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Original Article

The Correlation between Pack-Years of Smoking and Disease Activity, Quality of Life, Spinal Mobility, and Sacroiliitis Grading in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Sigara Paket Yılı ve Hastalık Aktivitesi, Yaşam Kalitesi, Spinal Mobilite ve Sakroileit Derecelendirmesi Arasındaki İlişki

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Objectives: This study aims to investigate the correlation between the pack-years of smoking and disease activity, quality of life, spinal mobility, and sacroiliitis grading and ankylosing spondylitis (AS) in Iranian patients with AS.

Patients and methods: A total of 160 AS patients were evaluated according to their smoking status and pack-years of smoking. The outcome measures were disease activity, quality of life, spinal mobility, and sacroiliitis grading, and these were assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Quality of Life (ASQoL), Bath Ankylosing Spondylitis Metrology Index (BASMI), and radiography, respectively.

Results: The smoking quantity was significantly higher in the patients with severe sacroiliitis than those with mild or moderate disease (p=0.001). A univariate analysis revealed an association between the pack-years of smoking and the BASDAI [regression coefficient (B)=0.05, standard error (SE)=0.02, 95% CI: 0.006 to 0.10; p=0.03], ASQoL (B=0.15, SE=0.06, 95% CI: 0.04 to 0.26; p=0.007), and BASMI (B=0.05, SE=0.02, 95% CI: 0.006 to 0.08; p=0.03). A multivariate analysis revealed a significant association between the pack-years of smoking and the BASDAI and ASQoL.

Conclusion: An independent correlation between smoking quantity with disease activity and quality of life was confirmed in a group of Iranian AS patients. There was also a relationship between smoking quantity and spinal mobility, however, it was dependent on other related factors. Patients who smoke should be encouraged to quit or smoke less to achieve a better outcome.

Key words: Ankylosing spondylitis; mobility limitation; quality of life; sacroiliitis; smoking.

Amaç: Bu çalışmada İranlı ankilozan spondilit (AS) hastalarında sigara paket yılı ve hastalık aktivitesi, yaşam kalitesi, spinal mobilite ve sakroileit derecelendirmesi ve AS arasındaki ilişki araştırıldı.

Hastalar ve yöntemler: Sigara içme durumlarına ve sigara paket yılına göre toplam 160 AS hastası değerlendirildi. Sonuç ölçümleri hastalık aktivitesi, yaşam kalitesi, spinal mobilite ve sakroileit derecelendirmesi olup, sırasıyla Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI), Ankilozan Spondilit Yaşam Kalitesi (ASQoL), Bath Ankilozan Spondilit Metroloji İndeksi (BASMI) ve radyografi ile değerlendirildi.

Bulgular: Hafif veya orta düzeyde hastalığı olanlara kıyasla, şiddetli sakroileiti olan hastalarda sigara içme miktarı anlamlı düzeyde daha yüksekti (p=0.001). Tek değişkenli analizde sigara paket yılı ve BASDAI [regression coefficient (B)=0.05, standard error (SE)=0.02, %95 CI: 0.006-0.10; p=0.03], ASQoL (B=0.15, SE=0.06, %95 CI: 0.04-0.26; p=0.007) ve BASMI (B=0.05, SE=0.02, %95 CI: 0.006-0.08; p=0.03) arasında bir ilişki izlendi. Çok değişkenli analizde ise, sigara paket yılı ve BASDAI ve ASQoL arasında anlamlı bir ilişkiye rastlandı.

Sonuç: Bir grup İranlı AS hastasında sigara miktarı ve hastalık aktivitesi ve yaşam kalitesi arasında bağımsız bir ilişki olduğu doğrulandı. Ayrıca içilen sigara miktarı ve spinal mobilite arasında da bir ilişki vardı; ancak bu başka ilintili faktörlere bağlıydı. Sigara içen hastalara, daha iyi sonuçlar elde etmeleri için, sigarayı bırakmaları veya daha az içmeleri telkin edilmelidir.

