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EFFECTS OF SMOKING IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS RECEIVING TUMOR NECROSIS FACTOR INHIBITORS THERAPY

TÜMÖR NEKROZİS FAKTÖR İNHİBİTÖRÜ TEDAVİSİ ALAN AKSİYAL SPONDİLOARTRİTLİ HASTALARDA SİGARANIN ETKİLERİ

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ABSTRACT

Objective: The aim of this study was to examine the impact of smoking on axial spondyloarthritis (axSpA) patients taking tumor necrosis factor inhibitors (TNFi).

Material and Method: Our study consisted of 211 patients who were diagnosed with axSpA and received TNFi treatment in the rheumatology outpatient clinic. The patients were evaluated retrospectively, cross-sectionally and grouped by intensity of smoking (pack-years). Those who smoked>20 pack-years were defined as heavy smokers. Groups were compared in terms of physical examination, laboratory values and disease evaluation indexes (Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life (ASQoL) and Beck Depression Inventory (BDI) scores. Mann-Whitney U and Spearman correlation analysis tests were used for data analysis

Results: Comparison of the smoker (n=121) and non-smoker groups (n=90) revealed BASMI was lower in the non-smoker group (p=0.04). Smoking intensity correlated with BDI (r=0.323, p<0.001), BASDAI (r=0.257, p=0.005), BASMI components (lomber lateral flexion (LLF) (r=-0.303, p=0.001), cervical rotation (CR) (r=-0.232, p=0.012), and tragus wall distance (TWD) (r=0.27, p=0.003)). Multivariate analysis revealed an association between the pack-years of smoking and the BASMI [regression coefficient (B)=0.067, standard error (SE)=0.22, 95%CI=0.02, 0.10; p=0.003],

ÖZET

Amaç: Bu çalışma tümör nekrozis faktör alfa inhibitörü (TNFi) alan aksiyal spondiloartrit (axSpA) hastalarında sigaranın etkisini değerlendirme amacıyla yapıldı.

Gereç ve Yöntem: Çalışmamıza Romatoloji polikliniğinde axSpA tanısıyla tümör nekroz faktör alfa (TNFα) inhibitörü tedavisi alan 211 hasta alındı. Hastalar retrospektif, kesitsel olarak değerlendirildi ve sigara içme yoğunluğuna (paket-yıl) göre gruplandırıldı. Sigarayı >20 paket yıl üzerinde içenler ağır içiçi olarak tanımlandı. Gruplar fizik muayene ölçümleri, laboratuar ve hastalık değerlendirme indeksleri (Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) ve Ankylosing Spondylitis Quality of Life (ASQoL) ve Beck Depression Inventory (BDI)) ile karşılaştırıldı. Verilerin analizinde Mann-Whitney U ve Spearman korelasyon analizi testleri kullanıldı.

Bulgular: Sigara içen (n=121) ve içmeyen (n=90) grup karşılaştırıldığında BASMI sigara içmeyen grupta düşük bulunmuştur (p=0,04). Sigara içme yoğunluğu ile yapılan korelasyon analizinde BDI (r=0,323, p<0,001), BASDAI (r=0,257, p=0,005) ve BASMI bileşenleri (lomber lateral fleksiyon (LLF) (r=-0,303, p=0,001) bulunmuştur. Multiple lineer regresyon analizinde sigara paket-yılı ile BASMI [regresyon katsayısı (B)=0,067, standart hata (SE)=0,22, %95CI=0,02, 0,10; p=0,003], BASFI'nin başlangıç ($_B$=tedavi öncesi) ve son değeri ($_L$=tedavi sonrası) arasındaki

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baseline ($_B$=pretreatment)-last value ($_L$=posttreatment) difference of BASFI [B=-0.063, SE=0.02, 95%CI=-0.10, -0.20; p=0.003], of BASDAI [B=-0.047, SE=0.02, 95%CI=-0.08, -0.007; p=0.026], ASQoL [B=-0.125, SE=0.04, 95%CI=0.04, -0.20; p=0.003]. In heavy smokers, significant worsening was found in LLF_L (p=0.01), CR_L (p=0.04), TWD_L (p=0.001), $BASFI_L$ (p=0.035) and $BASMI_L$ (p=0.001). Significant differences were found in the baseline ($_B$) and last ($_L$) BASDAI (p=0.042), $BASFI_L$ (p=0.002), $BASFI_{B-L}$ (p=0.07) and BASMI (p=0.03) values in the nonradiograpic-axSpA group in heavy smokers, compared to the AS group.

