



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 sebep olan faktörlerden biri olan ve hastalığın seyrini ve sero-pozitivitesini etkileyen sigara kullanımının Romatoid Artrit gelişimi üzerine etkilerinin incelenmesi.

Materyal ve Metod: 15.08.2009 – 15.06.2010 tarihleri arasında Süleymaniye Eğitim Hastanesine başvuran, Amerikan Romatoloji Kurulunun teşhis kriterlerine göre seçilen 73 kadın (%79) ve 19 erkek (%21) toplam 92 romatoid artritli olgu çalışmaya alınmıştır. Sigara kullanan hastaların detaylı öyküleri alınarak, hastalık gelişimi DAS28J'e (eklemlerde hastalık gelişim değeri 28) göre irdelenmiştir.

Bulgular:Sigara kullanan 46 hastada ilerleyen bir romatoid artrit olduğu ve 38 hastada (%82.6) DAS28J'e 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).

Sonuç: DAS28J verilerine göre değerlendirilme yapıldığında, sigara kullananların büyük bir kısmında hastalığın ilerlemiş olduğu görüldü. Seropozitif ve sigara arasında pozitif bir ilişki bulundu.

Anahtar Kelimeler: Sigara kullanımı, hastalık 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 system¹.

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)².

So far, serological support in the diagnosis of RA was mainly based on the presence of rheumatoid factors(RF) ⁽¹⁾ and Anti-CCP antibodies which are autoantibodies directed against the amino acids formed by the posttranslational modification of arginine³.

RA is characterized, in part, by increased production of the inflammatory cytokinesIL-1, IL-6, IL-8, IL-18 and TNF-alpha, seems to be a key mediator in the disease process⁴.

Many authors looked at the effect of smoking as a predictor for development of the rheumatoid arthritis through the RF production⁵ and enhancing the risk of developing anti-CCP positive RA in patients with the shared epitope³.

Regarding the relation of smoking and TNF-alpha production **J. R. Glossop**⁵, found that TNF-alpha production by peripheral blood mononuclearcells is elevated in smokers, furthermoreGiorgos S Metsiosetal⁽⁶⁾ claiming that Smokinghas also been linked to imbalances in the production of TNF-alphaand soluble TNF receptors, leading to a relative excess of TNF-alpha.This may be one of the mechanisms leading to the increased hypermetabolismspecifically in RA smokers. Jouni JK Jaakkola etal⁷ reporting maternal smoking results in fetal exposure to tobaccoand thus effects of tobacco products on immune system couldbegin during the fetal period this increases the risk of polyarthropathies includingJuvenile rheumatoid arthritis in

childhood..Padyukov L etal⁸ looked at an interaction between smokingand carriage of the HLA-DRB1 shared epitope claiming that this sharing increases the risk of developing RF positive RA. According to P Stolt1,2 etal⁹ Smokers of both sexes have an increased risk of developing seropositive, but not seronegative, RA,furthermoreZsuzsannabaka 1 etal¹⁰ 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 andHutchinson etal¹¹claiming 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 etal¹². Tobacco smoking has an adverse effect on patients with early RA and this is possibly immunologically mediated according to V.F Manfredsdottir 1 etal¹³. The effect of smoking on RA looked at by Harrison and Beverley J⁽¹⁴⁾ 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 FeskanichSe Db etal¹⁵ 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 ZsuzsannaBaka1 etal⁽¹⁰⁾ 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 etal¹⁶ concluding that RA patients who smoke have a more active disease, Lindsey A Criswell and coworker¹⁷ 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 of treatment Abhishek A etal¹⁸ found that RA patients who

smoke are less likely to respond to an anti-TNF-alpha agent and according to Scott Baltic¹⁹ 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. Ninty 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 DAS28j) ,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.

Gender	Smoker	Non Smoker
Female(73)	28(38.4)	45(61.6)
Male (19)	18(94.7)	1(5.3)

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

Sex	RF		P value
	Negative	Positive	
Female	26(35.6)	47(64.4)	0.006
Male	1(5.3)	18(94.7)	

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.

Gender	Non smoker	Smoker	P value
	N (%)	N (%)	
Female	45(61.6)	28(38.4)	0.000
Male	1(5.3)	18(94.7)	

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 therefor 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 it's immunological effect.

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

Smoking history	RF		P value
	Negative	Positive	
Non smoker	23(50.0)	23(50.0)	0.000
Smoke	4(8.7)	42(91.3)	

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 majority65 (70.7 %)of seropositive patients 51(78.5%) had high active diseases, 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) table5 .

Table (5) shows the association of disease activity with smoking and seropositivity for RF.

Variables	DAS28j			P value
	Less than 2.6 remission	Less than 3.2 low active	More than 5.1 high active	
	N (%)	N (%)	N (%)	
History of smoking:				0.04
Non smoker	3(6.5)	14(30.4)	29(63.0)	
Smoker	0(0)	8(17.4)	38 (82.6)	
Rheumatoid factor				0.01
Negative	3(11.1)	8(29.6)	16(59.3)	
Positive	0.(0)	14(21.5)	51(78.5)	

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 smoking²⁰.

