at baseline and higher percentage(93%) of rheumatoid serum factor were more often current smokers, therefor smokers having high levels of disease activity and more frequently develop disability during the first 2 years after RA diagnosis and smoking and seropositivity predict the development of severe extra-articular RA.V.F Manfredsdottir et al13, claimed that 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) (P<0.001, P=0.02, respectively).

There is no conflict of interest of the authors. The study is according to principles of Helsinki Declaration.

CONCLUSIONS
1. Smokers demonstrated a more active disease measured by DAS28 measurement for disease activity compared to non-smokers.
2. A positive correlation was found between smoking and seropositivity for RF.

Recommendations:
1. Our study also highlights the need for further research on smoking, RA, and, in addition, their effect modification by sex-related Factors like menopause.
2. Further research need to be done for the effect of smoking on bone mineral density in RA patients compared with non smoker RA patients.

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