Conclusion: Our study showed that smoking, especially heavy smoking, has a negative effect in every phase of axSpA. Smoking intensity may correlate with reduced response to TNFi.

Keywords: Axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthiris, tumor necrosis factor inhibitor therapy, smoking

farkı [B=-0,063, SE=0,02, %95CI=-0,10, -0,20; p=0,003], BASDAI [B=-0.047, SE=0,02, %95CI=-0,08, -0,007; p=0,026] ve ASQoL [B=-0,125, SE=0,04, %95CI=0,04, -0,20; p=0,003] arasında ilişki saptandı. Ağır sigara içicilerinde LLF_L (p=0,01),CR_L (p=0,04), TWD_L (p=0,001), $BASFI_L$ (p=0,035) ve $BASMI_L$ (p=0,001)'de anlamlı kötüleşme bulundu. Nonradyografik-axSpA grubunda ağır içicilerde AS grubuna göre $BASDAI_{B-L}$ (p=0,042), $BASFI_L$ (p=0,002), $BASFI_{B-L}$ (p=0,07) ve BASMI (p=0,03) değerlerinde anlamlı farklılıklar saptandı.

Sonuç: Çalışmamız sigara kullanımının özellikle sigara içme yoğunluğunun axSpA'nın her döneminde olumsuz etkisi olduğu göstermiştir. Sigara içme yoğunluğu, TNFi'ye verilen yanıtın azalmasıyla ilişkili olabilir.

Anahtar Kelimeler: Aksiyal spondiloartrit, ankilozan spondilit, non-radyografik aksiyal spondiloartrit, tümör nekrozis faktör inhibitörü tedavisi, sigara

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease involving the spine and sacroiliac joints, causing inflammatory back pain and progressive spinal stiffness (1). It includes AS and nr-axSpA. Various environmental and genetic risk factors may affect AS in terms of functional status and disease activity. Understanding these factors can give us an idea to determine how limitations occur, the pathogenesis of severe AS, and our treatment approach. By identifying risky groups, it may be possible to prevent functional limitations and improve the quality of life (2).

The interaction of genetic and environmental factors is important in the pathogenesis of AS and other inflammatory rheumatologic diseases, and it has been suggested that smoking, one of the environmental factors, increases functional limitation (3). Smoking has pro-inflammatory effects (4). Smoking may also have negative effects on the prognosis of other rheumatologic diseases (5). Smokers with rheumatoid arthritis (RA) require more intensive treatment. It has been shown that active smoking is the most significant environmental factor responsible for disease pathogenesis in RA and systemic lupus erythematosus (6). It is known that long-term consequences of smoking are detrimental for patients and worsen functional impairment disease activity and radiological progression in patients with axSpA (2, 7-12).

The mechanism for these detrimental effects of smoking is unclear despite the impact of smoking on RA being well established. On the treatment of smokers with RA, TNFI agents have been shown to be less effective (13). There are varying results regarding the effect of smoking in axSpA patients receiving TNFi treatment. Although some studies have shown that smoking reduces the response to TNFi treatment, others could not find any effect of smoking on treatment outcomes (14-17).

In this study, we evaluated both the response of TNFi treatment and the effects of smoking on spinal movement, functional status, disease activity and quality of life, in patients with axSpA.