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 Helesiki Declaration.

CONCLUSIONS

1. Smokers demonstrated a more active disease measured by DAS28j 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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REFERENCES

1. MünevverSerdaroğlu, HaşimÇakırbay, OrhanDeğer, SevilCengiz, and SibelKul . The association of anti-CCP antibodies with disease activity in rheumatoid arthritis. *Rheumatol Int.* 2008;28:965–70.
2. Klippel JH, Stone JH, Crofford LJ, White PH. *Primer on the Rheumatic Disease.* 13 edition. Springer Science & Business Media, New York, USA., 2008;16-17:118-9.
3. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigensmodified by citrullination. *Arthritis Rheum.* 2006;54:38–46
4. Arend WP. Physiology of cytokine pathways in rheumatoid arthritis. *Arthritis Rheum* 2001;45:101–6.
5. J. R. Glossop, P. T. Dawes and D. L. MattheyAssociation between cigarette smoking and release of tumour necrosis factor α and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis *Rheumatology.* 2006;45:1223-9
6. Giorgos S Metsios, A Stavropoulos-Kalinoglou, A M Nevill, K M J Douglas, Y Koutedakisand G D Kitas. Cigarette smoking significantly increases basal metabolic rate in patients with rheumatoid arthritis *Annals of the Rheumatic Diseases.* 2008;67:70-3.
7. Jouni JK Jaakkola and Mika Gissler.. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. *International Journal of Epidemiology.* 2005;34:664-71.
8. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum.* 2004;50:3085–92.
9. P Stolt, C Bengtsson, B Nordmark, S Lindblad, I Lundberg, L Klareskog, L Alfredsson. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control

- study, using incident cases .Ann Rheum Dis 2003;62:835-41. doi:10.1136/ard.62.9.835.
10. ZsuzsannaBaka, Edit Buzás and György Nagy. Rheumatoid arthritis and smoking: putting the pieces together.Arthritis Research & Therapy 2009,11:238 doi:10.1186/ar275.
 11. Hutchison, L Shepstone, R Moots, JT Lear, MP Lynch. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. Annals of Rheumatic Diseases 2001;60:223-7.
 12. Shirley A. Albano, Ernesto Santana-Sahagun, Michael H. Weisman Purchase Cigarette smoking and rheumatoid arthritis . Seminars in Arthritis and Rheumatis. 2001;31:146-59.
 13. V. F. Manfredsdottir, T. Vikingsdottir, T. Jonsson, A. J. Geirsson, O. Kjartansson, M. Heimisdottir, S. L. Sigurdardottir, H. Valdimarsson and A. Vikingsson. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis oxford Journal, medicine Rheumatology. 2006;45:734-40.
 14. Harrison, Beverley J. MD, MRCP . Influence of cigarette smoking on disease outcome in rheumatoid arthritis.Current Opinion in Rheumatology. 2002;14:93-7.
 15. Diane FeskanichScDb, Lisa A. Mandl MD, MPHc, Conclusions Karen H. Costenbader MD, MPHa,smoking Intensity, Duration, and Cessation, and the Risk of Rheumatoid Arthritis in Women. The American Journal of Medicine. 2006;119:503.
 16. Söderlin MK, Petersson IF, Bergman S,Svensson B; BARFOT study groupSmoking at onset of rheumatoid arthritis (RA) and its effect on disease activity and functional status: experiences from BARFOT, a long-term observational study on early RA. Scand J Rheumatol. 2011;40:249-55.
 17. Lindsey A Criswell MD, MPHa, Linda A MerlinoMScb, James R Cerhan MD, PhD, Ted R MikulsMDe, Amy S MudanoMPHe, Molly Burma MSNc, Aaron R Folsom MD, MPHf, Kenneth G SaagMDe. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal womenThe American Journal of Medicine. 2002;112:465-71.
 18. Abhishek A, Butt S,Gadsby K, Zhang W, DeightonCM.Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers.J Clin.Rheumatol. 2010;16:15-8.
 19. Scott Baltic. Sustained RA Remission Can Be Achieved Without Biologic Drugs. Arthritis Rheum. 2009;60:2262-71.
 20. AslıGençay Can, ZaferGünendi, Prognostic Factors in Rheumatoid Arthritis. Rheumatism. 2008;23:60-2.
 21. Frederick Wolfe . The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis.JRheumatol.2000;27:569-70.
 22. Eswar Krishnan, TuulikkiSokka, PekkaHannonen. Smoking–gender interaction and risk for rheumatoid arthritis. Arthritis Res Ther 2003, 5:R158-R162.
 - 23.Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? ClinExpRheumatol.2005;23:861-6.
 23. Nyhäll-Wählin BM, Petersson IF, Nilsson JA, Jacobsson LT, Turesson C; the BARFOT study group. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis.Rheumatology (Oxford).2009.

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