Indonesian Journal on Health Science and Medicine

Vol. 3 No. 1 (2026): July
DOI: 10.21070/ijhsm.v3i1.454

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Indonesian Journal on Health Science and Medicine

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Impact of Smoking on Adalimumab Response and Biomarkers in Rheumatoid Arthritis: Dampak Merokok terhadap Respons Adalimumab dan Biomarker pada Pasien Artritis Reumatoid

Ghasaq Kareem Abed, med.post25.43@qu.edu.iq (*)
Maternity and Pediatrics Teaching Hospital, Al-Qadisiyah Health Office, Al-Qadisiyah, Iraq

Asma Abdul Jaleel Swadi, asma.althuwaynee@qu.edu.iq
College of Medicine, University of Al-Qadisiyah, Al-Diwaniyah Province, Iraq

(*) Corresponding author

Abstract

General Background: Rheumatoid arthritis is a chronic autoimmune disease characterized by persistent inflammation and jointdestruction. **Specific Background:** Adalimumab, a TNF-α inhibitor, is widely used, yet variability in treatment response remains a challenge. **Knowledge Gap:** The combined relationship between smoking and key biomarkers including TNF-α, IL-6, and MMP-3 in patients receiving adalimumab has not been fully clarified. **Aims:** This study evaluates the association between smoking status, clinical response, and serum biomarker levels in rheumatoid arthritis patients treated with adalimumab. **Results:** A cross-sectional study of 75 patients and 55 controls showed that smoking prevalence was higher among non-responders, with significantly elevated TNF-α, IL-6, and MMP-3 levels and positive correlations with smoking. **Novelty:** The study simultaneously examines inflammatory and structural biomarkers in relation to smoking and treatment response. **Implications:** These findings highlight the role of smoking in persistent inflammation and suggest the relevance of MMP-3 as a biomarker for monitoring therapeutic response in clinical practice.

Keywords: Rheumatoid Arthritis, Adalimumab, Smoking, Biomarkers, Inflammation

Key Findings Highlights

- Higher cytokine and enzyme levels identified in non-responder group
- Significant correlation observed between tobacco exposure and inflammatory markers
- Distinct biomarker patterns differentiate clinical outcome groups

Published date: 2026-05-01

Introduction

Rheumatoid arthritis is a chronic, systemic autoimmune disorder considered by ongoing synovial inflammation, progressive damage to cartilage, and joint deformities, resulting in considerable functional impairment. It affects about 1% of the worldwide population and is linked to significant morbidity and a decreased quality of life 1.

The pathogenesis of rheumatoid arthritis is driven by a complex network of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which regulate immune activation, synovial proliferation, and joint destruction. IL-6 contributes to persistence of inflammation and disease progression2.

Adalimumab, a monoclonal antibody that targets TNF-α, is a key therapy for moderate-to-severe RA. It has shown substantial effectiveness in lowering disease activity, enhancing physical function, and preventing structural joint damage. However, a notable proportion of patients do not attain an adequate clinical response, underscoring the importance of identifying predictors of management results3.

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Smoking has emerged as an important environmental factor influencing disease severity and therapeutic response. It has been related with augmented systemic inflammatory action and elevated levels of inflammatory markers, which may contribute to disease progression4. In addition, smoking has been revealed to reduce the clinical response to anti-TNF therapy in patients with RA , leading to poorer treatment outcomes and lower rates of clinical improvement 5.

Matrix metalloproteinase-3 (MMP-3) is an enzyme involved in extracellular matrix degradation and cartilage destruction. Elevated levels of MMP-3 reflect synovial inflammation and structural joint damage, and it has been proposed as a useful biomarker for disease activity and treatment response 67

Despite available evidence, the combined effect of smoking on TNF-α, IL-6, and MMP-3 in patients treated with adalimumab remains insufficiently studied. Therefore, this study investigates the relationship between smoking, inflammatory biomarkers, and treatment response.