Anahtar sözcükler: Ankilozan spondilit; mobilite kısıtlılığı; yaşam kalitesi; sakroileit; sigara kullanımı.

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Ankylosing spondylitis (AS) is the most common disorder in a group of chronic rheumatic diseases called spondyloarthropathies, and it affects individuals worldwide at the age when they do their most productive work. Axial skeleton involvement is the primary manifestation of AS, but peripheral arthritis and extra-articular involvement also occur. The progressive course of the disease can result in chronic disability that requires assistance at work or even withdrawal from the workforce. Studies have also reported the important impact on healthcare and other resources that are utilized by AS patients.[1,2] The detrimental impact on the health, social, professional, and psychological status of these patients and the resulting economic burden placed on the related communities has caused researchers to investigate the factors which may play a role in the disease outcome. In addition to genetic factors, environmental factors such as physically demanding jobs, educational level, associated morbidities (nephrolithiasis, hypertension, etc.), a family history of AS, and age at disease onset have been reported to affect the clinical manifestations or severity of AS.[3-7]

Smoking is one of the modifiable lifestyle factors that has been proposed as being responsible for the more severe form of AS in recent years.[5] Conversely, to the best of our knowledge, only a few studies have focused on the relationship between the quantity of smoking (pack-years) and severity markers in AS.[3,5] Furthermore, a variety of environmental factors can affect disease activity, quality of life (QoL), and disease progression in communities and geographic regions with heterogeneous genetic patterns. Therefore, we sought to determine the correlation between pack-years of smoking on disease activity, QoL, and spinal mobility in a group of Iranian patients with ankylosing spondylitis (AS).

PATIENTS AND METHODS

A total of 160 patients with AS were recruited consecutively into a cross-sectional study from the Iranian AS Association, the Iranian Rheumatology Center, and the Rheumatology Clinic in Shariati Hospital (Tehran University of Medical Sciences, Tehran, Iran). The diagnosis of AS was established by a qualified rheumatologist, and the 1984 modified New York diagnostic criteria for AS was used for defining the disease.[8] Only patients who were 18 years of age and older with available detailed smoking data were included in the study. Written informed consent was obtained from the patients in accordance with the Declaration of Helsinki before enrolling, and the study protocol was approved by the ethics committee of the Research Department of Tehran University of Medical Sciences. All clinical examinations and physical measurements were performed by the same rheumatologist, and a structured questionnaire was utilized for data collection which included the following: smoking status, age, gender, educational level, age at diagnosis, age at disease onset, disease duration, drug treatments, associated morbidities [hypertension, diabetes mellitus (DM), peripheral arthritis, extra-articular manifestations (uveitis, inflammatory bowel disease, psoriasis, stone and non-stone renal diseases, cardiovascular disease, and pulmonary fibrosis), associated autoimmune diseases, a family history of AS, job activity (physically active, sedentary, or both) and human leukocyte antigen B-27 (HLA-B*27)]. The outcome measures that were included were disease activity, QoL, spinal mobility, and sacroiliitis grading (New York criteria) as established by conventional radiography (grade 2: minimal, grade 3: moderate, and grade 4: ankylosis). Validated Iranian versions of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life (ASQoL) questionnaires were applied to assess the disease activity and QoL, respectively.[9-11] In addition, the Bath Ankylosing Spondylitis Metrology Index (BASMI) was used for measuring spinal mobility.[12] The BASDAI, ASQoL, and BASMI scores were also calculated at approximately the same time for all of the patients during the study for uniformity. Smoking status (current smoker, non-smoker, or ex-smoker) and quantity of smoking (pack-years) were obtained via a patient-physician interview. The pack-years of smoking was computed by multiplying the quantity of packs smoked per day by the number of years smoked, and both the ex-smokers and non-smokers were assigned scores of 0.