MATERIAL AND METHODS

We included 211 patients received TNFi therapy in the outpatient clinic of Rheumatology between January 2000 and March 2013. Patients were classified according to the Assessment in SpondyloArthritis International Society (ASAS) and divided in two groups: AS patients with respect to the Modified New York Classification Criteria and nr-axSpA patients.

The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 22.03.2013, No: 06). The patient charts were evaluated retrospectively in this cross-sectional study. The demographic data, clinical, physical examination, laboratory findings and smoking status were recorded in a "disease evaluation form" that had been created previously. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are indicators of inflammation/disease activity in AS, were noted. Physical examination findings (modified Schober test (MST), chest expansion (CE), finger floor distance (FFD), tragus wall distances (TWD), lumbar lateral flexions (LLF), cervical rotation (CR), occiput wall distances (OWD), chin–chest distance (CCD), intermalleoler distance (IMD), laboratory BASMI, BASDAI, BASFI, ASQoL and BDI were evaluated after TNFi therapy (1). Pre-treatment values were considered the baseline ($_B$) values and post-treatment values were considered the last ($_L$) values. BASDAI and BASFI were used to evaluate TNFi treatment response.

The patients were questioned about their smoking habits. The current smokers and ex-smokers were included in the smokers group. Those who quit smoking were defined as those who did not smoke in the last 3 months. According

to the duration and amount of smoking of the patients, the smoking intensity was calculated as pack-years. Cigarette pack-years was obtained by multiplying the number of packs the patient smoked per day by the year he smoked. Smokers of more than 20 pack-years and less than 20 pack-years were considered heavy smokers and light smokers, respectively. The effects of smoking on physical examination, laboratory findings, functional status, disease activity, quality of life and depression were compared.

Statistical analysis

Descriptive statistics were used to present continuous variables (mean, standard deviation, minimum, median, maximum). The comparison of two independent and non-normally distributed variables was performed with the Mann-Whitney U test.

Spearman's rho correlation analysis was used to analyze the relationship between two non-normally distributed continuous variables. Multivariable linear regression analysis was applied to examine the effect of independent variables on the continuous dependent variables. Chi-Square (or Fisher Exact test where appropriate) was used to examine the relationship between categorical variables. Analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http=//www.medcalc.org; 2013). In all analyses, p values<0.05 were considered statistically significant.

RESULTS

A total of 211 patients with a mean age of 41.06±11.59 years were included in the study. There were 148 (70.1%) males and 63 (29.9%) females. The percentage of smokers and non-smokers were 56.9% and 43.1% respectively. The mean smoking intensity in the whole group was 15.31±14.07 in cigarette pack-years. The comparison of physical examination, laboratory values, disease functional status, spinal mobility assessment scales and quality of life indexes are shown in Table 1. MST_L (p=0.043), LLF_L (p=0.037), CE_L

Table 1: Comparison between smoking and non-smoking patients' physical examination, laboratory, and evaluation indexes

