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Türk Osteoporoz Dergisi
TURKISH JOURNAL OF OSTEOPOROSIS

Editörden / Editorial

Sevgili Meslektaşlarımız,

Değerli meslektaşlarımıza akademik çalışmalarını yayımlanmak üzere Emerging Sources Citation Index tarafından indekslenen dergimize düzenli olarak ilettikleri için çok teşekkür ederiz. Dergimiz kapsamında bu akademik çalışmaları yayınlamaktan büyük mutluluk duyuyoruz.

WCO-International Osteoporosis Foundation (IOF)- Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Kongresi (Osteoporoz, Osteoartrit ve Kas-İskelet Sistemi Hastalıkları Dünya Kongresi) 10-13 Nisan, 2025 tarihlerinde Roma, İtalya'da yer alacaktır.

Committee of Scientific Advisors of the IOF ve European Society for Clinical and ESCEO birlikte çok heyecan verici bir kongre bilimsel programı hazırladıklarını ve kas-iskelet sistemi sağlığı ve hastalıkları alanında dünyanın en iyilerini bu kongrede birleştireceklerini ifade etmişlerdir. Bu kongre kapsamında ülkemizden de birçok araştırıcının sunumları gerçekleşecektir.

Siz değerli meslektaşlarımıza mutluluğun ve başarının yaşamınızdan eksik olmamasını dileyerek, sevgi ve saygılarımı sunarım.

Editör
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Falls and Related Factors in Female Patients with Rheumatoid Arthritis

Romatoid Artritli Kadın Hastalarda Düşme ve İlişkili Faktörler

Halime Kibar, Derya Buğdaycı

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Abstract

Objective: Falls are associated with significant mortality, morbidity, and loss of function. It has been shown that the risk of falls is increased in patients with rheumatoid arthritis (RA). The purpose of the study was to evaluate the prevalence of falls in female RA patients and its association with clinical data, disease-related outcomes, functionality, and balance.

Materials and Methods: Ninety-four female patients included in this cross sectional observational study. The following were recorded: age, disease duration, body mass index, visual analog scale (0-100 mm), medication, disease activity score-28, Health Assessment Questionnaire, 6-meter walking time, Berg balance scale (BBS), use of a walking aid, and lower extremity arthritis. Patients were asked about falling in the past 12 months. In addition, it was questioned whether the patients had a fear of falling. The relationship between falls and patient data was investigated. Data on patients with and without a history of falling were compared.

Results: Ninety patients completed this study. Thirty percent of the patients had at least one fall in the last 12 months, and 52% had a fear of falling. Falls were correlated positively with balance problems. There was a significant difference in age, fear of falling, and BBS values between the patients with and without a history of falling. There were no differences in disease activity, pain, body mass index, medications, and functional parameters.

Conclusion: Awareness should be raised about falling in patients with RA. We suggest that balance should be evaluated to predict fall risk in patients with RA. Elderly patients with RA need to be followed more carefully, as falls will increase with age. Since the risk of osteoporosis is higher in RA, precautions should be taken to prevent falling and any problems it may cause.

Keywords: Balance, falls, female, rheumatoid arthritis

Öz

Amaç: Düşme ciddi mortalite, morbidite ve fonksiyon kaybıyla ilişkilidir. Romatoid artritli (RA) hastalarda düşme riskinin arttığı gösterilmiştir. Çalışmanın amacı kadın RA hastalarında düşme prevalansı ve bunun klinik veriler, hastalıkla ilişkili sonuçlar, işlevsellik ve denge ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: Kesitsel gözlemsel çalışmaya 94 kadın hasta dahil edildi. Yaş, hastalık süresi, vücut kitle indeksi, visuel ağrı skalası (0-100 mm), ilaç kullanımı, hastalık aktivite skoru-28, Sağlık Değerlendirme Anketi, 6 metre yürüme süresi, Berg denge skalası (BBS), yürüme yardımcısı kullanımı alt ekstremite artriti kaydedildi. Hastalara son 12 aydaki düşmeleri soruldu. Ayrıca hastaların düşme korkusu olup olmadığı da sorgulandı. Düşmeler ile hasta verileri arasındaki ilişki araştırıldı. Düşme öyküsü olan ve olmayan hastaların verileri karşılaştırıldı.

Bulgular: Doksan hasta bu çalışmayı tamamladı. Hastaların %30'unda son 12 ayda en az bir kez düşme yaşanmış, %52'sinde ise düşme korkusu mevcuttu. Düşmeler denge problemi ile pozitif yönde ilişkiliydi. Düşme öyküsü olan ve olmayan hastalar arasında yaş, düşme korkusu ve BBS değerleri açısından anlamlı fark vardı. Hastalık aktivitesi, ağrı, vücut kitle indeksi, ilaçlar ve fonksiyonel parametreler arasında fark bulunmadı.

Sonuç: RA'lı hastalarda düşme konusunda farkındalık artırılmalıdır. RA hastalarında düşme riskini öngörmek için dengenin ve düşme korkusunun değerlendirilmesi gerektiğini öneriyoruz. Yaş arttıkça düşmeler artacağından yaşlı RA'lı hastaların daha dikkatli takip edilmesi gerekir. RA'da osteoporoz riski daha yüksek olduğundan düşme ve yol açabileceği problemler oluşmadan önlem alınmalıdır.

Anahtar kelimeler: Denge, düşme, kadın, romatoid artrit

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by painful, swollen joints that can severely impair physical function (1). RA is 3:1 more common in women than men (2). Joint damage and deformity, muscle weakness, pain, and balance problems may occur in RA. These affect gait and mobility and increase the risk of falls (3-5). It has been previously reported that patients with RA have a higher risk of falling than the healthy population (6).

Falls are associated with mortality and morbidity and the need for early care. History of falls, gait deficit, balance disorder, use of assistive devices, and arthritis are risk factors for falling (7). Patients with RA from illness or corticosteroid-induced bone fragility are at greater risk of fracture and fall-related complications than the general population (8,9). The experience of falls may also result in a fear of falling, which has been linked to a lack of physical activity (10,11).

It is critical to assess the likelihood of falling and identify the risk factors for falling for these reasons. If fall-related factors are identified, measures can be taken. While some factors were found to be similar in previous studies, some results were different (6,12,13). It was stated that there was no complete standardization and there were few studies on this subject. This revealed the need for more studies.

The aim of this study was to evaluate falls in the last 12 months in female RA patients and their association with clinical data, disease-related outcomes, functionality, and balance.

Materials and Methods

Ninety-four female patients with RA who were admitted to the out-patient clinic between February 2023-May 2023 were included consecutively in this cross-sectional observational study. 4 patients were missing data. Ninety patients completed study. We performed a face to face interview and physical examination. All patients were previously diagnosed according to the American College of Rheumatology 1987 or 2010 diagnostic criteria patients >18 years with a good mental capacity were included in the study.

Exclusion criteria were having cognitive problems, diabetic foot, infection in lower extremities, vertigo, Parkinson, use of psychiatric drugs, lower extremity traumatic problems and surgical procedures.

Demographic and clinical features were recorded. Age, disease duration, body mass index (BMI) and medication were recorded. Disease activity score-28 (DAS-28) was calculated with an erythrocyte sedimentation rate (ESR) for disease activity.

Patients were asked about falling in the past 12 months. In addition, it was questioned whether the patients had a fear of falling or not.

The use of walking aid by the patients was questioned. The lower extremity arthritis (hip, knee, ankle, foot) joint involvements of the patients were asked and recorded.

Functions were measured by the Turkish version of Health Assessment Questionnaire (HAQ), a 6-meter walking test (14). The Turkish version of Berg balance scale (BBS) was used for balance assessment (15). A visual analog scale (VAS, 0-100 mm) was used for the patient's pain assessment.

We evaluated the prevalence of falls in female RA patients and its association with clinical data, disease-related outcomes, functionality, and balance.

Patients with RA were divided into 2 according to their history of falling in the last year: fallers and non-fallers. The characteristics of these groups were compared.

This study Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee and written informed consent was obtained from the patients (decision no: 2023-01-30, date: 09.01.2023). All procedures were designed with the Helsinki Declaration.

Statistical Analysis

Statistical analysis are made using SPSS version 22.0 package program. Descriptive statistics are summarized as mean and standard deviation. Categorical variables is presented by using percentages. The suitability of variables to normal distribution was examined using analytical methods (Anderson-Darling test) and verified with visuals. Normally distributed continuous data were compared with 2 Sample's t-tests, non-normally distributed continuous data were compared with Mann-Whitney U test and Fisher's exact test. Pearson Correlation test was used in correlation analysis. Multiple regression analysis and binary logistic regression analysis were performed. The p-value is taken as 0.05 in all statistics.

Results

The demographic and clinical characteristics are shown in Table 1. Correlations between falls in the last 12 months and other clinical and disease parameters are shown in Table 2. 33% of the patients had at least one fall in the last 12 months, and 52% had a fear of falling. Falls were correlated positively with BBS.

Table 3 presents to compare fallers and non-fallers. There was a significant difference in age, corticosteroid use, fear of falling and BBS values between the 2 groups.

Discussion

In this study, factors associated with falls were investigated in female patients with RA and the data of patients with and without a history of falling in the last 12 months were compared. We found that 33% female patients with RA had at least one fall in the last 12 months, and 52% had a fear of falling. We found a relationship between only falls and balance. When we compared the parameters of fallers and non-fallers, we found a difference between the two groups' age, balance scores, fear of falling and corticosteroid use.

Table 1. Characteristics of patients	
Age (years) (mean±SD)	55.5±12.75
Disease duration (years) (mean±SD)	12.51±9.66
BMI (kg/cm²) (mean±SD)	28.6±5.6
ESR (mm/hour) (mean±SD)	24.12±19.43
DAS-28 (mean±SD)	3.76±1.26
VAS (0-100 mm) (mean±SD)	49.01±6.79
HAQ (mean±SD)	0.73±0.56
6 mt walking time (second) (mean±SD)	7.89±4.8
BBS (mean±SD)	49.01±6.79
Walking aid (no/yes) (%)	80/10 (91/9)
Falls history in the last year (no/yes) (%)	60/30 (67/33)
Fear of falling (no/yes) (%)	43/47 (48/52)
Low extremity arthritis (no/yes) (%)	55/35 (71/39)
Syn DMARDs/biy DMARDs (%)	74/16 (82/18)
Corticosteroids (no/yes) (%)	49/41 (55/45)

Data are means, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, VAS: Visual analog scale, HAQ: Health Assessment Questionnaire, mt: Meter, BBS: Berg balance scale, Syn: Synthetic, Biol: Biological, DAS-28: Disease activity score-28

The frequency of falls in RA was found in different ranges in different studies. In studies in other countries, falls in patients with RA in the last 12 months were and 48.8% in Brazil, 28% in Japan and 28% in Türkiye (12,13,6). In a one-year prospective study in Germany, 20.2% of patients with RA had a fall experience (16). We think that the wide range in the literature is related to the habits and life-styles of societies. Factors such as nutrition, exercise and social support can affect falls. In addition, the methodology of the studies and the heterogeneity in the inclusion criteria affect the rates. For example, the inclusion of patients with vertigo may affect the rate of falls. In our study, patients diagnosed with vertigo and Parkinson's were excluded from the study. In general, although female patients are high in all studies on RA, our study only included women.

We identified a fear of falling in 52% of the patients. The fear of falling in patients with RA was reported 65.5% and 74.5% in previous studies, respectively (6,17). There was no relationship between the fear of falling and falls, but there was a difference between the fear of falling and the patient's fall history. The rate of fear of falling in the fallers was higher.

Balance has been defined as a multidimensional domain of muscle function, one of the most important indicators for predicting falls (7,18). Our study suggests that balance impairment may

Table 2. Multiregression analysis and odds ratios

Coefficients

Term	Coef	SE coef	z-value	p-value	VIF	Odds ratio	95% CI
Constant	8.6	6.99	1.23	0.219			
Disease duration (years)	-0.068	0.0375	-1.81	0.07	1.81	0.9343	(0.8680, 1.0056)
VAS (mm/100)	-0.0214	0.0173	-1.24	0.217	2.57	0.9788	(0.9461, 1.0126)
DAS-28	-0.162	0.426	-0.38	0.704	3.56	0.8508	(0.3694, 1.9598)
ESR	0.028	0.0199	1.41	0.159	1.66	1.0284	(0.9891, 1.0693)
HAQ	0,477	0.725	0.66	0.51	2.08	1.6119	(0.3894, 6.6722)
Age (years)	0.0227	0.0355	0.64	0.522	2.07	1.023	(0.9543, 1.0966)
6 mt walking time (sn)	0.0652	0.0969	0.67	0.501	1.88	1.0673	(0.8828, 1.2905)
BMI	-0.0558	0.0514	-1.09	0.277	1.14	0.9457	(0.8552, 1.0458)
BBS	-0.196	0.104	-1.88	0.06	4.32	0.8222	(0.6704, 1.0083)
Walking aid	-1.89	1.6	-1.18	0.239	2.85	0.1517	(0.0066, 3.4958)
Fear of falling	0.919	0.67	1.37	0.17	1.36	2.5062	(0.6746, 9.3100)
Low ekstremity arthritis	0.6	0.696	0.86	0.388	1.51	1.8229	(0.4657, 7.1358)
Syn DMARDs/biol DMARDs	1.107	0.887	1.25	0.212	1.62	3.0249	(0.5320, 17.1981)
Corticosteroids	0.992	0.675	1.47	0.142	1.45	2.6954	(0.7173, 10.1284)

Model summary

Deviance	Deviance	AIC	AICc	BIC	Area under	
R-Sq	R-Sq (adj)				ROC curve	
99.17%	73.86%	60.95	92.48	135.95	1	

Binary logistic regression: falls in the previous year versus BBS

Coefficients

BBS

Term	Coef	SE coef	z-value	p-value	VIF	
Constant	6.91	2.25	3.07	0.002		
BBS	-0.1562	0.046	-3.4	0.001	1	

Data are means, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, VAS: Visual analog scale, HAQ: Health Assessment Questionnaire, mt: Meter, BBS: Berg balance scale, Syn: Synthetic, Biol: Biologi, DAS-28: Disease activity score-28, CI: confidence interval

be a determining factor in falling. This result was compatible with the literature (6,18). We found that the balance evaluation of non-fallers was better than fallers. In the previous studies, BBS was used for balance assessment like our study. There are studies with the same result as our study (6,17). However, it was also stated that there is no difference between the balance of fallers and non-fallers (12,13). Toprak et al. (19) reported that balance disorders cause inactivity in patients with RA, which in turn increases the risk of falling and osteoporosis (19). They also stated that lower extremity problems may have increased the risk of balance disorder. We could not find a relationship between falling and lower extremity arthritis. We also compared lower extremity arthritis of fallers and non-fallers patients but found no difference. In addition, we could not determine a relationship between falling and the use of a walking aid and could not find a difference between the use of walking aids in the 2 groups.