Method

Study design and participants
This cross-sectional study included 130 participants: 75 RA patients satisfying the 2010 ACR/EULAR principles and 55 well controls. All RA sick stood treated with adalimumab monotherapy (40 mg subcutaneously every 2 weeks) for at least 6 months.
Patients were classified into:
•Responders (n = 35): DAS28 < 2.6 or improvement ≥ 1.2
•Non-responders (n = 40): DAS28 ≥ 2.6 and improvement < 1.2
Exclusion criteria
Use of any other biologic agent, acute infection or malignancy and pregnancy or lactation.
Data collection
Demographic and clinical data included age, sex, smoking status (current smokers vs non-smokers), disease duration, DAS28 score, and concomitant NSAID or steroid use.
Measurement of Biomarkers
Blood specimens were obtained. Serum concentrations of MMP-3, interleukin-6 (IL-6), in addition tumor necrosis factor-alpha (TNF-α) stood enumerated utilizing commercial ELISA kits in accordance with the manufacturer's guidelines. All assays were conducted in duplicate.
Statistical analysis
Information stood investigated by SPSS version 23. Continuous variables were expressed as mean ± SD and definite variables as number (%). Chi-square, independent t-test, ANOVA, and Pearson correlation were applied. P ≤ 0.05 was considered significant.

Results and Discussion

1. General characteristics compared among study groups
General characteristics compared among study groups are shown in table 1. Comparison of mean age revealed no significant difference (p = 0.603). There was also no significant difference in proportions of males and females between groups (p = 0.870).
Smoking rate was higher in a significant manner in failure group in comparison with response group, 32.5 % versus 5.7 %, respectively (p = 0.004).
Table 1. General characteristics compared among study groups

Characteristic	Response group *n* = 35	Failure group *n* = 40	*p*
Age (years)			
	47.57 ±10.68	46.40 ±8.76	0.603 N
	27 -65	29 -60	
Gender			
Male, *n* (%)	12 (34.3 %)	13 (32.5 %)	0.870 N
Female, *n* (%)	23 (65.7 %)	27 (67.5 %)	
Smoking			
Yes	2 (5.7 %)	13 (32.5 %)	0.004 S
No	33 (94.3 %)	27 (67.5 %)	

S: significant; **N**: not significant

2. Comparison of TNF-a mean levels among study groups
Comparison of TNF-a mean levels among study groups is shown in table 2. This comparison revealed significant difference (p < 0.001). The level was significantly highest in failure group (48.98 ±8.27) followed by response group (42.32 ±6.21) then by control group (37.19 ±9.61).
Table 2 Comparison of TNF-a mean levels among study groups

Characteristic	Response group *n* =35	Failure group *n* = 40	Control group *n* = 55	*p*

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TNF-a				
Mean ±SD	42.32 ±6.21 b	48.98 ±8.27 a	37.19 ±9.61 c	<0.001 S
Range	21.49 -46.02	21.49 -61.35	22.55 -78.19	

TNF-a: **SD**: standard deviation; **S**: significant; small letters (a, b and c) were used to show the results of post-hoc LSD multiple comparison test so that letter a takings the uppermost rate surveyed by letter b then letter c; like letters indicated no important variation; whereas, different letters indicated important alteration

3. Comparison of IL-6 mean levels among study groups
Comparison of IL-6 mean levels among study groups is shown in table 3. This comparison revealed significant difference ($p < 0.001$). The level was significantly highest in failure group (21.86 ±10.91) followed by response group (17.73 ±6.97) then by control group (14.40 ±3.92).

Table 3: Comparison of IL-6 mean levels among study groups

Characteristic	**Response group** ***n*** **=35**	**Failure group** ***n*** **= 40**	**Control group** ***n*** **= 55**	***p***
IL-6				
Mean ±SD	17.73 ±6.97 b	21.86 ±10.91 a	14.40 ±3.92 c	<0.001 S
Range	2.99 -31.45	8.47 -78.86	4.17 -25.51	

IL-6: interleukin; **SD**: standard deviation; **S**: significant; small letters (a, b and c) were used to show the results of post-hoc LSD multiple comparison test so that letter a takings the uppermost rate surveyed by letter b then letter c; like letters indicated no important variation; whereas, different letters indicated important alteration

4. Comparison of MMP3 mean levels among study groups
Comparison of matrix metalloproteinase 3 (MMP3) mean levels among study groups is shown in table 4. This comparison revealed significant difference ($p < 0.001$). The level was significantly highest in failure group (41.65 ±5.94) followed by response group (35.2 ±5.66) then by control group (30.82 ±2.73).