	Non-smokers (n=90)		Smokers (n=121)		P
	Mean±SD	Median, Range	Mean±SD	Median, Range	
Age (years)	38.34±1.10	38 (18-66)	43.11±1.16	42.5 (18-82)	**0.003***
Gender (F/M)	49/42		99/21		**<0.001***
Duration of illness (years)	12.92±9.07	10 (0.7-43)	17.35±10.32	15 (2-49)	**0.001***
Duration of TNFi (month)	40.67±25.94	36.5 (3-108)	44.00±21.80	43 (2-111)	0.225
ESR_L (mm/h)	49.4±3.35	46.5 (3-126)	49.83±3.35	41 (4-120)	0.92
CRP_L (mg/L)	29.98±3.82	14.7 (0,4-178)	37.9±4.54	22.6 (0.3-265)	0.19
FFD_L (cm)	12.48±13.12	10 (0-60)	20.68±15.15	20 (0-63)	**<0.001***
CE_L (cm)	3.37±1.87	3 (0.5 -8)	2.81±1.81	2.9 (0-10)	**0.037***
OWD_L (cm)	6.4±8.05	5 (0-41)	8.28±8.28	7.5 (0-34)	**0.049***
$BASMI_L$	3.05±2.44	2 (0-8)	3.71±2.47	3.5 (0-9)	**0.043***
MST_L (cm)	3.6±1.83	4 (0-7)	3.08±2.01	3.5 (0-7)	**0.043***
LLF_L (cm)	13.73±8.06	12 (2-56)	11.53±6.89	11(2-51)	**0.037***
CR_L (°)	59.83±2.50	62.5 (0-90)	54.41±2.46	60 (0-90)	0.1
IMD (cm)	91.58±24.98	90 (25-140)	91.19±23.09	95 (35-133)	0.94
TWD_L (cm)	15.98±7.08	14 (8-48)	17.77±7.41	16.5 (6-40)	**0.044***
$BASDAI_B$	4.09±0.58	4 (4-8.9)	4.02±0.24	4 (3.6-6.6)	0.28
$BASDAI_L$	3.83±2.54	3.7 (0-9.5)	3.48±2.23	3.2 (0-9)	0.20
$BASDAI_{B-L}$	0.25±2.58	0.35 (-5.5, -4.5)	0.54±2.28	0.8 (-5, 6.2)	0.52
$BASFI_B$	4.05±0.73	4 (1.8-9)	4.10±0.91	4 (2.3-13)	0.58
$BASFI_L$	2.7±2.67	1.7 (0-9.8)	3.04±2.43	2.7 (0-9.7)	0.41
$BASFI_{B-L}$	1.29±2.68	2.2 (-8.05, 4)	1.08±2.49	1.85 (-5.7, 7.4)	0.25
$ASQoL_L$	6.81±5.62	6 (0-18)	6.09±4.99	5 (0-17)	0.32

*Statistically significant p values are shown in bold. p values <0.05 are significant. Mann–Whitney test was used for comparisons. TNFi: Tumor necrosis factor-alpha inhibitors, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, FFD: finger floor distance, CE: chest expansion, OWD: occiput wall distances, BASMI: Bath Ankylosing Spondylitis Metrology Index, MST: modified Schober's test, LLF: lumbar lateral flexions, CR: cervical rotation, IMD: intermalleolar distance, TWD: tragus wall distances, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life Scale, B: baseline, L: last value.

(p=0.037) were lower and OWD_L (p=0.049), TWD_L (p=0.044), FFD_L (p<0.001) values were higher in the smoking group compared to non-smokers. BASMI, which evaluates spine mobility, was higher in the smoker group (p=0.043). The difference between the baseline and last values of ESR and CRP was significant in both groups (p <0.001).

When the non-smoker group (13.7±8.11) and the ex-smoker groups (10.5±6.27) were compared, LLF_L was significantly decreased in the ex-smoker group (p=0.028). The MST_B was significantly more limited in the ex-smoker group (p=0.04). FFD_B was significantly lower in the non-smoker group (14.27±14.35) compared to the ex-smoker group (24.74±17.91) (p=0.002). FFD_L was 12.38±13.17 in the non-smoker group, and 22.26±15.10 in the ex-smoker group, in which it was significantly more limited (p<0.001).

Smokers were divided into two groups according to duration of smoking, i.e. less (1st group) or more (2nd group) than 10 years of smoking. OWD_B (p=0.04), TWD_L (p=0.005) and CCD_L (p=0.02) levels were higher and MST_L, LLF_L, AR_L, CE_L (p=0.03, p=0.005, p=0.031 respectively) were lower in the 2nd group than in the 1st group. In comparison, $BASFI_L$ and $BASMI_L$ values were detected to be high in 2nd group (p=0.02, p=0.01).

When the heavy smoker group with more than 20 cigarette pack-years is compared with the light smoker group, FFD_B, FFD_L, CR_L, CE_L, $BASFI_{B-L}$ (p=0.03, p=0.007, p=0.004, p=0.002, p=0.03 respectively) were lower and OWD_L (p=0.02), TWD_L (p=0.001), CCD_L (p=0.006), $BASMI_L$ (p=0.001), $BASFI_L$ (p=0.03) were higher in the heavy smoker group. There were no differences in the $BASDAI_B$ and $BASFI_B$ between the two groups (p>0.05).