We did not found relationship between patients' age, disease duration, disease activity and falls. Lourenço et al. (12) found the same result. Mikos et al. (20) stated that they did not find a relationship between falls and the disease duration. However, when we compared fallers and non-fallers, there was a difference in their ages. The average age of fallers was higher than non-fallers. There was no difference between disease duration. Wiegmann et al. (21) also reported the same results. However, in other studies, no difference was found between age and disease duration of fallers and non-fallers (6,13).

We evaluated ESR as an indicator of inflammation in patients and calculated disease activity with DAS-28. We did not found difference between the patients' inflammation and DASs. The same result was found in other studies where inflammation and disease activity were evaluated by the same method (6,13). Wiegmann et al. (21) evaluated disease activity with CRP and they found no difference between the disease activity of the two groups. Zonzini et al. (17) evaluated disease activity with clinical disease activity index and found that the disease activity of with recurrent fallers was higher than non-fallers (17).

We found no relationship between falls and pain. Mikos et al. (20) did not found any relationship between falls and pain, too. While on the other hand Akyol et al. (6) stated that the pain of the fallers were higher than non-fallers. Akyol et al. (6) included only RA patients using biological agents in their studies. We included patients in our study without discrimination in terms of biological disease-modifying anti-rheumatic drugs (DMARDs), synthetic DMARDs and corticosteroid use. There was no relationship between falls and patients' medications. When we compared the medications of patients, there was no difference in the use of biological DMARDs and synthetic DMARDs, but there was a difference in the use of corticosteroids. The rate of corticosteroid use was higher in faller group. Inflammation levels may actually be higher in the group using corticosteroids, and pain and disease activity may be suppressed due to the level of inflammation with corticosteroid use. Thus, there may be no difference in these parameters between fallers and non-fallers. It is known that corticosteroids have affects negatively on bone density and muscle mass. However, in our study, no measurements or evaluations were made regarding muscle density, muscle strength or bone mineral evaluation. This constitutes a limitation in our study. For this reason, we cannot comment on how corticosteroids affect falls.

We evaluated the functionality of patients with Health Assessment Questionnaire (HAQ) and 6 meter walking time. We did not find a relationship between functionality and falls. We also did not find a difference when we compared the functionality of fallers and non-fallers. HAQ was used as a method of evaluation in functionality in previous studies. However, when the relationship between falls and functionality was investigated, different results were found (12,16,20). When the results of fallers and non-fallers were compared, Zonzini et al. (17) and Akyol et al. (6) found that the functionality of non-fallers was better. But, in parallel with our results, it was shown that there was no difference in the two groups (12,14).

We did not found relationship between falls and BMI. We found

Table 3. Comparision of non-fallers and fallers

	Non-fallers (n=60)	Fallers(n=30)	p-value
Age (years)	52.5 ± 12.2	61.47 ± 11.85	0.001
Disease duration (years)	12.43 ± 8	12.66 ± 11.39	0.732
BMI (kg/cm²)	29.0 ± 6.47	28.6 ± 4.9	0.59
ESR (mm /hour)	21.8 ± 17.6	28.8 ± 22.2	0.062
DAS28 score	3.70 ± 1.15	3.90 ± 1.47	0.51
VAS (0-100 mm)	40.16 ± 25.67	42.83 ± 28.93	0.774
HAQ	0.68 ± 0.48	0.57 ± 0.86	0.248
6 mt walking time (second)	7.06 ± 1.7	9.5 ± 7.7	0.59
BBS	51.0 ± 5.7	45.0 ± 7.0	<0.001
Walking aid (No/Yes)(%)	56/4 (94/6)	24/6 (80/20)	0.078
Fear of falling (No/Yes)(%)	36/24 (60/40)	7/23(23.3/76.6)	0.002
Low extremity arthritis (No/Yes)(%)	38/22 (63.4/36.6)	17/13 (55.7/43.3)	0.647
Syn DMARDs/Biy DMARDs (%)	50/10 (83.3/16.6)	24/6 (80/20)	0.772
Corticosteroids (No/Yes)(%)	37/23 (61.7/38.3)	12/18 (40/60)	0.047

Data are means, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, VAS: Visual analog scale, HAQ: Health assessment questionnaire, mt: Meter, BBS: Berg Balance Scale, Syn: Synthetic, Biol: Biological

no difference between the BMI values of fallers and non-fallers. The same result was found in previous studies (13,16,17). But, Akyol et al. (6) found that the BMI value of fallers was significantly higher than non-fallers.

Study Limitations

This study has some strengths and limitations. In a study on balance, Bouchaala et al. (22) reported that balance was affected by the stiffness of the ecliptic during the hours of the day. In our study, patients were evaluated between the hours of 9-12 in the morning. We find our study strong in this aspect. The first limitation of the study was designed as a cross-sectional one. For this reason, a cause-and-effect relationship cannot be established. The second limitation is that the study did not have a control group. We included only female patients in our study because most of our patients were women. Analyses of male patients might show different results.

Conclusions

As a result, awareness should be raised about falls in patients with RA. RA patients are already at risk for osteoporosis because of their disease. While the risk of falling in the normal population increases in elderly patients, elderly patients with RA should be followed more closely. This is essential for the prevention of fractures and subsequent complications. We suggest that balance should be evaluated to predict fall risk in RA patients. Patients should be informed about falls and medical and social precautions should be taken. In particular, corticosteroid use and the follow-up should have been made considering the risk of falling. It is important in preventing falls and their consequences. There were no declared conflicts of interest that would have affected this article.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2023-01-30, date: 09.01.2023).

Informed Consent: Written informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Concept: H.K., D.B., Design: H.K., D.B., Data Collection or Processing: H.K., Analysis or Interpretation: H.K., D.B., Literature Search: H.K., D.B., Writing: H.K., D.B.

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The Relationship Between Bone Mineral Density and Sympathetic Skin Response in Postmenopausal Women

Postmenapozal Kadınlarda Kemik Mineral Yoğunluğu ile Sempatik Deri Yanıtı Arasındaki İlişki

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Abstract

Objective: Osteoporosis (OP) is a common condition characterized by decreased bone mass. The sympathetic nervous system is involved in bone remodeling and vasomotor symptoms in postmenopausal women. This study aimed to assess the relationship, using sympathetic skin response (SSR) measurements, between autonomic dysfunction and OP in postmenopausal women experiencing vasomotor symptoms.
Materials and Methods: A total of 101 postmenopausal women aged 45-65 with complaints of hot flashes and sweating were included. The study was a single-center, cross-sectional, observational investigation. Based on dual-energy X-ray absorptiometry results, participants were categorized into OP, osteopenia, and normal groups. SSR latencies and amplitudes, recorded bilaterally from hands and feet, were compared among the groups. Correlations between bone mineral density (BMD) and SSR results were analyzed.
Results: There were no significant differences in SSR latencies between the groups (p>0.05). Although SSR amplitudes were lowest in the OP group, the differences were not statistically significant (p>0.05). No significant correlation was found between BMD scores and SSR measurements (p>0.05).
Conclusion: The study found no association between autonomic dysfunction, as indicated by SSR responses, and BMD scores in postmenopausal women.
Keywords: Sympathetic skin response, bone mineral density, autonomic dysfunction, osteoporosis

Öz

Amaç: Osteoporoz (OP), azalmış kemik kütlesi ile karakterize edilen yaygın bir durumdur. Sempatik sinir sistemi, postmenopozal kadınlarda hem kemik yeniden şekillenmesinde hem de vazomotor semptomların gelişiminde rol oynar. Bu çalışma, vazomotor semptomlar yaşayan postmenopozal kadınlarda sempatik deri yanıtı (SDY) ölçümleri kullanılarak, otonomik disfonksiyon ile OP arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: Çalışmaya, sıcak basması ve terleme şikayeti olan 45-65 yaş arası toplam 101 postmenopozal kadın dahil edilmiştir. Çalışma, tek merkezli, kesitsel ve gözlemsel bir araştırma olarak tasarlanmıştır. Dual enerji X-ışını absorpsiyometrisi sonuçlarına göre katılımcılar OP, osteopeni ve normal gruplara ayrılmıştır. SDY latans ve amplitüd değerleri ellerden ve ayaklardan bilateral olarak kaydedilmiş ve gruplar arasında karşılaştırılmıştır. Kemik mineral yoğunluğu (KMY) ile SDY sonuçları arasındaki korelasyonlar analiz edilmiştir.
Bulgular: Gruplar arasında SDY latans değerlerinde anlamlı bir fark bulunmamıştır (p>0,05). SDY amplitüdleri OP grubunda en düşük olmasına rağmen, bu fark istatistiksel olarak anlamlı değildir (p>0,05). KMY skorları ile SDY ölçümleri arasında da anlamlı bir korelasyon bulunmamıştır (p>0,05).
Sonuç: Çalışma, postmenopozal kadınlarda SDY yanıtları ile KMY skorları arasında otonomik disfonksiyon göstergesi olabilecek bir ilişki tespit edememiştir.
Anahtar kelimeler: Sempatik deri yanıtı, kemik mineral yoğunluğu, otonomik disfonksiyon, osteoporoz

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Introduction

Osteoporosis (OP) is a prevalent condition characterized by microstructural deterioration in bone tissue and progressive loss of bone mass. Hormonal factors, nutritional status, and biomechanical stress regulate the remodeling process of bone. Systemic hormones and local factors also regulate osteoblastic and osteoclastic activities (1,2).

There is evidence of a close relationship between the sympathetic nervous system and bone metabolism. Several studies have suggested that the sympathetic nervous system mediates bone remodeling. Norepinephrine binds to beta (β)2-adrenergic receptors specifically found in osteoblasts, inhibiting osteoblast activity and thereby impeding bone formation. Additionally, adrenergic nerves can activate the receptor activator of nuclear factor-kappa B ligand (RANKL) in osteoblasts, triggering RANKL-mediated osteoclastogenesis and bone resorption (3,4). Leptin, one of the hormones involved in regulating norepinephrine release, exerts anti-osteogenic effects by binding to hypothalamic receptors (5). An animal study demonstrated that the infusion of leptin into the third ventricle reduced bone mass and bone formation parameters, highlighting its critical role in the regulation of bone formation (6).

The role of the sympathetic system in investigating postmenopausal OP has been explored using ovariectomized mouse models. The β-adrenergic blockade, when applied in adult mice following ovariectomy, has partially mitigated bone loss by preventing a general decrease in bone mineral density (BMD) (7). Clinical observations on postmenopausal women have yielded similar findings. The use of β-blockers in postmenopausal individuals has been correlated with higher BMD scores, demonstrating associations with better trabecular microarchitecture in the femur length and lumbar spine (8,9).

Vasomotor symptoms (such as hot flashes and night sweats) are pronounced in postmenopausal women. It is known that the autonomic dysfunction arising from a decrease in estrogen levels is linked to high sympathetic activation (10). On the other hand, studies have found an association between decreased bone mass and vasomotor symptoms in postmenopausal women (11).

Sympathetic skin response (SSR) is a neurophysiological examination used to assess vasomotor and sudomotor activity stimulated by cholinergic sympathetic fibers of the autonomic nervous system (12). SSR has been employed to demonstrate the role of sympathetic function in various diseases within neurological, dermatological, and rheumatological fields (13-17). During the examination, responses are recorded from the palmar and plantar surfaces, where sweat glands are most densely distributed (18). The study aimed to investigate the relationship between BMD and SSR in postmenopausal women with autonomic dysfunction.

Materials and Methods

Study Design

The study was designed as a single-center cross-sectional investigation at the University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation between June 2022 and December 2022. Before commencing the study, approval was obtained from the Clinical Research Ethics Committee of the Health Sciences University of Türkiye, Antalya Training and Research Hospital on March 31, 2022, with decision number 7/17. Our study adheres to the principles of the 2013 Helsinki Declaration. Informed voluntary consent was obtained from participants by signing an informed consent form. The sample size was calculated using G-Power 3.1.9.4 software, considering an effect size (f) of 0.3, α of 0.05, and power of 0.80 for each group, resulting in a total of 84 volunteers (28 per group).