Statistical methods

Univariate and multivariate regression models were employed to correlate the pack-years of smoking with the BASDAI, ASQoL, and BASMI. An independent two samples t-test was used to compare continuous variables between the current and non-current smokers, and a chi-square test was used for comparing the sacroiliac grading between the same two groups. Additionally, the Kruskal-Wallis test was employed for comparing the pack-years of smoking between the patients with different sacroiliitis grading. The Predictive Analytics SoftWare (PASW) version 18 for Windows program (SPSS Inc., Chicago,

IL, USA) was utilized for statistical analysis. and a *p* value of <0.05 was considered to be significant.

RESULTS

Of the 160 affected individuals, 119 (74.4%) were positive for the HLA class 1 allele HLA-B*27 with a male-to-female ratio of 3.85. Forty-seven of the study participants were currently smoking (29.4%), 14 had quit (8.8%), and 99 did not smoke (61.8%). Furthermore, the maximum number of pack-years of smoking was 63. The characteristics of the current smokers and non-current smokers (ex-smokers and non-smokers) are shown in Tables 1 and 2.

Sacroiliitis grading (minimal: 2, moderate: 3, and ankylosis: 4) was compared between the current and non-current smokers (Table 2), and ankylosis was significantly more common in the current smokers (p=0.001). Moreover, the pack-years of smoking was significantly different between the affected individuals according to the sacroiliitis grading. For severe sacroiliitis (ankylosis), we found that the mean ± standard error (SE) for the pack-years of smoking was 5.480±1.55, the 25th percentile was 0, the median was 0.6, and the 75th percentile was 8.15. In addition, the mean ± SE for the pack-years of smoking for those with moderate sacroiliitis was 1.66±0.52, the 25th percentile was 0, the median was 0, and the 75th percentile was 0.7. Finally, the patients with minimal sacroiliitis had a mean ± SE of 2.37±1.29 for the pack-years of smoking while the 25th percentile, median, and 75th percentile were all 0 (p=0.001). In other words, the pack-years of smoking was higher for the AS patients with sacroiliac ankylosis than for those with moderate or minimal sacroiliitis.

The Bath Ankylosing Spondylitis Disease Activity Index, ASQoL, and BASMI scores were compared between the current smokers and non-current smokers, and the BASMI score was significantly higher in the current smokers (p=0.003) (Table 1). In addition, a trend toward higher scores (mean ± SE) for the current smokers was also observed in the BASDAI and ASQoL (p=0.13 and p=0.26, respectively) (Table 1).

Regression analysis

Univariate models showed a significant relationship between the pack-years of smoking (as an independent variable) and the BASDAI [regression coefficient (B)=0.05, standard error (SE)=0.02, 95% CI: 0.006 to 0.10; p=0.03], ASQoL (B=0.15, SE=0.06, 95% CI: 0.04 to 0.26; p=0.007), and BASMI (B=0.05, SE=0.02, 95% CI: 0.006 to 0.08; p=0.03). Other independent variables which were tested separately in the univariate models of the BASMI, BASDAI and ASQoL were the following: age, gender, HLA-B*27 status, educational level, age at diagnosis, age at disease onset, disease duration, job activity, associated morbidities, associated autoimmune diseases [diabetes mellitus (DM) or hyperthyroidism], a family history of AS, extra-articular manifestations, associated psychiatric disorders (depression diagnosed by a psychiatrist), and drug treatments. To control the effect of probable confounding variables, independent variables with a *p* value of <0.1 were entered in the multivariate models of the BASDAI, BASMI, and ASQoL, and these models are shown in Tables 3,

Table 1. The demographic and clinical features of the current smokers and non-current smokers in the patients with ankylosing spondylitis

	Current smokers	Non-current smokers
	Mean±SE	Mean±SE
Age (years)	37.94±1.25	37.66±0.98
Age at symptom onset (years)	22.85±0.99	23.42±0.67
Age at diagnosis (years)	31.79±1.24	30.96±0.95
Disease duration (years)	15.09±1.17	14.45±0.81
Chest expansion (cm)	3.83±0.32	4.39±0.17
Finger-to-floor distance (cm)	23.29±2.25	16.2±1.28
Modified Schober's test (cm)	2.71±0.30	3.75±0.18
Intermalleolar distance (cm)	96.94±3.61	94.52±2.26
ASQoL score (0-18)	8.77±0.87	7.63±0.46
BASMI score (0-10)	4.74±0.32	3.64±0.15
BASDAI score (0-10)	4.96±0.33	4.35±0.22