The significant correlations between smoking intensity (pack-years) and physical examination, laboratory and assessment indices are shown in Table 2. Cigarette pack-years was found to have moderate positive correlation with age and BDI, moderate negative correlation with CR_B, low negative correlation with LLF_L, CR_L and CE_L, and low positive correlation with OWD_L, TWD_L, CCD_L and $BASDAI_L$ (Spearman's rho p<0.05).

Table 2: Correlation analysis between smoking intensity (pack-years) and physical examination, laboratory, and assessment indexes

Cigarette pack-years	r	p
Age	**0.323**	**<0.001***
CR_B	**-0.65**	**0.042***
LLF_L	**-0.303**	**0.001***
CR_L	**-0.232**	**0.012***
CE_L	**-0.255**	**0.005***
OWD_L	**0.198**	**0.032***
TWD_L	**0.27**	**0.003***
CCD_L	**0.25**	**0.006***
$BASDAI_L$	**0.257**	**0.005***
BDI	**0.323**	**<0.001***

*p values <0.05 are significant. Pack–years of smoking (product of years of smoking and packs of cigarette per day). r is determined by Spearman's rank correlation test. B: baseline, L: last value.
CR: cervical rotation, LLF: lumbar lateral flexions, CE: chest expansion, OWD: occiput wall distances, TWD tragus wall distances, CCD: chin–chest distance, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BDI: Beck Depression Inventory, B: baseline, L: last value.

In the multivariable linear regression analysis, cigarette pack-years, heavy smokers, and smokers (light and heavy smokers) were modeled as independent variables (Table 3). Cigarette pack-years was found to be significant by backward variable method. The model is statistically significant (p<0.001). 1 unit change in cigarette pack-years increased ASQoL by 0.125 (p<0.001), BASMI by 0.067

Table 3: Multivariable linear regression analyses showing cigarette pack-years associated with ASQoL, BASMI, BASDAI, BASFI

	ASQoL			BASMI			$BASFI_{B-L}$			$BASDAI_{B-L}$		
	β	**SD**	**p**	**β**	**SD**	**p**	**β**	**SD**	**p**	**β**	**SD**	**p**
Coefficient	4.394	0.814	**<0.001**	2.585	0.435	**<0.001**	2.205	0.41	**<0.001**	1.201	0.414	**0.005**
Cigarette pack-years	0.125	0.040	**0.003**	0.067	0.022	**0.003**	-.063	0.02	**0.003**	-.047	0.021	**0.026**
	R^2=0,105 p=0.003 F=9.599			R^2=0,104 p=0.003 F=9.620			R^2=0,104 p=0.003 F=9.581			R^2=0,066 p=0.026 F=5.147		

p values <0.05 are significant. β: Standardized coefficient. B: baseline, L: last value. ASQoL: Ankylosing Spondylitis Quality of Life Scale, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

units (p<0.001), and decreased $BASFI_{B-L}$ difference by 0.063 units (p<0.001), as well as $BASDAI_{B-L}$ difference by 0.047 units (p <0.001).

All patients diagnosed with axSpa includes AS (n=142) and nr-axSpA (n=69). No statistically significant difference was found between the groups in terms of smoking status, amount and duration of smoking. Then the effects of smoking was compared in both AS and nr-axSpA groups, according to the patient classification criteria. No significant difference was found in terms of physical examination, laboratory, and evaluation indices in the nr-axSpA group. In the AS group, FFD_B was significantly lower in the first non-smoker group (14.52±14.12) compared to the smoker group (28.54±17.34) (p<0.001). FFD_L was significantly lower in the non-smoker group (13.5±13.16) than in the smoking group (23.23±4.56) (p<0.001). In the AS and nr-axSpa groups, no statistically significant difference was found in terms of distribution of parameters between non-smokers and ex-smokers.