Participants

The study included 120 postmenopausal women aged 45-65 years who applied to the physical medicine and rehabilitation outpatient clinic for various reasons and reported experiencing hot flashes and sweating once a day. Exclusion criteria comprised a history of systemic diseases (diabetes mellitus, coronary artery disease, hypertension, thyroid dysfunction), neurological disorders (cerebrovascular diseases, polyneuropathy), secondary OP, collapse fractures, malignancy, regular medication use (including calcium-channel blockers, β-blockers, glucocorticoids, anti-diabetic agents, anti-resorption agents, anti-arrhythmia agents, oral contraceptives, anti-coagulants), psychiatric diseases, and inflammatory rheumatic diseases. Fourteen patients meeting the exclusion criteria and five patients unwilling to participate voluntarily were excluded from the study. A total of 101 patients were categorized into three groups based on dual-energy X-ray absorptiometry (DEXA) results: those with a T-score of -2.5 standard deviations (SDs) or below were classified as having OP, those with T-scores between -1 and -2.5 SD had osteopenia, and those with T-scores above -1 SD were considered normal (19). The BMD of the lumbar spine, femoral neck, and total hip was assessed using DEXA (Lunar DPX-L model, Lunar, Madison, Wisconsin, USA).

Outcome Measures: Sympathetic Skin Response

SSR was conducted using an electroneuromyography device (Nihon Kohden Neuropack S1 MEB-9400K) in a quiet room with a temperature between 22 °C and 24 °C. Patients were positioned in a supine posture, and skin temperatures were maintained at 32 °C. Active electrodes were placed on the palmar surface of the hand and the plantar surface of the foot, while reference electrodes were placed on the dorsal surface of the hand and foot. To prevent habituation, stimuli of irregular intervals lasting more than a minute were applied at 20-30 mA.

When habituation occurred, the stimulus was delayed by five minutes. Skin potentials were analyzed for 10 seconds, and the average value was recorded. Latency was measured in seconds, considering the onset of the first negative deflection, and amplitude was measured in millivolts as peak to peak.

Statistical Analysis

SPSS version 25.0 for Windows was used for the analyses. The assumption of normality was assessed using the Shapiro-Wilk test. One-way analysis of variance was applied for data exhibiting parametric distribution, while the non-parametric Kruskal-Wallis test was utilized for non-normally distributed data. Pearson correlation was used for relationships among variables demonstrating normality, and Spearman correlation was employed for relationships among variables not meeting the assumption of normality. A significance level of $p<0.05$ was considered statistically significant in the analyses of the obtained data.

Results

The mean ages were 56.76±5.36 years in the osteoporotic group, 56.19±6.06 years in the osteopenic group, and 53.52±4.21 years in the normal group. There was a statistically significant difference in age and body mass index (BMI) among the groups ($p<0.05$). In the OP group, the average age was higher, and the BMI was higher in the normal group. There was no statistically significant difference in demographic characteristics, including menopausal age and menopausal duration, among the groups ($p>0.05$) (Table 1).

There was no statistically significant difference among the groups in the mean latencies of SSR recorded from the hands and feet ($p>0.05$). Although the mean amplitude of SSR was the lowest in the osteoporotic group, it was not statistically significant ($p>0.05$) (Table 2).

There was no statistically significant correlation between the BMD hip and lumbar scores and the amplitude and distal latency results of SSR ($p>0.05$) (Table 3).

Discussion

Studies have demonstrated the modulation of adrenergic receptors in the brain by estrogens (19,20). In postmenopausal OP, estrogen deficiency has been found to narrow the width of the thermoneutral zone by increasing brain norepinephrine. Consequently, disturbances in thermoregulation, such as hot flashes and excessive sweating, occur (10). Numerous tests assess the function of the autonomic nervous system, which include the evaluation of vasomotor and sudomotor symptoms. These tests encompass cardiovascular assessments, pupil reaction tests, lacrimal secretion tests, and SSR. In SSR studies, prolonged latency and low amplitude are considered indicative of sympathetic denervation (18,21).

Table 1. Demographic characteristics of the osteoporosis, osteopenic, and normal groups

	Osteoporotic (n=34)	Osteopenic (n=36)	Normal (n=31)	
	Mean±SD	Mean±SD	Mean±SD	p-value
Age, years	56.76±5.36	56.19±6.06	53.52± 4.21	0.036[1]
BMI, kg/m^2	26.42±3.99	26.57±3.54	28.68±4.24	0.040[1]
Menopause age, years	47.00±5.67	47.31±5.93	46.77±5.55	0.591[2]
Duration of menopause, years	9.76±6.57	8.89±6.32	6.74±6.63	0.055[2]

[1]One-way ANOVA, [2]Kruskal-Wallis test, BMI: Body mass index, SD: Standard deviation

Table 2. Sympathetic skin response data of upper and lower limbs in osteoporosis, osteopenic, and normal groups

		Osteoporotic (n=34)	Osteopenic (n=36)	Normal (n=31)	
		Mean±SD	Mean±SD	Mean±SD	p-value
Latency, s	Right hand	1.300±0.271	1.228±0.267	1.331±0.323	0.320[1]
	Left hand	1.306±0.298	1.269±0.295	1.331±0.332	0.690[1]
	Right foot	2.048±0.420	1.993±0.401	2.077±0.414	0.622[2]
	Left foot	2.047±0.384	2.034±0.383	2.080±0.441	0.722[2]
Amplitude, mV	Right hand	3.12±1.72	3.53±1.43	3.43±1.58	0.427[2]
	Left hand	3.12±1.59	3.36±1.30	3.47±1.95	0.790[2]
	Right foot	1.41±0.86	1.43±0.81	1.83±1.32	0.629[2]
	Left foot	1.30±0.86	1.40±0.87	1.88±1.40	0.246[2]

[1]One-way ANOVA, [2]Kruskal-Wallis test, s: Second, mV: Milivolt, SD: Standard deviation

Table 3. Results of the correlation of sympathetic skin response data of upper and lower limbs and BMD hip and spine scores

		BMD hip g/cm² (n=101)		BMD spine g/cm² (n=101)	
		r	p-value	r	p-value
Latency, s	Right hand	0.001	0.991[1]	-0.018	0.862[1]
	Left hand	0.032	0.749[1]	-0.020	0.846[1]
	Right foot	0.010	0.921[2]	0.069	0.494[2]
	Left foot	0.042	0.678[2]	0.071	0.483[2]
Amplitude, mv	Right hand	0.091	0.367[2]	0.132	0.187[2]
	Left hand	0.071	0.481[2]	0.084	0.406[2]
	Right foot	0.100	0.319[2]	0.088	0.382[2]
	Left foot	0.149	0.136[2]	0.172	0.085[2]

[1]Pearson correlation, [2]Spearman correlation, s: Second, mV: Milivolt, SD: Standard deviation, BMD: Bone mineral densitiy

The role of the sympathetic nervous system in OP has been demonstrated, yet its mechanism remains a subject of debate. Animal experiments and case reports have shown that sympathetic dysfunction can lead to OP (22,23). Roshanzamir et al. (24) suggested in their study involving 42 patients with electric burns and 50 control subjects that sympathetic nervous system dysfunction caused by electric burns is associated with OP. The results indicated that decreased BMD is correlated with prolonged latency and low amplitude in SSR. In a reverse perspective, animal experiments have suggested that blocking sympathetic nerve activity increases bone mass and prevents the progression of OP (25,26). Advanced age and low BMI are well-established risk factors for OP (27). In this study, the age of patients in the OP group was higher, and the BMI was lower.

Gast et al. (11) study involving 5600 female patients demonstrates that individuals with vasomotor symptoms exhibit higher sympathetic activation, and there is a correlation between hot flashes and a decrease in bone mass. Tosun et al. (28) identified prolonged latency and low amplitude in SSR examinations in the osteoporotic group compared to the control group in their study investigating autonomic dysfunction in postmenopausal OP. In the study conducted by Ashraf et al. (29) with 33 postmenopausal osteoporotic patients and 31 control subjects, significant latency delays were observed in both hand and foot SSR examinations in the osteoporotic group compared to the control group. Additionally, amplitudes were significantly lower in the osteoporotic group compared to the control group. In the osteoporotic group with more vasomotor symptoms, changes in SSR examinations were more pronounced. In this study, lower amplitude responses were observed in the osteoporotic group compared to the osteopenic and normal groups. Additionally, distal latency delays were shorter in the osteoporotic group compared to the control group. However, these differences were not statistically significant. In the study conducted by Ashraf et al. (29), vasomotor symptoms such as the frequency of hot flashes over 24 hours, the number of hot flashes per week, and the incidence of night sweats were comprehensively evaluated. Due to the heterogeneity in the distribution of vasomotor symptoms among the groups, their study found more significant changes in SSR in the osteoporotic group. In contrast, the study observed a homogeneous distribution of vasomotor symptoms across all groups. However, since the BMI parameter was higher in the control group, the thickness of the adipose tissue may have masked the conduction responses in the SSR evaluations (30,31).

Maser et al. (32) study, which investigated the relationship between autonomic nervous system function measurements in 66 type 1 diabetic patients and decreased BMD, demonstrated that measures of heart rate variability and circulating norepinephrine levels did not influence BMD in type 1 diabetes. Kado et al. (33) study, which evaluated the resting heart rate of 9702 women aged 65 and older, revealed an increased risk of hip, pelvic, and rib fractures in women with a resting heart rate exceeding 80 beats per minute. The cause of this association was attributed to the development of OP, linked to increased sympathetic activity and the consequent elevation of IL-6 production triggered by released catecholamines (34). As far as we know, there has been no identified study in the literature examining the correlation between BMD and SSR. In the present study, no significant correlation was observed between the BMD scores and SSR latencies and amplitudes for all patients. This suggests that BMD scores may not be directly associated with autonomic dysfunction.

The exclusion of systemic diseases and neurological diseases that may affect the autonomic nervous system and electrophysiological measurements to avoid possible confounders in the study design are among the strengths of the study.

Study Limitations

Among the limitations of this study is the lack of examination of other assessments commonly investigated in autonomic dysfunction, such as thermoregulation sweating tests, cardiovascular evaluations, and the assessment of the parasympathetic system. This limitation arises from the difficulty in performing detailed and comprehensive evaluations due to the high volume of patients examined simultaneously and constrained time resources in outpatient settings. Additionally,

the duration of patients' vasomotor symptoms was not investigated. Furthermore, low BMI, a risk factor for OP, was not evenly distributed in the demographic data.

Conclusion

In conclusion, this study did not identify a significant association between SSR which indicates autonomic dysfunction, and BMD scores in postmenopausal women. The limitations of the study, including the lack of assessment of other measures of autonomic function and the insufficiently detailed inquiry into vasomotor symptoms, may have influenced these results. To address these limitations and achieve a more comprehensive understanding, future research should include advanced tests evaluating various aspects of autonomic function and randomized studies with detailed assessments of vasomotor symptoms. Such studies could enhance our understanding of the potential relationships between autonomic dysfunction and bone health, and elucidate more complex interactions that were not captured in our study.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Health Sciences University of Türkiye Antalya Training and Research Hospital (date: 31.03.2022, decision number: 7/17).

Informed Consent: Written informed consent was obtained prior to the study from all subjects.

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Footnotes

Authorship Contributions

Concept: G.Ç., Ş.K.D., Design: G.Ç., M.B.F., Data Collection or Processing: G.Ç., M.H.S., Analysis or Interpretation: M.B.F., Ş.K.D., Literature Search: G.Ç., M.H.S., Writing: G.Ç., M.H.S.

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Digital Guidance: Quality and Readability Analysis of Artificial Intelligence-Generated Spondyloarthropathy Texts

Dijital Rehberlik: Yapay Zeka ile Oluşturulan Spondiloartropati Metinlerinin Kalite ve Okunabilirlik Analizi

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Abstract

Objective: The aim of this study was to comprehensively evaluate the quality and readability of the content of artificial intelligence (AI)-generated texts about spondyloarthropathy (SpA).

Materials and Methods: The most frequently searched keywords related to the SpA-group were identified through Google Trends. The keywords were sequentially entered into AI chatbots (ChatGPT, Bard, Copilot). The Ensuring Quality Information for Patients (EQIP) tool was used to assess the clarity of information and quality of writing. Flesch-Kincaid readability tests (reading-ease and grade-level) and Gunning Fog index (GFI) were used to assess the readability of the texts.

Results: The mean EQIP score of the texts was 66.44. The mean Flesch-Kincaid reading ease score was 38.06. The mean score for Flesch-Kincaid grade level is 11.38. The mean GFI score is 13.91. Our study concludes that the AI chatbots' responses on SpA are generally of "good quality with minor problems". It was determined that the texts produced were complex enough to require approximately 11 years of training. When the quality and readability characteristics of the texts generated by the AI chatbots were compared, the EQIP scores of the texts generated by Copilot were higher than those generated by both ChatGPT and Bard ($p<0.001$, $p=0.004$, respectively). Furthermore, ChatGPT-generated texts were found to require a higher level of education than those generated by both Copilot and Bard ($p=0.002$, $p=0.004$, respectively).

Conclusion: This study reveals that AI chatbots' texts about SpA have certain shortcomings in terms of quality and readability. As a result, it emphasizes that online resources and AI tools play an important role in information delivery in the healthcare field, but quality and readability control should be ensured. This can facilitate patients' access to accurate, reliable, and comprehensible information.