SE: Standard error; ASQoL: Ankylosing spondylitis quality of life; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

Table 2. Articular and extra-articular features, associated morbidities, treatments, and other characteristics of the current smokers and non-current smokers in the patients with ankylosing spondylitis

	Current smokers		Non-current smokers (ex-smokers, non-smokers)		Total number	
	(n=47)	(29.4%)	(n=113)	(70.6%)	(n=160)	(100%)
Gender						
Male	47	100	80	70.8	127	79.4
HLA-B*27 positive	39	83	80	70.8	119	74.4
Inflammatory bowel disease	3	6.4	8	7.1	11	6.9
Uveitis	9	19.1	13	11.5	22	13.8
Psoriasis	2	4.3	5	4.4	7	4.4
Cardiovascular disease	2	4.3	3	2.7	5	3.1
Pulmonary fibrosis	1	2.1	1	0.9	2	1.36
Nephrolithiasis	5	10.6	14	12.4	19	11.9
Diabetes mellitus	0	0	5	4.4	5	3.1
Hypertension	6	12.8	9	8	15	9.4
Asthma	4	8.5	6	5.3	10	6.3
Associated autoimmune disease	4	8.5	11	9.7	15	9.4
Family history of ankylosing spondylitis	12	25.5	37	32.7	49	30.6
Psychiatric comorbidities (depression)	12	25.5	36	31.9	48	30
Non-steroidal anti-inflammatory drugs	43	91.5	108	95.6	151	94.4
Sulfasalazine	33	70.2	85	75.2	118	73.8
Steroids	15	31.9	47	41.6	62	38.8
Any biologics (infliximab, etanercept, or both)	6	12.8	13	11.5	19	11.9
Type of job						
Sedentary	20	44.4	24	21.8	44	28.4
Active	12	26.7	48	43.6	60	38.7
Both	13	28.9	38	34.5	51	32.9
Sacroiliitis grading						
2	8	17	44	38.9	52	32.5
3	21	44.7	54	47.8	75	46.9
4	18	38.3	15	13.3	33	20.6
Peripheral arthritis	30	63.8	51	45.1	81	50.6

HLA-B*27: Human leukocyte antigen-B*27 (a class 1 allele).

4, and 5, respectively. The pack-years of smoking were positively and independently associated with the higher BASDAI (Table 3) and ASQoL scores (Table 5). However, the univariate association between the pack-years of smoking and BASMI was lost in the multivariate model (Table 4).

DISCUSSION

This survey assessed the disease activity, spinal mobility, QoL, and radiographic sacroiliitis grading in patients with AS and revealed that there was a correlation between the pack-years of smoking and

Table 3. Multivariate regression model showing the relationship between pack-years of smoking and the Bath Ankylosing Spondylitis Disease Activity Index in the patients with ankylosing spondylitis

Model	Regression coefficients			95% Confidence interval for B	
	B	Standard error	*p*	Lower boundary	Upper boundary
(Constant)	4.3	0.88	Less than 0.001	2.49	5.96
Pack-years	0.05	0.02	0.05	0	0.094
Educational level	−0.20	0.12	0.10	−0.43	0.04
Age at diagnosis (years)	0.02	0.02	0.20	−0.01	0.06
Nephrolithiasis	1.02	0.54	0.06	−0.05	2.09
Psychiatric comorbidities (depression)	0.87	0.38	0.02	0.12	1.62

B: Regression coefficient.