Comparing non-smokers (58 AS, 32 nr-axSpA) and ex-smokers (32 AS, 10 nr-axSpA), a difference was found between MST_B (p=0.04), FFD_B (p<0.001), FFD_L (p<0.001) and LLF_L (p=0.03) in the AS group. There was no difference between non-smokers and ex- smokers in the nr-axSpA group in terms of physical examination, laboratory and evaluation indexes.

Subgroup analysis

In the comparison between the smokers in the AS and nr-axSpA groups (56 light smokers, 23 heavy smokers), there was no difference in terms of physical examination, laboratory and evaluation indexes in the AS group. BDI was significantly higher in the AS group (p=0.022). In the nr-axSpA group, MST_B, CE_L, TWD_L were more limited in the heavy smoker group (p=0.024, p=0.002, p=0.022, respectively). Among the evaluation indexes, $BASDAI_L$, $BASFI_L$, BASMI, $BASFI_{B-L}$, $BASDAI_{B-L}$ and ASQoL were higher in heavy smokers (p=0.018, p=0.004, p=0.008, p=0.001, p=0.018, p=0.039, respectively) (Table 4).

Table 4: Evaluation of light and heavy smokers by AS and nr-AxSpA groups

Mean+SD Median (Min-Max.)	AS			nr-AxSpA		
	Light (n=39)	Heavy>20 years (n=14)	p	Light (n=17)	Heavy>20 years (n=9)	p
MST_B	2.92±2.07 2 (0-8)	2.59±0.97 2.5 (1-4.5)	0.905	5.16±1.43 5.5(3-6.5)	1.16±1.60 0.5(0-3)	**0.024***
CE_L	2.80±1.95 3 (0-10)	2.32±1.58 2.25 (0-5.5)	0.394	4.07±1.49 4(1.5-8)	2.05±1.37 2(0.5-5)	**0.002***
TWD_B	18±8.39 16 (7-40)	19.42±4.86 20 (10-30)	0.236	13.55±5.44 12(6-28)	20.44±9.4 16(12-39)	**0.022***
$BASFI_B$	4.09±0.59 4 (4-7.7)	4±0 4 (4-4)	0.549	4.53±2.18 4 (4-13)	4±0 4 (4-4)	0.833
$BASFI_L$	2.81±2.3 2 (0-9.45)	3.31±2.39 3.2 (0-6.85)	0.431	1.78±2.06 1 (0-6.9)	4.37±1.88 4.35 (1.1-7.05)	**0.004***
$BASDAI_B$	4.01±0.06 4 (4-4.4)	4.19±0.69 4 (4-6.6)	0.427	4±0 4 (4-4)	3.96±0.13 4 (3.6-4)	0.672
$BASDAI_L$	3.27±2.09 3.2 (0-8.2)	4.32±2.86 4.65 (0-9)	0.149	2.62±2.09 2 (0.25-7.7)	4.6±1.88 5.2 (1.85-6.8)	**0.018***
$BASMI_c$	3.79±2.63 3 (0-8)	4.71±1.86 5 (1-8)	0.207	1.76±1.99 1 (0-6)	4.44±2.24 4 (2-8)	**0.008***
ASQoL	5.74±4.53 5 (0-17)	8.36±4.83 7.5 (2-17)	0.067	4.29±4.55 3 (0-14)	8.33±4.47 10 (1-15)	**0.039***
BDI_L	9.44±9.56 7 (0-40)	13.5±7.6 10.5 (5-29)	**0.022**	9.76±10.23 7 (0-34)	12.89±9.24 10 (2-31)	0.241
$BASFI_{B-L}$	1.28±2.25 2 (-5.45-4)	0.69±2.39 0.8 (-2.85-4)	0.358	2.75±2.17 3 (-2.9-7.4)	-0.37±1.88 -0.35 (-3.05-2.9)	**0.001***
$BASDAI_{B-L}$	0.74±2.09 0.8 (-4.2-4)	-0.14±3.2 -0.65 (-5-6.2)	0.173	1.38±2.09 2 (-3.7-3.75)	-0.64±1.91 -1.2 (-2.8-2.15)	**0.018***