Keywords: Spondyloarthropathy, artificial intelligence chatbot, ChatGPT, Bard, Copilot, quality assessment, readability

Öz

Amaç: Bu çalışmanın amacı, spondiloartropati (SpA) ile ilgili yapay zeka destekli oluşturulan metinlerin içeriğinin kalitesini ve okunabilirliğini kapsamlı bir şekilde değerlendirmektir.

Gereç ve Yöntem: Google Trends üzerinden SpA grubu ile ilgili en sık aranan anahtar kelimeler belirlendi. Belirlenen anahtar kelimeler sırayla yapay zeka sohbet robotlarına (ChatGPT, Bard, Copilot) girildi. Bilginin netliği ve yazım kalitesi açısından değerlendirmek için Hastalar için Kaliteli Bilgi Sağlama aracı (EQIP) kullanıldı. Metinlerin okunabilirliğini değerlendirmek için Flesch-Kincaid okunabilirlik testleri (okuma kolaylığı ve sınıf düzeyi) ve Gunning Fog indeksi (GFI) kullanıldı.

Bulgular: Metinlerin EQIP skoru ortalama değerleri 66,44'tür. Flesch-Kincaid okuma kolaylığı skoru ortalama değeri ise 38,06'dır. Flesch-Kincaid sınıf düzeyi için ortalama skor 11,38'dir. GFI skoru ortalaması ise 13,91'dir. Çalışmamız, yapay zeka sohbet robotlarının SpA konusundaki yanıtlarının genel olarak "küçük sorunlarla birlikte iyi kaliteli" olduğu sonucuna varmaktadır. Üretilen metinlerin yaklaşık 11 yıl eğitim gerektirecek karmaşıklıkta olduğu belirlendi. Yapay zeka sohbet robotlarına oluşturduğu metinler kalite ve okunabilirlik özellikleri karşılaştırıldığında, Copilot tarafından üretilen metinlerin EQIP skorları, hem ChatGPT hem de Gemini tarafından üretilenlere göre anlamlı derecede daha yüksekti (sırasıyla, $p<0,001$, $p=0,004$). Ayrıca, ChatGPT tarafından üretilen metinlerin, hem Copilot hem de Gemini tarafından üretilenlere göre daha yüksek bir eğitim seviyesi gerektirdiği belirlendi (sırasıyla, $p=0,002$, $p=0,004$).

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Abstract

Sonuç: Bu çalışma, yapay zeka sohbet robotlarının SpA hakkındaki metinlerinin kalite ve okunabilirlik konusunda belirli eksikliklerin bulunduğunu ortaya koymaktadır. Sonuç olarak, çevrimiçi kaynakların ve yapay zeka araçlarının sağlık alanında bilgi sunumunda önemli bir rol oynadığını, ancak kalite ve okunabilirlik kontrolünün sağlanması gerektiğini vurgulamaktadır. Bu, hastaların doğru, güvenilir ve anlaşılır bilgilere erişimini kolaylaştırabilir.

Anahtar kelimeler: Spondiloartropati, yapay zeka sohbet robotu, ChatGPT, Bard, Copilot, kalite değerlendirmesi, okunabilirlik

Introduction

Spondyloarthropathy (SpA) is a term used to describe a group of diseases that share various both hereditary and clinical characteristics. Common characteristics of SpA include axial skeleton involvement, peripheral arthritis, enthesitis, dactylitis, acute anterior uveitis, psoriasis, or inflammatory bowel disease. This group of diseases is classified as axial or peripheral based on the predominant clinical feature. The axial form is characterized by involvement of the spine and/or sacroiliac joints and includes subtypes such as ankylosing spondylitis and non-radiographic axial spondyloarthritis, whereas the peripheral form is characterized by peripheral arthritis, enthesitis, and/or dactylitis (1-3).

SpA typically begins in the third decade of life and is a significant group of diseases that can cause chronic pain and disability (4). Prevalence studies usually do not include imaging and HLA-B27 testing, making it difficult to determine the exact prevalence of SpA. However, studies in North America estimate the prevalence of SpA to be between 0.4% and 1.3% (5). Another study found that the global prevalence of SpA varies between 0.21% and 1.61% in different geographical regions (6).

Artificial intelligence (AI) is the evolution of algorithms designed to perform tasks associated with intelligent behavior. These algorithms encompass many areas such as natural language understanding, image recognition, decision-making, problem-solving, and learning from experience (7). In the healthcare sector, AI is utilized in various areas such as medical imaging, diagnosis, drug development, patient monitoring, and robot-assisted surgery (8).

Recent studies show that the use of AI-powered chatbots is on the rise (9). These robots are designed to generate appropriate and consistent responses to user inputs, addressing patients' needs, resolving their questions, providing health information, and assisting with appointment scheduling (10,11). However, there are uncertainties and reliability issues when obtaining health-related information online. Additionally, individuals with limited understanding of medical terms may struggle to assess the reliability and validity of the information they acquire (12). Therefore, it is crucial for patients to access information that is accessible, comprehensible, and reliable. Well-structured and trustworthy information can help patients learn about their diseases, understand treatment options, and implement preventive measures (13,14).

There are numerous studies in the literature investigating the quality and readability of health information related to medical conditions. However, there is no study in the literature that evaluates the health information generated by AI chatbots for the SpA group. The aim of this study is to comprehensively evaluate the quality and readability of AI-generated texts related to SpA.

Materials and Methods

The study was conducted on May 10, 2024, at the Medical Faculty Hospital of our University. No human or animal participants were included in this study; Hence, ethical approval was not required. Similar studies in the literature have followed the same approach Since this study did not involve patient intervention, individual patient consent was not required (15).

The most frequently searched keywords related to SpA, ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, and reactive arthritis were identified using Google Trends. Before starting the searches, all browser data were completely cleared to ensure the results were not influenced. The search criteria were set to include data from 2004 to the present, covering the entire world and all categories. The most relevant keywords were selected from the related queries section of the results. The twenty-five most frequently used keywords were recorded for each search, except for enteropathic arthritis. Nine keywords were obtained for the enteropathic arthritis query. Exclusion criteria for the study included repetitive and irrelevant terms, which were removed from the analysis. In total, thirty keywords were identified (Table 1). The number of keywords to be evaluated was determined considering similar studies in the literature (12,15,16).

Three separate accounts were created for the AI chatbots Bard Version 2.0.0 (https://bard.google.com/), Copilot (https://copilot.microsoft.com/), and ChatGPT (https://chat.openai.com/) dedicated to this study. The selected thirty keywords were entered sequentially into the chat interfaces of the AI chatbots. Each keyword was processed to lead to a separate interaction on different chat pages to minimize the potential impact of previous queries and responses. The resulting responses were systematically documented for subsequent analysis, focusing particularly on quality, comprehensiveness, and readability. Texts were copied into Microsoft Office Word 2016 (Microsoft Corporation, Redmond, WA) and saved. Marks such as options and bullet points were removed during the evaluations. All answers were recorded on the internet. (Access adress: https://archive.org/details/19_20240703_202407/gemini/1/, https://archive.org/details/5_20240703_202407/chatgpt/1/ https://archive.org/details/6_20240703/copilot/1/)

Table 1. Most searched keywords related to spondyloarthropathy group		
Ankylosing spondylitis	Undifferentiated spondyloarthropathy	Reactive arthritis symptoms
Ankylosing spondylitis pain	Inflammatory spondyloarthropathy	Reactive arthritis treatment
Ankylosing spondylitis arthritis	Spondyloarthropathy symptoms	Reactive arthritis
Ankylosing spondylitis symptoms	Spondyloarthropathy treatment	Reactive arthritis causes
Ankylosing spondylitis treatment	Spondyloarthropathy	Septic arthritis
Ankylosing spondylitis test	Seronegative arthritis	Enteropathic arthritis
Ankylosing spondylitis disease	Sacroiliitis	Reactive arthritis diagnosis
Psoriatic spondyloarthropathy	Psoriatic arthritis pain	Psoriatic arthritis signs
Psoriasis arthritis	Psoriatic arthritis treatment	Methotrexate psoriatic arthritis
Psoriatic arthritis symptoms	Psoriasis and psoriatic arthritis	Psoriatic arthritis nails

Evaluation of the Texts

The obtained 90 texts were evaluated for clarity and writing quality using the Ensuring Quality Information for Patients (EQIP) tool. A form containing 20 EQIP items was used to evaluate the texts (17). Each item was assessed with responses of "yes", "partly", "no", or "not applicable" (N/A).

Since access permission was required for the health services contact number information and the responses were not produced in PDF format for the reader to take notes, these criteria were not evaluated (11). In addition, supporting the generated responses with visuals is another criterion that was not evaluated for Copilot and ChatGPT, which are text-based AI models.

The total score was calculated by assigning 1 point for "yes" responses, 0.5 points for "partly" responses, and 0 points for "no" responses. Items marked "not applicable" were excluded from the total number of items. The overall score was then divided by the number of valid items and expressed as a percentage. The EQIP score was categorized according to the score ranges recommended in the EQIP development publication: sources scoring between 76% and 100% were classified as "well-written and high-quality", those scoring between 51% and 75% as "good quality with minor issues", those scoring between 26% and 50% as having "serious quality issues", and those scoring between 0% and 25% as having "severe quality issues" (18).

Each text was independently evaluated by two physical medicine and rehabilitation specialists (İ.C.Ö and E.Ö.) in separate settings to minimize bias. In case of any discrepancies, the assessment was carried out again and a solution was found by consensus among the experts.

To assess the readability of the texts, the Flesch-Kincaid readability (FKRE) tests (readability ease and grade level) and the Gunning Fog index (GFI) were utilized. Texts were evaluated using a calculator (https://readabilityformulas.com/readability-scoring-system.php).

The FKRE ease score is calculated using the formula: 206.835-(1.015 x average sentence length)-(84.6 x average syllables per word). The higher the score on the test, the more readable the content is. A score below 30 indicates a reading level comparable to that of university graduates.

The Flesch-Kincaid grade level (FKGL) Score is calculated using the formula: 0.39 x (total words/Total sentences) + 11.8 x (total syllables/total words) - 15.59. The result indicates the educational level of the audience the text is aimed at. For example, a result of 10 and above suggests the text is aimed at a high school level audience (19).

The GFI is an assessment based on sentence length and the complexity of words. GFI is calculated using the formula: (number of words/number of sentences)+[(number of words with three or more syllables x 100)/(number of words)] x 0.4. According to the formula, shorter sentences indicate better readability. A score above 12 indicates a difficult text to read (19).

Readability scores were analysed and compared with the sixth grade readability level recommended by the American Medical Association and the National Institutes of Health. The accepted readability level for the FKRE formula was 80.0, whereas for the other 2 formulae it was 6 (20).

Statistical Analysis

Version 27.0 of the Statistical Package for the Social Sciences was used to analyze the study data. For normally distributed variables, descriptive statistics were shown as mean±standard deviation; For non-normally distributed variables, they were shown as median (minimum-maximum). Both visually (using probability plots and histograms) and analytically (using the Kolmogorov-Smirnov test) was the normality of the variable distribution evaluated.

The Kruskal-Wallis test was used to compare more than two groups when the data were non-normally distributed. The Mann-Whitney U test was used for pairwise comparisons, and the Bonferroni correction was used. Intraclass correlation coefficient (ICC) analysis was performed to determine the consistency in EQIP assessments. P-values of less than 0.05 were used to classify results as statistically significant.

Results

When examining the countries with the highest search frequencies related to SpA, the top three are New Zealand, Australia, and the United Kingdom (Figure 1). Similarly, for searches related to reactive arthritis and enteropathic arthritis,

the leading countries are the United Kingdom, New Zealand, and Australia. For ankylosing spondylitis, the top three countries are Australia, New Zealand, and Ireland. In searches for psoriatic arthritis, Germany, Austria, and Switzerland rank the highest.

Table 2 presents the mean, standard deviation, median, minimum, and maximum values of the EQIP, FKRE, FKGL, and GFI scores. The EQIP scores of the texts range from 54.14 to 78.12, with an average of 66.44. The FKRE scores range from 0 to 60.60, with an average score of 38.06. The FKGL scores range from 7.5 to 24.5, with an average score of 11.38. The GFI scores range from 8.61 to 26.38, with an average score of 13.91.

Table 3 contains the median, minimum, and maximum values of the EQIP, FKRE, FKGL, and GFI scores for the texts generated by the AI chatbots. Significant statistical differences were found in the EQIP, FKRE, FKGL, and GFI scores of the texts created by the AI chatbots ($p<0.001$, $p<0.001$, $p=0.001$, $p=0.003$, respectively) (Table 3).

According to the results of the pairwise group comparisons, after Bonferroni correction, the EQIP scores of the texts generated by the Copilot chatbot were found to be significantly higher than those generated by both the ChatGPT and Bard chatbots ($p<0.001$ and $p=0.004$, respectively).

In terms of FKRE scores, the texts produced by the ChatGPT chatbot were found to be significantly lower than those produced by both the Copilot and Bard chatbots ($p=0.005$ and $p<0.001$, respectively). Similarly, for FKGL scores, the texts generated by the ChatGPT chatbot were significantly higher than those produced by both the Copilot and Bard chatbots ($p=0.002$ and $p=0.004$, respectively).