Table 4: Comparison of MMP3 mean levels among study groups

Characteristic	**Response group** ***n*** **=35**	**Failure group** ***n*** **= 40**	**Control group** ***n*** **= 55**	***p***
MMP3				
Mean ±SD	35.2 ±5.66 b	41.65 ±5.94 a	30.82 ±2.73 c	<0.001 S
Range	15.22 -36.13	29.07 -53.42	19.5 -36.41	

MMP3: matrix metalloproteinase 3; **SD**: standard deviation; **S**: significant; small letters (a, b and c) were used to show the results of post-hoc LSD multiple comparison test so that letter a takings the uppermost rate surveyed by letter b then letter c; like letters indicated no important variation; whereas, different letters indicated important alteration

Correlation study
Immune markers correlations to smoking are demonstrated in table 5. All markers showed significant and positive correlations to smoking.
Table 5: Immune marker correlations to smoking

Characteristics	**Smoking**	
	r	***P***
TNF-a	0.440	<0.001 S
IL-6	0.445	<0.001 S
MMP-3	0.354	0.002 S

S: significant
In the current study observation smoking rate was significantly higher among the failure group compared to the response group. Therefore, it can be proposed that the response of RA patients to ADA is greatly affected by smoking. In line with current observation, poor response to treatment has been reported and was found to be related with the strength of preceding smoking, regardless of smoking grade at start of anti-TNF therapy[8].

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Moreover, smoking was found to be a prognostic of poor response to anti-TNF management for up to 12 months, and heavy smokers had the poorest treatment persistence[9]. Similarly, smoking is a poor predictor of responsiveness to anti-TNF therapy in RA and smoking at the time of anti-TNF initiation decreased the likelihood of obtaining at least a moderate EULAR response via 80%[5][10] [11] .
Contrary to our findings, some studies found no difference in response to anti-TNF treatment in RA between smokers and non-smokers. However, they emphasized that prospective controlled studies involving tobacco exposure are necessary to better define the response to anti-TNF-α agents [12] .
The reason why smokers react less well to anti-TNF therapy is unknown. Anti-rheumatic medication bioavailability may be impacted by smoking. Additionally, smoking may be associated with behavioral and socioeconomic factors that could potentially influence treatment outcomes [13] .
In this study, comparison of TNF-a mean levels among study groups revealed that the level stayed meaningfully highest in the failure groping followed by the response groping then by the control group. Therefore, it is a reliable marker for treatment response. Its high level in failure group may indicate the existence of continuing inflammatory state attributed to smoking.
It has been shown that adalimumab treatment can restore TNFα levels in RA patients to those of healthy control subjects, which is consistent with the findings of the current investigation.[14]
Similarly, IL-6 levels were significantly higher in the failure group followed by response group then by control group. Thus, we can consider IL-6 as a relatable marker for evaluation of treatment response. Its high level in failure group may indicate the existence of continuing inflammatory state attributed to smoking.
Since the pathophysiology of RA involves a network of cytokines, blocking one cytokine, like TNF-α, may have an impact on other cytokines, particularly IL-6, which is one of the most frequently expressed cytokines in RA patients and has overlapping effects with TNF-α [15].

Matrix metalloproteinases (MMPs) are a large group of zinc-dependent proteases capable of degrading extracellular matrix components such as collagen, gelatin, elastin, and casein. MMP-3, a member of this family, is formed within joints and contributes to the progression of inflammation by cleaving extracellular matrix elements, including collagen types III, IX, and X, as well as the telopeptides of collagen types I, II, and XI, and by activating several pro-MMPs, comprising pro-MMP-1, pro-MMP-7, pro-MMP-8, pro-MMP-9, and pro-MMP-13.[7].

In our study, the level of MMP3 was significantly highest in failure group followed by response group then by control group indicating that this marker is a good indicator of response to treatment with anti-TNF agents. Our results are supported by previous studies showing that enhancement in serum MMP-3 ranks at 4 weeks after beginning of ADA treatment can predict decrease at 52 weeks in RA sick[7].
Thus, serum measurement of MMP3 is an effective indicator of response of RA patients treated by ADA and that estimation of baseline levels in such patients may prove to be necessary before initiation of therapy. The higher level of such marker in failure group may be related to resistance to treatment created by persistent systemic inflammation attributed to smoking .
Additionally, Smoking showed significant positive correlation with interleukin-6 (IL-6), TNF, levels. This supports the hypothesis that smoking contributes to a heightened inflammatory state, which may reduce the effectiveness of anti-TNF therapy [4].

Conclusions

Smoking is linked to poor response to Adalimumab in RA, with higher TNF-alpha, Interleukin-6, and Matrix Metalloproteinase-3 levels indicating persistent inflammation and joint damage.

Acknowledgments
The authors thank all study participants for their cooperation.
Funders
No money was established for this training.
Conflict of Attention Statements
The authors declare no struggle of attention.

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