*Statistically significant p values are shown in bold. p values <0.05 are significant. Mann–Whitney test was used for comparisons. B: baseline, L: last value, MST: modified Schober's test. CE: chest expansion, TWD: tragus wall distances, BASFI: Bath Ankylosing Spondylitis Functional Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BDI: Beck Depression Inventory, ASQoL: Ankylosing Spondylitis Quality of Life Scale.

DISCUSSION

In this study, we confirmed the negative impact of smoking on disease activity, functional limitation and response to TNFi. Especially intensity of smoking (pack-years) plays a significant role. The increase in the pack-years and the decrease in $BASDAI_{B-L}$and $BASFI_{B-L}$ in multivariable regression analysis suggest that high intensity smoking decreases the response to TNFi treatment.

Villaverde et al.'s literature review shows that smoking is closely related to the dose effect on the progression of anatomical damage in axSpA, and disease activity and physical limitations were found to be worse in smoking patients (18). In our study, we found that smoking affected MST, FFD, LLF, CE, ODW, TDW values after treatment and determined high BASMI in smokers. In the study conducted by Chen et al. on Chinese AS patients, a comparison of the smoker and the non-smoker groups yielded a significant decrease in MST, AR, LLF, and CE, and an increase in OWD (6). Averns et al. measured and compared the MST, FFD, OWD and total spine movements of patients with AS who had an average disease duration of 20 years and smoked at least 10 cigarettes a day for at least 10 years and those who did not smoke, and found significant limitations in smokers (7). In another study by Kaan et al., restrictions in MST, CE, FFD and increased BASDAI, BASFI values were found in 48 AS patients (8). On a larger series of patients, Doran et al., Ward et al. and Zhung et al. found an association of smoking with impaired functional performances (2, 3, 19).

In their study on American AS patients, Wards et al. showed that smoking accelerated radiographic deterioration (20). In two large systematic reviews, it was reported that smoking increased radiological deterioration (18, 21). In our study, in accordance with these values, MST and LLF significantly decreased and FFD and BASMI values increased in the smoker group. This study was retrospective and radiographic information of some patients was unavailable. For this reason, the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which is the radiological scoring used in prospective studies of biological treatment, could not be determined in our study. In the study performed by Chang et al. with 647 early axSpA patients, a negative effect of smoking was shown on radiological progression, clinical disease activity, functional condition, and quality of life (10).There also has been a study showing that smoking causes radiological deterioration independent of TNFi treatment (22).

In our study, physical mobility of ex-smokers was restricted compared to nonsmokers. In previous studies, no significant difference was found when comparing non-smokers and those who quit (3). When we evaluated the groups according to the duration of smoking, it was shown that there was a significant difference in the LLF, AR, CE, OWD, TWD, IMD, CCD and BASFI and BASMI values in the group who smoked for more than 10 years. In the literature, there is no classification based on duration of smoking but intensity of smoking as per cigarette pack-years. Functional limitations in smokers more than 10 years were observed independent of smoking intensity. In heavy smokers with respect to light smokers, BASFI and BASMI were high, some physical mobility functions were limited and $BASFI_{B-L}$ was decreased. In this study we found a weak correlation between smoking intensity and physical examination, BASDAI and a moderately positive correlation between smoking intensity and BDI. Findings in physical examination and BASDAI were similar to other studies (7, 23). In the study conducted by Zhao et al., while the incidence of depression was high in current smokers, no significant difference was found between smoking intensity and depression at the third and sixth months of the TNFi treatment (16). In a study on the effect of smoking intensity and duration on functional limitation, Ward et al. showed that there is more functional limitation in current smokers compared to those who never smoked or quit, but they could not find a relationship between cigarette pack-years and restriction (3). Even though Reed et al. showed that smoking was associated with poor outcomes in their study on 126 patients with AS, they could not find a relationship with cumulative exposure (24). In Chen's study, it was shown that high smoking intensity was associated with poor disease outcomes (7).