Additionally, the GFI scores of the texts generated by the Copilot chatbot were found to be significantly higher than those generated by both the ChatGPT and Bard chatbots ($p=0.003$ and $p=0.007$, respectively) (Table 3).

When the median readability scores of all AI (ChatGPT, Copilot and Gemini) responses were compared with the sixth grade reading level, a statistically significant difference was observed in all scores compared to the sixth grade level ($p<0.001$). According to all scores, their answers had a readability above the sixth grade level (Table 4). The ICCs for EQIP were 0.904 for ChatGPT, 0.896 for Copilot, 0.873 for Gemini ($p<0.001$).

Figure 1. Interest in spondyloarthropathy-related searches across countries: 2004-2023 (based on Google Trends data)

Discussion

Our study concludes that the responses of AI chatbots regarding SpA are generally of "good quality with minor issues". It was determined that the average FKRE score was 38 and the texts produced were complex enough to require approximately 11 years of training. This is the first study to evaluate the quality and readability of responses generated by AI chatbots for the most frequently searched keywords related to the SpA group.

When examining the countries with the highest search frequencies related to SpA, the top three are New Zealand, Australia, and the United Kingdom. Similarly, for searches related to reactive arthritis and enteropathic arthritis, the

Tablo 2. Statistics of EQIP, FKRE, FKGL and GFI scores

	Minimum	Maximum	Median	Mean	Standard deviation
Ensuring Quality Information for Patients score	54.14	78.12	66.66	66.44	5.52
The Flesch-Kincaid reading ease score	0	60.60	41.35	38.06	12.06
The Flesch-Kincaid grade level score	7.5	24.5	10.75	11.38	2.66
Gunning Fog index score	8.61	26.38	13.25	13.91	3.2

EQIP: Ensuring Quality Information for Patients, FKRE: Flesch-Kincaid readability, FKGL: Flesch-Kincaid grade level, GFI: Gunning Fog index

Table 3. Comparison of EQIP, FKRE, FKGL and GFI Scores of texts generated by artificial intelligence chatbots

Median (min-max)	ChatGPT	Copilot	Bard	p-value
Ensuring Quality Information for Patients score	63.63 (54.54-71.87)[a]	72.72 (59.37-78.12)[b]	66.66 (54.54-75)[a]	<0.001
The Flesch-Kincaid reading ease score	31.65 (0-50.4)[a]	42.35 (21.1-59.1)[b]	43 (28.6-60.6)[b]	<0.001
The Flesch-Kincaid grade level score	12.35 (9.3-24.5)[a]	10.5 (8-12.3)[b]	10.45 (7.5-13.5)[b]	0.001
Gunning Fog index score	14.22 (10.9-26.38)[a]	12.33 (8.61-15.24)[b]	13.87 (9.16-19.94)[a]	0.003

[a,b]superscripts indicate the difference between groups. There is no difference in groups with a common letter
EQIP: Ensuring Quality Information for Patients, FKRE: Flesch-Kincaid readability, FKGL: Flesch-Kincaid grade level, GFI: Gunning Fog index, Min-max: Minimum-maximum

Table 4. Comparison of FKRE, FKGL and GFI Scores of texts generated by artificial intelligence chat robots according to the 6th grade reading level median

Median	ChatGPT	p-value	Copilot	p-value	Gemini	p-value
Ensuring Quality Information for Patients score	63.63	<0.001	72.72	<0.001	66.66	<0.001
The Flesch-Kincaid reading ease score	31.65	<0.001	42.35	<0.001	43.00	<0.001
The Flesch-Kincaid grade level score	12.35	<0.001	10.50	<0.001	10.45	<0.001
Gunning Fog index score	14.22	<0.001	12.33	<0.001	13.87	<0.001

FKRE: Flesch-Kincaid readability, FKGL: Flesch-Kincaid grade level, GFI: Gunning Fog index

leading countries are the United Kingdom, New Zealand, and Australia. For ankylosing spondylitis, the top three countries are Australia, New Zealand, and Ireland. In searches for psoriatic arthritis, Germany, Austria, and Switzerland rank the highest. These findings indicate how the tendency to access information on different types of SpA varies across countries. The research highlights the importance of geographical differences in awareness and access to information regarding these specific medical conditions. These data suggest that global health education and information efforts should focus more on specific regions.

Our study concludes that the responses of the three different AI chatbots are generally of "good quality with minor issues". The EQIP evaluations showed that all the texts reviewed followed a logical order, had a clear design, and addressed the reader respectfully and personally. However, some of the texts received zero points on certain evaluation criteria. We believe that even small improvements in these areas could elevate the texts from the "good quality" category to the "well-written and high-quality" category.

In intergroup comparisons, it was found that the EQIP scores of the texts generated by Copilot were significantly higher than those of the texts generated by ChatGPT and Bard. A determining factor for this difference could be that Copilot included references at the end of each text. It was observed that approximately half of the Bard texts included references, whereas ChatGPT did not include any references. Additionally, another factor contributing to the difference is that the majority of Bard's responses were supported by visuals. In a study evaluating different AI chatbots about erectile dysfunction, it was similarly observed that the EQIP scores of texts produced by Copilot were higher than those produced by ChatGPT and Bard (12).

Accessible, accurate, and easily understandable information is crucial in supporting individuals coping with SpA. High-quality and straightforward texts help patients understand the complexity of their condition, the available treatment options, and preventive measures. However, complex and difficult-to-understand online health information can lead to misunderstandings and even health risks (21).

In a study by Fahy et al. (22) evaluating ChatGPT responses related to anterior cruciate ligament injury, it was found that there were readability problems. Similarly, in a study examining responses related to spinal cord injury, it was observed that ChatGPT caused difficulties in terms of readability (16). Similar to our results, other studies in the literature also found that there were readability problems (15,23). In intergroup comparisons, the texts generated by ChatGPT required a higher educational level compared to those produced by Copilot and Bard. The results of a different study evaluating AI chatbots on erectile dysfunction were similar to our findings (12). To solve this problem, the importance of evaluating the quality of texts produced especially in the field of health with indices such as EQIP and readability indices such as FKRE, FKRL, GFI should be emphasized by teaching AI. In order to make the necessary arrangements, improvements should be made and audited in the database. These improvements will be a step towards ensuring patient safety while increasing health literacy. When these conditions are met, it can make patients more aware of the acceptance of the disease, the importance of treatment and the control of the process.

We did not find a study evaluating the responses of AI chatbots for the SpA group in the literature; However, other research in this area has provided us with several important findings. For example, a study analyzing YouTube videos related to SpA in terms of quality and reliability found that there are useful videos as well as misleading videos, and that these videos often contain inaccurate clinical features and unproven alternative treatments (24). Another study on the quality and readability of online information about ankylosing spondylitis found that less than half of the websites had high-quality content and that the average readability levels of the websites were lower than recommended (25). These findings underscore the need for SpA patients and healthcare professionals to be cautious when accessing online information.

In today's world, there is an increasing tendency for patients to seek information about health issues through online resources and AI-based chat tools (26). However, research indicates that these online resources are inadequate in terms of quality and readability (27-31). According to the results of our study, it is necessary to improve the quality and readability of AI chatbots as well. Consequently, patients and their families may suffer due to access to incorrect information (32). Therefore, ensuring the accuracy, quality, and readability of health information is of great importance. Compliance with quality and readability standards facilitates patients' access to reliable information and enhances health literacy (33). However, each patient is unique, and the treatment process requires a personalized approach. Therefore,

online resources and AI tools cannot replace healthcare professionals (34,35). The importance of the physician-patient relationship should always be emphasized.

Although the number of keywords evaluated in our study is approximately the same level as similar studies, there may be limitations in making generalizations.

Study Limitations

This limitation can be considered as a constraint of our study. Additionally, only English keywords were evaluated in the study. Evaluating keywords in different languages can broaden the scope of the results. Another limitation of our study is the use of a single calculator to evaluate the readability of websites. In the study conducted by Gül et al. (20), the correlation between different calculators was assessed, and medium strong correlation correlation results were obtained. Therefore, we also chose to use a single calculator.

Conclusion

This study reveals that AI chatbots' texts about SpA have certain shortcomings in terms of quality and readability. In conclusion, it emphasizes that online resources and AI tools play an important role in information delivery in the healthcare field, but quality and readability control should be ensured. This can facilitate patients' access to accurate, reliable and comprehensible information.

Ethics

Ethics Committee Approval: Since this study was not conducted on humans, it did not require an ethics committee certificate.

Informed Consent: Since this study was not conducted on humans, patient consent was not required.

Footnotes

Authorship Contributions

Concept: İ.C.Ö., V.H., E.Ö., Design: İ.C.Ö., V.H., E.Ö., Data Collection or Processing: İ.C.Ö., V.H., E.Ö., Analysis or Interpretation: İ.C.Ö., Literature Search: İ.C.Ö., Writing: İ.C.Ö.

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Reliability and Validity of the Turkish Version of Pain Modulation Index

Ağrı Modülasyon İndeksi'nin Türkçe Versiyonunun Geçerlilik ve Güvenilirliği

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Abstract

Objective: Chronic pain has significant impact on individuals and society. It is not just a symptom but is considered to be a separate disease in its own right. The aim of this study is to translate into Turkish and assess the validity and reliability of the "Pain Modulation index", which was developed to be used as an indicator of the changing central pain processing process in individuals presenting with chronic pain.
Materials and Methods: Study included 125 patients who had chronic pain. The Turkish translation was carried out using the "forward-backward translation" method. After adjustments were made according to the feedback of 10 volunteers, the study was started on the patient population. To evaluate the reliability of the scale, the test-retest was conducted with a 15-day interval. To evaluate its validity, Pain Detect and the Central Sensitization Inventory were applied on the first visit, along with the Pain Modulation index.
Results: Since the scale has 2 factors, the Cronbach's alpha coefficient was calculated separately for the factors, and it was found to be 0.89 for factor 1 and 0.82 for factor 2. intraclass correlation coefficient values were determined as 0.95 for factor 1 and 0.92 for factor 2. the results of the Turkish version of the pain modulation scale were found to correlate significantly with pain detect and central sensitization inventory ($p<0.05$).
Conclusion: The Turkish version of the pain modulation scale is a fast and easily applicable scale with high validity and reliability for clinical and epidemiological studies in patients presenting with chronic pain.
Keywords: Central sensitization, pain, nociplastic pain, pain modulation scale, surveys and questionnaires

Öz

Amaç: Kronik ağrı, hem birey hem de toplum üzerinde önemli etkiye sahiptir. Sadece bir semptom olmayıp, kimi zaman kendi başına bir hastalık süreci haline gelebilmektedir. Bu çaışmanın amacı, kronik ağrı ile başvuran hastalarda santral ağrı işlenim süreçlerini değerlendirmek amacıyla geliştirilmiş olan Ağrı Modülasyon indeksinin Türkçe'ye çevrilmesi ve geçerlilik ve güvenilirliğinin değerlendirilmesidir.
Gereç ve Yöntem: Çalışmaya kronik ağrısı mevcut olan 125 hasta dahil edilmiştir. Türkçe'ye çeviride ileri ve geri çeviri yöntemi kullanılmıştır. 10 sağlıklı gönüllü üzerinde denendikten ve geri bildirimlerine göre düzeltmeleri gerçekleştirildikten sonra, hasta popülasyon üzerinde uygulanmıştır. Güvenilirliği değerlendirebilmek için, 15 gün ara ile gönüllülere anket tekrar uygulamıştır. Geçerliliğinin değerlendirilmesi amacı ile ise pain detect ve santral sensitizasyon envanterleri de ilk vizitte hastalara uygulanmıştır.
Bulgular: Ölçek 2 alt başlıktan oluşmakta olup, her iki alt başlık için Cronbach alfa katsayısı ayrı ayrı hesaplanmıştır. Birinci alt grup için 0,89, ikinci alt grup için ise 0,82 olarak hesaplanmıştır. Sınıf içi korelasyonlar birinci alt başlık için 0,95 ve ikinci alt başlık için 0,92 olarak hesaplanmıştır. Ayrıca ağrı modülasyon indeksi skorları, pain detect ve santral sensitizasyon envanteri skorları ile korele saptanmıştır ($p<0,05$).
Sonuç: Ağrı modülasyon indeksinin Türkçe versiyonu, kronik ağrılı durumlarda, hem klinikte hem de araştırma amaçlı çalışmalarda hızlı ve kolayca uygulanabilen, geçerli ve güvenilir bir ölçektir.
Anahtar kelimeler: Merkezi sensitizasyon, ağrı, nosiplastik ağrı, ağrı modülasyon ölçeği, anketler ve soru formları

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Introduction

Chronic pain is reported to affect more than 30% of the World population. It results in wide ranging negative consequences such as high healthcare costs, loss of work-force and increased disability (1). Pain is a highly subjective sensation that can be influenced and caused by psychological parameters. The International Association for the Study of Pain (IASP) and the latest International Classification of Diseases has categorized pain into nociceptive, neuropathic and nociplastic pain (2). This latest classification aims to better describe painful conditions resulting from the hypersensitivity of the central nervous system in the absence of nociceptive or neuropathic input as nociplastic pain, of whose etiology and mechanism is still not fully understood (3). Central sensitization is the proposed mechanism that results from disordered pain modulation pathways in the central and peripheral nervous system. Although nociplastic pain seems to have many overlapping qualities with neuropathic pain and central as well as peripheral sensitization most probably plays a similar role in its development, the two are separate entities.