Table 4. Multivariate regression model showing the relationship between pack-years of smoking and the Bath Ankylosing Spondylitis Metrology Index in the patients with ankylosing spondylitis

Model	Regression coefficients			95% Confidence interval for B	
	B	Standard error	*p*	Lower boundary	Upper boundary
(Constant)	1.87	0.76	0.02	0.37	3.37
Pack-years	0.01	0.02	0.44	−0.02	0.05
Age (years)	0.04	0.03	0.19	−0.02	0.10
Gender	0.70	0.32	0.03	0.08	1.32
Type of job	0.31	0.15	0.04	0.02	0.60
Educational level	−0.36	0.09	Less than 0.001	−0.53	−0.19
Age at diagnosis (years)	0.01	0.02	0.71	−0.04	0.06
Disease duration (years)	0.04	0.03	0.13	−0.01	0.09
Nephrolithiasis	0.52	0.38	0.18	−0.24	1.27
Hypertension	0.84	0.45	0.06	−0.05	1.72
Asthma	0.63	0.51	0.22	−0.37	1.63

B: Regression coefficient.

these profiles. In the univariate analysis, the pack-years of smoking was significantly associated with disease activity, spinal mobility, and QoL. Regarding other probable confounding factors in the multivariate analysis, a significant correlation was maintained for disease activity and QoL but not for spinal mobility. In addition, the severity of radiographic sacroiliitis was influenced by smoking quantity. These facts indicate that the pack-years of smoking may at least be considered to be an independently associated factor for higher disease activity and poorer QoL.

A few studies concerning AS and one study focused on early axial spondyloarthropathies showed a connection between cigarette smoking and higher disease activity along with poorer Qol.[7,13-17] However, the relationship between smoking and radiographic severity has not been consistent in the literature.[3-15,18]

To our knowledge, the first survey which exposed the connection between smoking and AS patient outcomes was by Averns et al.[15] in 1996. This investigation was included AS patients with a median duration of 20 years, and the authors found significant differences between smokers and non-smokers with regard to the finger-floor distance, Schober's test, total spinal involvement, occiput-to-wall distance, functional status, stiffness, and spinal radiographic damage.

In a survey by Kaan and Ferda,[13] they determined that there was an connection between smoking (more than five pack-years) and higher disease activity (based on the BASDAI developed by Garrett et al.[9]) along with higher mobility restriction (based on chest expansion, hand-ground distance, the modified Schober's test, and occiput-to-wall distance).

The study by Bodur et al.,[17] which was evaluated related variables associated with QoL in patients with AS, revealed a poorer QoL (as measured by ASQoL) in smokers than non-smokers. However, the QoL based

Table 5. Multivariate regression model for relationship between pack-years of smoking and the Ankylosing Spondylitis Quality of Life in the patients with ankylosing spondylitis

Model	Regression coefficients			95% Confidence interval for B	
	B	Standard error	*p*	Lower boundary	Upper boundary
(Constant)	9.29	1.96	Less than 0.001	13.16	5.43
Pack-years	0.11	0.05	0.04	0.21	0.003
Age at diagnosis (years)	0.03	0.04	0.45	0.12	−0.05
Disease duration (years)	0.01	0.05	0.82	0.12	−0.09
Nephrolithiasis	1.80	1.21	0.14	4.18	−0.59
Hypertension	2.58	1.38	0.06	5.30	−0.14
Educational level	−0.85	0.26	0.001	−0.33	−1.37
Psychiatric comorbidities (depression)	2.72	0.85	0.002	4.38	1.05

B: Regression coefficient.

on the short form-36 (SF-36) subscale scores did not differ significantly between the two groups.