In multivariable linear regression analysis with cigarette pack-years, one unit change per cigarette pack-years increased ASQoL and BASMI, decreased $BASFI_{B-L}$ and the $BASDAI_{B-L}$ difference. The increase in ASQoL with increasing smoking pack-years is similar to the ones reported in the literature (10, 23-26). Although some evaluations (young age, short duration of illness, high BASDAI, etc.) have been made in axSpA that predict a good response to TNFi treatments, smoking was not one of the factors (27). There are different results in the literature regarding the response to TNFi therapy. Ciurea et al, in a large longitudinal study, found a poor BASDAI and ASDAS response, especially in current smokers with high C reactive protein values (14). Glintborg et al. also found lower BASDAI responses of current and ex-smokers than non-smokers in a large cohort study (15). In some studies, no smoking effect was found in response to TNFi. (16-17, 28-29). In our study, the decrease in the difference of BASDAI and BASFI values before and after the treatment with increasing smoking pack-years suggests a decrease in treatment response.

In our study comparing AS and nr-axSpA patients, a significant difference was found in physical restriction (FFD) among smokers in the AS group. When the heavy smokers who smoked> 20 pack-years and light smokers were compared, unlike the others, a significant difference was found in the nr-axSpA group, and not in the AS

group. In the nr-axSpA group, a significant deterioration was found in physical examination parameters among the heavy-smoker group, including MST_B, CE_L, TWD_L, $BASDAI_L$, $BASFI_L$, $BASMI_L$, $BASFI_{B-L}$, $BASDAI_{B-L}$ and ASQoL. In our study, the only parameter that changed ASQoL was continuing to smoke very intensively. In the study of Jones et al., it was observed that continuing smoking worsened the quality of life (30). Results in the literature regarding the effect on quality of life are heterogeneous and the level of evidence is weak (18).

In patients with early axSpA (AS and nr-axSpA), it has been shown by magnetic resonance imaging that smoking worsens radiological progression (10). Chung *et al.* evaluated 647 axSpA patients. They showed that structural damage and inflammation in both the sacroiliac joint and spine were significantly higher in the smoking group compared to the non-smoking group. AS and nr-axSpA groups were evaluated in subgroup analysis. In AS, BASFI, QoL, radiological damage and nr-axSpA, BASDAI and QoL are positively correlated with smoking (10). A subgroup analysis between AS, nr-axSpA was not performed in similar studies on smoking, except for the study of Chung et al. In our study, functional limitations were found in smokers in all stages of the disease, but it was observed that continuing to smoke heavily in the early stages of the disease was associated with physical limitation, poor disease activity and quality of life. Prospective studies are needed to determine the effectiveness of smoking for treatment response.

Our retrospective data did have some limitations. At the beginning of the treatment, some physical examination data and radiography data were missing. In our evaluation of the difference between $BASDAI_{B-L}$ and $BASFI_{B-L}$ in response to TNFi treatment, the lead time to check post-treatment values could not be standardized in all patients due to the cross-sectional study design, therefore the last visit data were used.

Similar to previous studies as well as in our study, we showed that smoking increases physical restraint and smoking intensity has an effect on response to TNFi treatment. In our study, we found that there are functional limitations in those who have a smoking period of more than 10 years, regardless of the smoking intensity. Significantly, there is a negative correlation between response to TNFi treatment and increasing smoking intensity. In the nr-AxSpA group, it has been shown that smoking more than 20 pack-years worsens the functional limitation and quality of life. More prospective studies are needed on the effect of smoking during the nr-axSpA period. After quitting smoking the natural course of the disease may positively change and response to TNFi treatment can increase. Therefore, quitting smoking, a variable lifestyle component, is vital.

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