Objective quantification and classification of pain using standardized tests facilitates diagnostic and treatment approaches in the management of chronic pain. Different scales have been developed such as Pain Detect, The Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale, Douleur Neuropathique 4 Questions which assess the quality and severity of neuropathic pain and have been widely used in clinical studies. Nociplastic pain which results from the disordered modulation of pain in the absence of nerve injury is a new concept that is hard to measure and categorize. Current neuropathic pain assessment questionnaires are unable to differentiate neuropathic from nociplastic pain.

Austin et al. (4) first developed an 18-item index to better recognize disorders of pain modulation in 2019, which they named Pain Modulation index (PMI) This measure does not classify the painful condition as neuropathic or nociplastic, but instead tries to diagnose the underlying central sensitization process. In this study, we aimed to translate the PMI into Turkish and asses it's validity and reliability in the Turkish population.

Materials and Methods

An application was made to the Ege University Hospital Ethics Committee and approval was obtained with file number E.227599 (decision no: 21-7T/44, date: 08.07.2021). The original developers of PMI were asked for their approval via e-mail for the translation of the index into Turkish. The study was registered at clinicaltrials.gov with the registration number 21-7T/44.

Translation

Translation of the original index into Turkish was carried out separately by two physicians who are efficient in both languages. It was then back translated into English by two professional translators. This version of the index was first asked to 10 volunteers to assess its comprehensibility and clarity. After this first pilot application and according to volunteers' feedback, the final version was approved.

Sample Size

Sample size calculation was carried out similar to the original article, using the ratio of sample size to item number which in our case was found to be a minimum of 90 volunteers for a ratio of 5:1 (4,5).

Patient Selection

Volunteers were recruited from the physical and rehabilitation medicine outpatient clinic of our university hospital. Patients who had ongoing non-cancer pain of more than 3 months of duration were invited to take part in the study. All patients meeting the eligibility criteria were informed about the study and those who accepted to participate were asked to sign the written informed consent form before any further data collection and examination.

Patient Visits

Patient demographics and clinical diagnosis were recorded. All patients were asked to fill out the Turkish version of the PMI in addition to pain detect and central sensitization inventory on the first visit. Visual analog scale (VAS) pain levels were recorded. Patients were reached by phone and invited to the hospital between day 14-21 to fill out PMI for a second time, in order to assess reliability of the questionnaire.

Study Parameters

a. PMI: This index is composed of 2 factors, first one containing 11 and second one containing 7 items. Factor 1 mainly assesses pain qualities such as allodynia and hyperalgesia and responsiveness to medication. Factor 2 includes questions relating to mood, cognitive and behavioral symptoms. Each item is scored from 0 to 3. Higher scores denote more dysfunctional pain modulation. Original English version was developed by Austin et al. (4).

b. Pain Detect: Pain detect questionnaire was developed in Germany and is widely used in clinical and research settings (6). Its Turkish validation was reported in a study by Alkan et al. (7). The questionnaire is scored between 0 and 38. Lower scores denote lack of neuropathic pain while higher scores suggest possibility of neuropathic pain.

c. Central Sensitization Inventory: This inventory was developed by Mayer et al. (8) to assess the hyperactivity and hypersensitivity of pain pathways. It consists of 25 items, each one scored from 0 to 4. Scores higher than 40 denote the presence of central sensitization. Düzce Keleş et al. (9) carried out its Turkish validity and reliability study.

Statistical Analysis

Demographic and clinical parameters were presented using descriptive statistics namely mean±standard deviation for numeric data and number (percent) for categorical data. Reliability of PMI was assessed using the test-retest method. For

internal consistency of PMI, test and re-test scores for factor 1 were used to calculate a Cronbach alpha coefficient for each factor. Factor internal consistency and homogeneity was assessed by calculation an intraclass correlation coefficient for each item and for each factor. Reliability of PMI was assessed by carrying out correlation analyses between PMI factor 1, PMI factor 2, Pain Detect, Central Sensitization Inventory and VAS pain scores.

Results

One-hundred and twenty-five patients were enrolled in the study between August 2021 and July 2022. All participants had non-cancer painful conditions for more than 3 months of duration.

Demographics and Disease Characteristics

Patient characteristics are presented in Table 1. Of the 125 volunteers, 42 had neck pain and 42 had lower back pain. The remainder consisted of patients with shoulder, knee and Fibromyalgia related widespread pain.

Pain levels measured using VAS and pain detect, central sensitization inventory and PMI scores are presented in Table 2.

Reliability and Validity of PMI

Internal consistency was found to be high for both factor 1 and factor 2 of the PMI. Cronbach alfa coefficient was found to be 0.89 and 0.82 for factor 1 and factor 2 respectively.

Reliability assessment using correlation analysis between test and re-test scores revealed that both factor 1 and factor 2 of PMI were reliable. Item by item and total factor correlation analysis results between first and second applications of PMI are presented in table 3. total item intraclass correlation coefficient for factor 1 and factor 2 were found to be 0.95 and 0.92 respectively.

It was found that for most items of the PMI, female patients had significantly higher scores than male patients ($p<0.05$) except for items 1, 8, 9 and 13 of factor 1 (Table 4). We detected a significant correlation between factor 1 and factor 2 scores, and between each pairing of factor 1, factor 2, pain detect, central sensitization inventory and VAS scores ($p<0.05$). Correlation analysis results between different pain assessment questionnaires are given in Table 5.

Discussion

Pain is described as a disturbing sensation that is produced as a reaction to noxious and potentially dangerous stimuli from our environment, that acts as a defense mechanism (10). But apart from this primitive mechanism, psychological mechanisms and learning from previous experience also affects how and when an organism perceives pain (11). Until very recently, pain was broadly categorized as nociceptive and neuropathic pain. This dual classification failed to describe some patients with chronic pain without overt noxious stimuli and who could not be categorized into either category (12). Nociplastic pain was proposed in 2016 as a third classification option for those patients who had findings of disordered central pain processing (2). Nociplastic pain is defined by IASP as" pain of at least 3 months duration, that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". Central sensitization is not part of the definition of nociplastic pain, yet the two concepts have many overlapping qualities that are at least present in the region of pain (2,13). Diagnostic criteria of nociplastic pain contains items relating to central sensitization namely static or dynamic mechanical allodynia, heat or cold allodynia, and/or painful after-sensations

Table 1. Demographic and disease characteristics

Age, years, mean±SD	49.5512.40±
Sex, n (%)	
Female	97 (77.6%)
Male	28 (22.4%)
Marital status, n (%)	
Married, co-habitation	90 (72%)
Single	35 (28%)
Education, n (%)	
Literate	1 (0.8%)
Primary education	19 (15.2%)
Secondary education	40 (32%)
College or higher	65 (52%)
Occupation, n (%)	
Blue collar	2 (1.6%)
White collar	79 (63.2%)
Homemaker	30 (24%)
Retired	13 (10.4%)
Student	1 (0.8%)
Pain duration, n (%)	
3-6 months	27 (21.6%)
6-12 months	9 (7.2%)
12 months<	89 (71.2%)
Pain localization, n (%)	
Neck	42 (33.6%)
Lower back	42 (33.6%)
Shoulder	7 (5.6%)
Knee	12 (9.6%)
FMS, widespread	22 (17.6%)
Pain detect classification, n (%)	
Non-neuropathic pain	70 (56.0%)
Possible neuropathic pain	33 (26.4%)
Neuropathic pain	22 (17.6%)

SD: Stanard deviation

Table 2. Scores of clinical parameteres, mean±SD	
Central sensitization inventory	41.29±17.83
Pain detect	11.56±7.81
Pain modulation index	
Test factor 1	17.27±9.19
Test factor 2	12.35±5.16
Re-test factor 1	17.96±8.91
Re-test factor 2	12.55±5.10
VAS current pain level	6.30±2.70
VAS worst pain level	8.02±2.39
VAS average pain level	7.10±2.34
VAS: Visual analog scale, SD: Standard devitaion	

Table 3. Test-retest scores and intraclass correlation coefficient (ICC) of items from PMI			
	Mean score±SD	**Re-test mean score±SD**	**ICC**
Items (factor1)	17.2±9.1	17.9±8.9	0.95
Item 1	1.34±1.10	1.34±1.05	0.89
Item 2	1.62±1.18	1.70±1.10	0.87
Item 3	1.24±1.28	1.36±1.26	0.89
Item 4	1.33±1.24	1.36±1.19	0.93
Item 5	1.59±1.25	1.68±1.22	0.91
Item 6	1.49±1.19	1.57±1.18	0.90
Item 7	1.69±1.17	1.80±1.10	0.87
Item 8	1.71±1.21	1.78±1.15	0.91
Item 9	1.89±1.17	1.89±1.14	0.90
Item 10	1.74±1.28	1.86±1.23	0.90
Item 11	1.63±0.98	1.63±0.94	0.84
Items (factor 2)	12.3± 5.1	12.5±5.1	0.92
Item 1	1.65±1.00	1.74±0.94	0.85
Item 2	1.62±1.07	1.70±1.01	0.90
Item 3	1.82±1.06	1.87±1.00	0.87
Item 4	2.10±1.00	2.06±0.98	0.90
Item 5	1.96±1.05	1.92±1.00	0.89
Item 6	1.86±1.08	1.88±1.05	0.88
Item 7	1.33±1.07	1.37±1.02	0.90
SD: Standard deviation, ICC: Interclass correlation coefficient			

after any of the evoked pain hypersensitivity assessments (13). Central sensitization may be present in all types of chronic painful conditions such as osteoarthritis, intervertebral disc herniation, rheumatological conditions and fibromyalgia. Nociplastic pain may be accompanied by migraine headaches, temporomandibular dysfunction, irritable bowel syndrome and mood disorders which are also commonly present in patients with central sensitization. Differentiation of pain subtypes is needed to effectively manage and treat these painful conditions (14). The definition of painful concepts is an everchanging field, recognition of central sensitization and disordered pain processing mechanisms may aid the clinician in diagnosing nociplastic pain more easily. PMI is the first inventory developed to assess the disordered pain processing that results in central sensitization.

In the Turkish translation of PMI, similar to the original index, we have found a high correlation between factor 1 and factor 2 sub scores (4). In our study, most of the patients had mechanical lower back and neck pain. A smaller number of patients had fibromyalgia and rheumatological conditions that presented with widespread pain. Our index scores correlated strongly with central sensitization inventory scores, which was previously

Table 4. Comparison of item scores between male and female patients			
Items	**Sex**	**mean±SD**	**p-value**
Factor 1			
Item 1	F	1.41±1.143	0.161
	M	1.11±0.956	
Item 2	F	1.78±1.157	0.003*
	M	1.04±1.105	
Item 3	F	1.32±1.303	0.199
	M	0.96±1.201	
Item 4	F	1.47±1.226	0.014*
	M	0.82±1.188	
Item 5	F	1.73±1.238	0.020*
	M	1.11±1.227	
Item 6	F	1.67±1.179	0.001*
	M	0.86±1.044	
Item 7	F	1.80±1.160	0.039*
	M	1.29±1.150	
Item 8	F	1.81±1.202	0.078
	M	1.36±1.193	
Item 9	F	1.93±1.295	0.482
	M	1.75±1.295	
Item 10	F	1.98±1.225	0.000*
	M	0.93±1.184	
Item 11	F	1.76±0.933	0.005*
	M	1.18±1.056	
Factor 2			
Item 1	F	1.76±0.977	0.016*
	M	1.25±1.005	
Item 2	F	1.69±1.074	0.198
	M	1.39±1.066	
Item 3	F	1.98±1.010	0.002*
	M	1.29±1.084	
Item 4	F	2.27±0.919	0.001*
	M	1.54±1.105	
Item 5	F	2.07±0.961	0.000*
	M	1.39 ±1.084	
Item 6	F	2.03±1.033	0.000*
	M	1.36±0.970	
Item 7	F	1.54±1.100	0.000*
	M	0.79±0.787	
*p<0.05, F: Female, M: Male, SD: Standard deviation			

Table 5. Correlation analysis results for pain assessment questionnaires					
r	**VAS pain**	**CSE**	**PD**	**PMI factor 1**	**PMI factor 2**
VAS pain	1				
CSE	0.487**	1			
PD	0.487**	0.533**	1		
PMI factor 1	0.544**	0.736**	0.612**	1	
PMI factor 2	0.466**	0.824**	0.440**	0.699**	1
**p>0.01, r: Correlation coefficient, VAS: Visual analog scale, CSE: Central sensitization inventory, PD: Pain detect, PMI: Pain modulation inventory					

found to be a valid and reliable questionnaire to assess pain in knee osteoarthritis in patients who had symptoms of central sensitization (15). Similar to our study, the authors found central sensitization and pain detect scores correlated well with each other. Úbeda-DıOcasar et al. (16) also reported that central sensitization inventory and pain detect scores correlated well. In our study we found that women had higher scores in 14 of the 18 items of PMI. This finding is compatible with previous reports that utilized pain detect, central sensitization inventory and LANSS (6,17). This further supports our claim that PMI is a valid measure of chronic disordered pain processing, which is more commonly reported in female patients (18). Central sensitization plays a part in almost all chronic painful conditions. Pain Detect, LANSS and other neuropathic pain assessment indexes classify neuropathic pain using characteristics of central sensitization. The new classification system proposed by IASP that separates neuropathic pain from nociceptive pain, which lacks a clear neuropathic origin may predispose these indexes categorize nociplastic pain together with neuropathic pain. The use of a new index such as PMI that does not classify pain as neuropathic or nociceptive but diagnose a disordered pain processing pathway that leads to central sensitization may help avoid miscategorization of patients, especially for research purposes.