The Data from an Epidemiological Study on Insulin Resistance Syndrome (DESIR) study (a large multi-center study in France) was conducted on patients with spondyloarthropathies with a disease duration of less than three years, and it showed an independent association between smoking and an earlier onset of inflammatory back pain, higher activity, poorer QoL, and worsening functional status.[18] Furthermore, this study showed that the inflammatory back pain occurred one and a half years earlier in 37% of the smokers compared with the non-smokers. The earlier onset of back pain was not dependent on age, gender, race, HLA-B*27 status, or other probable confounding variables. Moreover, more progressive inflammation and damage was seen in the spinal magnetic resonance imaging (MRI) results of the smokers compared with the non-smokers in their study. However, the quantity of smoking (pack-years) was not clarified by Chung et al.[18] in their analysis of the DESIR study. However, we chose to define the number of pack-years of smoking; therefore, the cumulative effects of smoking on outcome measures were quantified in our study. Moreover, in contrast to the Chung et al.[18] study in which both current and ex-smokers were analyzed and then compared with non-smokers, we compared current smokers with ex-smokers and non-smokers. Furthermore, given that the benefits for those who quit smoking begin immediately, the pack-years of smoking was considered to be 0 for individuals who quit at the time of evaluation in our study.

The first study which revealed the dose-dependent relationship between smoking and the outcomes of AS was in a survery by Mattey et al.[5] in 2011 that included a total of 612 AS patients across the United Kingdom. They determined that the correlation between smoking and higher disease activity, poorer QoL, and a lower functional status did not depend on age, gender, or disease duration.

In addition, Ward et al.[3] revealed that radiographic severity is predicted by a history of smoking as well as age at disease onset, male gender, and some HLA alleles.

In their research, Poddubnyy et al.[19] showed an independent association between smoking and the progression of spinal radiographic damage in patients with early axial spondyloarthropathy. However, they determined that other variables like the BASDAI, BASFI, peripheral arthritis, a family history of AS, and treatments at baseline were not associated with the severity of spinal radiographic damage.

It is known that tobacco smoke may affect the immune system in a variety of ways, including the expansion of auto-reactive B-lymphocytes and circulating T-lymphocytes and an increase in the production of pro-inflammatory cytokines such as interleukin 1, 6, 8, tumor necrosis factor α (TNF α), and granulocyte-macrophage colony stimulating factor (GMCSF). In addition, there can be an increase in matrix metalloproteinases (MMP-8, MMP-9) activation and neutrophil counts along with enhanced oxidative stress (OS) stimulation and the production of free radicals.[19-26] Moreover, smokers do not respond as well to treatment compared with non-smokers, which might be another reason for the higher disease activity and subsequent increased restriction in spinal mobility in AS smokers versus AS non-smokers. This has been shown to be true with rheumatoid arthritis (RA), but future investigation is needed to confirm that it takes place in AS patients as well.[27]

One of the advantages of our study was that we separated the current smokers from the ex-smokers. This is important because in some other studies they are grouped together. Another advantage was that we defined the quantity of smoking (pack-years), which has not always been the case in previous studies. However, A limitation of our study was that since it was cross-sectional, we could not definitively conclude that smoking was responsible for the aforementioned outcomes. In other words, there can be a relationship between smoking and outcomes in the opposite direction. Therefore, AS patients with higher disease activity, more spinal mobility restriction, and poor quality of life are probably more willing to smoke. Hence, another study in which the patients are followed up for a period of time should be undertaken to establish whether pack-years of smoking is a risk factor for poorer outcomes. Another limitation was the lack of radiographic and MRI evaluation for spinal damage as an outcome variable. This occurred because we had incomplete access to the spinal radiographic imaging of the patients. However, assessment for sacroiliitis grading with conventional pelvic X-ray was performed for all patients.

In conclusion, we determined that pack-years of smoking was independently associated with higher disease activity and poorer QoL in a group of Iranian AS patients. Additionally, the reduced spinal mobility that occurred with increased smoking was probably

due to other associated factors during disease progression. Furthermore, the increased quantity of smoking in patients with sacroiliac ankylosis rather than those with milder forms of sacroiliitis suggests that there is more severe disease in smokers than non-smokers. Therefore, AS patients should be encouraged to quit or decrease their smoking since this might modify the disease course and outcome by lowering systemic inflammation and possibly provide a better treatment response. In turn, this might lower other associated morbidities to levels that are similar to individuals without AS. However, future trials are needed in order to verify this hypothesis.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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