Most of the volunteers in our study were high school or college educated. Patients with lower education levels and who are illiterate may have a harder time expressing different symptoms related to central sensitization and also have difficulties in answering these types of questionnaires. In our study, questions were answered by the patients themselves, but in real life situations, patients who have difficulty understanding some questions or who are illiterate may need help from healthcare providers in order to better diagnose and classify chronic painful conditions. PMI being a brief and easy to understand tool, may be helpful in these kinds of situations where time and staff are limited.

We have enrolled enough volunteers to assess the Index's validity and reliability. But this cross-sectional study needs to be supported by prospective and long-term interventional studies to assess the sensitivity of PMI to changes of pain severity with treatment. Our patient group consisted mainly of mechanical lower back and neck pain sufferers. A larger study with more patients with fibromyalgia and other regional and generalized pain syndromes would help PMI become a commonly used tool for assessing central sensitization and central pain processing disorders.

Conclusion

Turkish version of PMI is a reliable and valid tool for the assessment of chronic pain that can be used both in the clinical setting and for research purposes.

There still remains the need for further studies evaluating its validity in different painful conditions and its sensitivity to change with treatment of nociplastic pain.

Ethics

Ethics Committee Approval: An application was made to the Ege University Hospital Ethics Committee and approval was obtained with file number E.227599 (decision no: 21-7T/44, date: 08.07.2021).

Informed Consent: Patient consent was obtained for this study.

Foonotes

Authorship Contributions

Concept: E.C.S., S.H., E.Ç., Design: E.C.S., S.H., E.Ç., Data Collection or Processing: E.C.S., E.Ç., Analysis or Interpretation: E.C.S., S.H., Literature Search: E.C.S., Writing: E.C.S., E.Ç.

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Complex Decongestive Therapy for Lower Extremity Lymphedema: Results from a Tertiary Care Center

Alt Ekstremite Lenfödem Tedavisinde Kompleks Dekonjestif Tedavi: Bir Üçüncü Basamak Merkezin Sonuçları

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Abstract

Objective: Complex decongestive therapy (CDT) is the gold standard of lymphedema treatment. In this retrospective study, we aimed to evaluate the effectiveness of CDT in patients with lower extremity lymphedema.
Materials and Methods: In this retrospective study, demographic data, disease characteristics, percentage of excess volume, and lymphedema volume to body mass index (LV/BMI) ratio of lower extremity lymphedema subjects were analyzed.
Results: Treatment outcomes of 198 extremities from 127 patients were analyzed. Pre- and post-treatment LV/BMI values were significantly higher in the venous insufficiency group. Lymphedema grade was found to have a positive and significant correlation with BMI ($p<0.05$). Post-treatment LV/BMI values showed a positive correlation with patients' activity levels and number of radiotherapy sessions ($p<0.05$).
Conclusion: We have observed that primary lymphedema responds equally well to CDT as does cancer-related lymphedema. We have also detected similar volume reduction values with CDT in patients with chronic venous insufficiency.
Keywords: Complex decongestive therapy, lymphedema, rehabilitation, venous insufficiency

Öz

Amaç: Kompleks dekonjestif tedavi (KDT), lenfödem tedavisinde altın standart olarak kabul edilmektedir. Bu retrospektif çalışmada, alt ekstremite lenfödem tedavisinde KDT'nin etkinliğini değerlendirmek amaçlanmıştır.
Gereç ve Yöntem: Bu retrospektif çalışma, üniversite hastanemizde alt ekstremite lenfödemine yönelik KDT uygulanmış olan hastaların, demografik özellikleri, hastalık özellikleri, volüm farkları, lenfödem volümünün vücut kitle endeksine (LV/VKİ) oranı değerleri incelenmiştir.
Bulgular: Toplam 127 hastaya ait 198 ekstremitenin tedavi sonuçları incelenmiştir. Venöz yetmezliğe bağlı alt ekstremite lenfödemi bulunan hastalarda, tedavi öncesi ve sonrası LV/VKİ oranları anlamlı olarak daha yüksek saptanmıştır. Lenfödem evresi ile VKİ arasında anlamlı bir pozitif ilişki saptanmıştır ($p<0,05$). Tedavi sonrası LV/VKİ oranı ile hastaların aktivite düzeyleri ve radyoterapi seans sayısı arasında da anlamlı ilişki bulunmuştur ($p<0,05$).
Sonuç: Sonuçlarımız, primer lenfödemin de, KDT'ye kansere bağlı lenfödem kadar iyi yanıt verdiğini desteklemektedir. Ayrıca, kronik venöz yetmezlik hastalarında da KDT ile benzer volüm azalması elde edildiği gözlenmiştir.
Anahtar kelimeler: Kompleks dekonjestif tedavi, lenfödem, rehabilitasyon, venöz yetmezlik

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Introduction

Lymphedema is defined as the accumulation of protein rich lymphatic fluid in the interstitial tissues as a result of congenital or acquired insufficiency of the lymphatic system, that results in the gradual swelling, inflammation, adipose hypertrophy and fibrosis in the affected body area (1). Limbs are most commonly affected but trunk, abdominal structures or head and neck may also be involved. Lymphedema can be classified as primary or secondary, according to the presence of a discernable precipitating injury to the lymphatic system. Cancer and cancer treatment is the most common cause of lymphedema in the developed world, followed by infections, chronic venous insufficiency, and congenital lymphatic obstruction. Surgery, lymph node dissection, metastasis and radiation therapy all play a role in the development of cancer related lymphedema.

In addition to local complications such as infection, pain and ulceration, lymphedema causes significant morbidity such as depression, anxiety and limitation of daily activities (2). Although lower extremity lymphedema is more common and its etiology more varied, breast cancer related upper extremity lymphedema is the most thoroughly researched subgroup of lymphedema. There is still no definite cure for lymphedema and all treatment strategies aim to manage the swelling and related complications. Complex decongestive therapy (CDT) is still the most effective treatment strategy in controlling symptoms, but results differ according to etiology, site and extent of involvement.

Most studies assessing the effectiveness and results of lymphedema treatment focus on upper extremity lymphedema, more specifically cancer related upper extremity lymphedema. But treatment results and related factors are not as thoroughly researched as upper extremity lymphedema. The evidence regarding the effectiveness of additional treatment methods such as low-level laser therapy or pneumatic compression devices is still lacking. For this reason, the aim of this study was to retrospectively document the characteristics and treatment results of lower extremity lymphedema patients treated in our tertiary lymphedema rehabilitation clinic.

Materials and Methods

We have reviewed and recorded data from the patient files of those patients that had received at least one cycle of treatment for lower extremity lymphedema in the lymphedema care and treatment unit of our university hospital. For this study, we included patient records of those subjects that received CDT and had control limb measurements in their files that were followed up between 2010-2021. Ethical approval was obtained from Ege University Faculty of Medicine Clinical Research Ethics Committee for this retrospective study (decision no: 15-1.1/1, date: 29.06.2015).

Only adult patients were included in the study. Subjects that did not have lower extremity lymphedema (including those that were referred to us prophylactically), pediatric patients and lower extremity swelling caused by other reasons (lipedema, tumors etc.) were excluded.

Demographic characteristics including age, height, weight, body mass index (BMI) as well as disease characteristics such as cause of lymphedema, history of chemotherapy and radiotherapy, number of removed lymph nodes, duration of lymphedema, lymphedema grade, duration of time to initiation of therapy, number of treatment sessions, presence of fibrosis, and patients' activity level were recorded and presented in Table 1.

In our routine patient follow-up, we use the limb circumference method for the calculation of excess lymphedema volume (LV) and for comparison between both sides. In this method, lower extremity circumference is measured with a tape measure, starting from the 1st metacarpophalangeal joint, ankle joint and every 4 cm proximally. Extremity volumes are then calculated with the help of a spreadsheet formula, the truncated cone volumes calculated using limb circumference measurements (3). For unilateral lymphedema, percentage of excess volume was calculated using the excess volume reported by Forner-Cordero et al. (4). Since most patients had bilateral lower extremity lymphedema, absolute limb volume differences were not sufficient to assess treatment outcomes. For this purpose, we have used the LV to BMI ratio, which was previously found to correlate well with degree of excess LV and lymphedema grade (5).

In our routine patient care, each new patient presenting to our lymphedema unit goes through a detailed evaluation. Every patient receives education regarding lymphedema self-management protocol (SMP) including education about risk factors, precipitating situations, hygiene, protection of extremity from trauma, moisturization and suitable exercises. Exercise not only increases lymph drainage but also helps prevent limitation of joint movement. Proper exercises including stretching, range of motion, pumping, aerobic and strengthening exercises are tailored according to patients' status and needs and are reassessed regularly (6). Each patient is informed about weight control and overweight and obese patients are referred to a dietician and receive recommendations regarding weight loss. SMP also includes manual lymph drainage (MLD) techniques. CDT remains to be the cornerstone of conservative management of lymphedema. First phase or intensive phase of CDT, in addition to SMP and MLD, consists of compression therapy, usually in the form of bandaging of the affected area to increase drainage and rapidly reduce LV by creating a pressure gradient. This phase may also include pneumatic compression therapy. Second phase or maintenance phase continues to employ skin care, exercise and if necessary, compression garments to sustain limb volumes (7). In our center, all patients that receive compression bandage therapy also receive lower extremity pneumatic compression treatment as part of the compression therapy (BioCompression systems SC-3008-DL, USA). In our study, no patient showed adverse reactions to pneumatic compression therapy. After the completion of the intensive phase of CDT, every patient receives a prescription for compression garments and is followed up regularly during the maintenance phase.

Kinesiotaping may be added to treatment programs and is applied once or twice weekly in patients receiving CDT. Similarly, patients with fibrotic thickening of the skin may receive extracorporeal shock wave therapy (ESWT) once a week during

the intensive phase of CDT. These treatment options, if applied, were recorded. Most patients that have fibrosis in their affected extremity receive low-level laser therapy. Laser therapy is applied by a physical therapy technician before each bandaging session.

Statistical Analysis

Statistical analyses were carried out using statistical software package SPSS version 20.0 (International Business Machines Corp., Armonk, NY, USA). Demographic and clinical parameters were presented using descriptive statistics (frequency distributions, mean and standard deviation). Before and after-treatment values for LV/BMI were compared using Paired Samples t-test. Before and after-treatment percentage of excess volume values were compared using Paired Samples t-test. Excess volume and LV/BMI values belonging to cancer and venous insufficiency patient subgroups, and values belonging to different treatment groups were compared with independent samples t-test. Correlations between patient parameters and treatment outcomes were assessed with Pearson's correlation analyses.

Results

Files belonging to 166 patients were assessed for inclusion in the study. Twenty-three patients had lipedema and were excluded. Twenty-six patients had no treatment records. After excluding these cases, a total of 127 patients were included in the study. All patients were of Caucasian ethnicity. Fifty-six patients had received treatment for unilateral lower extremity lymphedema while 71 had bilateral lower extremity lymphedema. Treatment outcomes of a total of 198 extremities were recorded and analyzed. Patient demographic and clinical characteristics are presented in Table 1.

Only 1 patient had grade 1 lymphedema, all remaining subjects had grade 2 or grade 3 lymphedema. The mean age of patients was 55.5±14.3 years. Seventy nine percent of subjects were female. Nearly half of subjects (44%) had cancer related lymphedema, followed by lymphedema related to venous insufficiency (23.6%). Other etiologies were far less common. Cancer related lymphedema patients had gained approximately 8.2±9.8 kg after surgery and most of them had received both chemotherapy and radiotherapy (59% and 66% respectively). Mean duration of time from the start of lymphedema related symptoms to the initiation of therapy was 75.8±107.6 months and mean duration of follow-up was 25.7±15.2 months. Almost one third of patients had had at least one episode of lymphangitis.

One hundred and ninety-eight extremities were included in the study and a majority (72.7%) of those had received kinesiotaping in addition to SMP and compression bandaging therapy. LV/BMI ratio decreased significantly with CDT ($p<0.05$) and mean percentage of decreased volume was found to be 11.6%. When grouped according to treatment types, all patients regardless of group, showed statistically significant improvement after treatment ($p<0.05$).

Table 1. Demographic and clinical characteristics of patients (n=127)

Age, year, mean±SD	55.5±14.3
Female sex, n (%)	101 (79.5)
Extremity involvement, n (%)	
Unilateral lower extremity	56 (44.1)
Bilateral lower extremity	71 (55.9)
Lymphedema grade, n (%)	
Grade 1	1 (0.8)
Grade 2	65 (51.2)
Grade 3	61 (48.0)
Grade 4	0
BMI, kg/m^2, mean±SD	31.8±7.0
Etiology, n (%)	
Cancer	56 (44.09)
Endometrium	17 (13.4)
Ovarian	10 (7.9)
Cervix	9 (7.1)
Prostate	4 (3.1)
Malignant melanoma	3 (2.4)
Other	13 (10.2)
Venous insufficiency	30 (23.6)
Surgical complication, other than cancer	12 (9.4)
Primary lymphedema	27 (21.3)
Infection	2 (1.6)
Cancer grade, n (%)	
Grade 1	10 (7.9)
Grade 2	25 (19.7)
Grade 3	13 (10.2)
Grade 4	8 (6.3)
History of radiotherapy, n (%)	33 (26.0)
History of chemotherapy, n (%)	37 (29.1)
Number of removed lymph nodes, mean±SD	10.8±16.9
Weight gained after surgery, kg, mean±SD	8.2±9.8
Genital lymphedema present, n (%)	34 (26.8)
Fibrosis is present, n (%)	62 (48.8)
Stemmer sign positive, n (%)	122 (96.1)
Physical activity level, n (%)	
Sedentary	25 (19.7)
Leisure walks	85 (66.9)
Regular exercise	16 (12.6)
Athlete	1 (0.8)
Duration from first symptom until first treatment (months), mean±SD	75.8±107.6
Duration of follow-up, months, mean±SD	25.7±15.2
Had at least one episode of lymphangitis, n (%)	36 (28.3)
Genital lymphedema present, n (%)	34 (26.8)
Treatment duration, days, mean±SD	22.7±6.9

SD: Standard deviation, BMI: Body mass index, n: Number

Of the extremities included in our study, 53 had a history of lymphangitis. Limb volumes and percentage of decreased volumes according to a history of lymphangitis are presented in Table 2 and Table 3. Patients with or without a history of lymphangitis showed similar levels of treatment response.

Cancer related lymphedema patients were the majority in our patient cohort and a total of 77 extremities were treated with CDT. The second most common group consisted of chronic venous insufficiency related lymphedema and a total of 53 extremities were included in the study. A comparison between the two groups is presented in Table 4. When we compared treatment results from these two groups, venous insufficiency group had significantly higher mean BMI values ($p<0.05$).

Table 2. Treatment characteristics and results of 198 extremities from 127 patients, with pre- and post-treatment limb volume differences

Treatment type, n (%)	Percentage of decreased volume, mean±SD	LV/BMI, pre-treatment, mL m^2/kg, mean±SD	LV/BMI, post-treatment, mL m^2/kg, mean±SD
SMP+compression bandaging+kinesiotape+pneumatic compression therapy, 144 (72.7)	11.4±8.9	151.9±32.3	134.5±26.2*
SMP+compression bandaging+ESWT+pneumatic compression therapy+LLLT, 31 (15.7)	12.1±10.0	162.7±53.1	143.8±58.5*
SMP+compression bandaging+ESWT+kinesiotape+pneumatic compression therapy+LLLT, 23 (11.7)	11.6±9.7	128.4±27.2	144.0±25.1*
All extremities, 198 (100)	11.6±9.2	152.7±35.8	135.2±33.5*

*Difference between pre-treatment and post-treatment values is significant; $p<0.05$; Paired samples t-test
SMP: Self-management protocol (patient education, exercise and manual lymph drainage), LV: Limb volume, BMI: Body mass index, ESWT: Extracorporeal shock wave therapy, LLLT: Low-level laser therapy, SD: Standard deviation

Table 3. Comparison of limb volumes and decrease in volumes between patients with or without a history of lymphangitis

	Limbs with a history of lymphangitis (n=53)	Limbs without a history of lymphangitis (n=145)	p-value
Percentage of decreased volume, mean±SD	10.0±8.7	12.1±9.2	0.2
LV/BMI, pre-treatment, mL m^2/kg, mean±SD	154.7±34.8	151.9±36.3	0.6
LV/BMI, post-treatment, mL m^2/kg, mean±SD	138.2±28.6	134.2±35.1	0.5

LV: Limb volume, BMI: Body mass index, SD: Standard deviation, independent samples t-test

Table 4. Comparison of treatment outcomes between cancer related and venous insufficiency related lymphedema patients' extremities

	Cancer related lymphedema (n=77)	Venous insufficiency related lymphedema (n=53)	p-value
LV/BMI, pre-treatment, mL m^2/kg, mean±SD	155.3±43.1	137.1±17.0	0.00*
LV/BMI, post-treatment, mL m^2/kg, mean±SD	136.8±42.3	121.6±15.8	0.01*
Decreased volume, %, mean±SD	12.7±9.6	11.1±7.9	0.32
Lymphedema duration, months, mean±SD	70.4±53.2	89.3±82.0	0.1
BMI, kg/m^2, mean±SD	29.9±5.6	35.6±7.3	0.00*
	Cancer related lymphedema (n=77)	**Primary lymphedema (n=42)**	**p-value**
LV/BMI, pre-treatment, mL m^2/kg, mean±SD	155.3±43.1	165.4±34.0	0.2
LV/BMI, post-treatment, mL m^2/kg, mean±SD	136.8±42.3	149.7±27.4	0.08
Decreased volume, %, mean±SD	12.7±9.6	8.9±8.0	0.02*
Lymphedema duration, months, mean±SD	70.4±53.2	198.3±189.2	0.00*
BMI, kg/m^2, mean±SD	29.9±5.6	31.4±7.3	0.2

*Level of significance, $p<0.05$, independent samples t-test. n: Describes number of extremities
SD: Standard deviation, LV: Limb volume, BMI: Body mass index

Table 5. Correlations between treatment parameters

	Age	BMI	Activity level	Percentage of decreased volume	LV/BMI, pre-treatment	LV/BMI, post-treatment
	r	r	r	r	r	r
Age	1.0	0.2	-0.2	0.1	0	0.1
BMI	0.2	1	-0.1	0	0	0.1
Activity level	-0.2	-0.1	1	-0.2	0.1	0.31*
Removed lymph nodes, n	-0.5	-0.3*	0.1	0.1	0.1	0.1
CT cycles, n	-0.3	-0.2*	0	0.2	0.1	0
RT sessions, n	0	-0.3*	0.1	0	0.1	0.2*
Lymphedema grade	0.2*	-0.2*	-0.2	0.2	0	-0.1
Treatment duration (days)	0	0.1	-0.1	-0.1	0.1	0.1

*p<0.05 correlation is significant
BMI: Body mass index, LV: Limb volume, SD: Standard deviation, CT: Chemotherapy, RT: Radiotherapy, r: Correlation coefficient

Other demographic factors were similar between the two groups (p>0.05). Pre- and post-treatment LV/BMI values were significantly higher in the venous insufficiency group, although comparison of decreased volume percentages between the two groups was found to be insignificant (p>0.05). When we compared cancer related lymphedema patients with primary lymphedema patients, the percentage of decreased volume was found to be significantly more in the cancer patient group (p<0.05), although pre- and post-treatment LV/BMI values did not differ significantly in the two groups (p>0.05).

Correlation analyses between demographic and clinical parameters are presented in Table 5. Lymphedema grade was found to have a positive and significant correlation with BMI (p<0.05). BMI was also positively correlated with the number of removed lymph nodes as well as number of chemotherapy cycles and radiotherapy sessions (p<0.05). Pre-treatment LV/BMI ratio was not found to correlate with any clinical parameters, but post-treatment LV/BMI values showed a positive correlation with patients' activity levels and number of radiotherapy sessions (p<0.05). Curiously, no disease parameters were found to be correlated with the percentage of decreased LV.

Discussion

In this study, we have observed that most patients with lower extremity lymphedema, regardless of etiology, respond well to CDT.

Cancer and cancer treatment has become the most common cause of lymphedema in the developed world. Nearly 30% of breast cancer survivors develop upper extremity lymphedema. Overall incidence of lymphedema after different types of cancer has been reported to be around 15% (8). Although in some sources, chronic venous insufficiency has been reported to be the most common precipitator of lymphedema, our patient population composed by 56% of cancer related lymphedema cases, followed by venous insufficiency in 30% of cases. Our being a tertiary lymphedema center with a majority of our patients referred to us from the oncology department may explain this predominance of cancer related lymphedema in our patients. It has also been reported that lymphedema resulting from chronic venous insufficiency often goes unnoticed and underdiagnosed until reaching higher volumes, and this may be the case in our center (9). Mean disease duration until referral to the lymphedema unit was found to be 7 years. In accordance with the literature, our patients were predominantly female (79.5%) (10). Studies reporting a higher proportion of venous insufficiency patients also report higher proportions of male lymphedema patients. Our percentages are in accordance with the previously reported numbers (9,10).

Obesity has previously been reported to be related to the development and progression of lymphedema (9). Seidel et al. (11) reported that obesity (BMI ≥30.0) was significantly more frequent in patients with advanced chronic venous disease. Increased intrabdominal and venous pressure in obese individuals may explain this relationship (12). In addition, obesity has been linked to increased inflammation and inflammation in turn has been proposed as one of the risk factors for fibrosis and progression of lymphedema (11). In some cases, obesity has been reported as the sole precipitator of lymphedema and these cases have been named "obesity-induced lymphedema" (13). In patients with secondary lymphedema, higher BMI has been correlated with higher lymphedema grades (9).

Although there is no known cure for lymphedema and tissue fibrotic changes are for the most part irreversible, CDT remains the golden standard of lymphedema treatment (14). Its effectiveness in the management of cancer-related lymphedema has been proven although fewer studies assess its effectiveness in other subtypes of lymphedema. Compression therapy with short-stretch bandages is the cornerstone of the intensive phase. All patients in our study had received compression bandage therapy as part of the intensive phase of CDT. Some authors report that compression bandage application alone is enough to reduce LVs during the intensive phase and it yields similar results to a more complex CDT program (15). In our clinic, every patient receives lower extremity pneumatic compression therapy in addition to compression bandaging. All patient groups,

regardless of addition of laser therapy, ESWT or kinesiotaping, showed significant reduction in extremity volumes ($p<0.05$).

Fibrosis in lymphedema has been linked to many factors. Protein rich fluid which is normally degraded by macrophages in the interstitium builds up and starts an inflammatory reaction. Minor trauma that may go unnoticed can result in a lymphangitis episode that may further worsen fibrosis and tissue swelling. We have found no difference in treatment outcomes between patients with or without a history of lymphangitis. Primary lymphedema patients generally present with bilateral lower extremity lymphedema. Onset may be during childhood or early adulthood. In this study, we have included results from our adult primary lymphedema patients but did not include pediatric patients, since comparison between children and adults would be difficult and results could be misleading. Primary lymphedema patients had, as expected, longer disease durations but pre- and post-treatment LV/BMI values were similar in cancer patients and primary lymphedema patients. A small but statistically significant difference was detected when we compared the percentages of volume decrease between the two groups, with cancer-related lymphedema patients having higher reduction in LVs. This may be due to the more chronic nature of primary lymphedema and the relative increase in fibrotic tissues with longer disease duration. Fibroadipose proliferation has been presented as one of the factors contributing to the development of lymphedema after the initial lymphatic injury. Although we do not know why not all patients with lymph vessel or lymph node dissection develop lymphedema, fibrotic proliferation may be one of the aggravating factors (16).

Low-level laser treatment is a non-invasive treatment that has been proposed to reduce inflammation, induce lymph vessel regeneration and prevent tissue fibrosis (17). Although there are not large randomized controlled studies assessing the effects of laser therapy on lower extremity lymphedema, it has been shown to be effective in reducing limb volumes in breast cancer-related lymphedema patients (18,19). Its ease of use and relatively low cost makes low-level laser therapy a suitable addition to the treatment protocol, especially for those patients with fibrotic thickening of the skin.

Pre- and post-treatment LV/BMI values were significantly higher in the venous insufficiency group compared to the cancer related lymphedema group although percentage of volume decrease was similar both groups. Patients in the chronic venous insufficiency group had significantly higher BMI values. The use of LV/BMI ratio aims to decrease the effect of body mass and weight differences while comparing patients with different body compositions. Although LV/BMI ratio is used in order to decrease the effect of obesity on lymphedema measurements when comparing different patients, factors related to obesity such as decreased physical activity, co-morbidities and chronic inflammation may indirectly influence the results of treatment strategies. In rare cases, obesity has been reported to cause lymphedema without additional risk factors (20). CDT has also been reported to be helpful in healing of chronic venous ulcers (21). Use of pneumatic compression devices has also been shown to be beneficial for the treatment of phlebolymphedema (22). Each patient that is referred to our clinic and receives CDT receives, before compression bandaging, pneumatic compression treatment for 20 minutes. Pneumatic compression has been utilized extensively in the treatment of lymphedema and chronic venous insufficiency (23).

Evidence for the effectiveness of kinesiotape applications in the treatment of lymphedema is still scarce. However, it has been reported that kinesiotaping is well tolerated and may reduce LVs significantly (24). Some authors state that kinesiotape application may be as effective as compression bandaging in reducing excess volume in upper extremity lymphedema patients (25). It is important to note that some patients may not tolerate compression bandaging or pneumatic compression therapy well and kinesiotaping may play a supportive function as part of the larger CDT approach. We did not come across a study assessing the effectiveness of kinesiotaping in the management of lower extremity lymphedema but in light of upper extremity studies, we often add kinesiotaping to our routine patient care for its relative ease of application and low cost. None of the patients in our cohort had reported any adverse effects related to kinesiotaping.

ESWT is being more commonly employed as a component of lymphedema treatment as new data emerges regarding its effectiveness in the treatment of lymphedema. We employ ESWT as an adjunct to CDT, although it has been shown to reduce LVs by itself (26). It exerts beneficial effects on lymphedematous tissues by promoting lymphangiogenesis and increasing the density of lymphatic vessels (27). Fifty-four of the 198 lymphedematous extremities included in our study received ESWT treatment in addition to compression bandaging and/or kinesiotaping. Aside from mild discomfort during application, none of the patients reported severe discomfort or pain and no patients needed to quit ESWT treatment. We usually prescribe ESWT treatment for lower extremity lymphedema if there is prominent fibrosis, in order to stimulate circulation and lymphangiogenesis. We could not compare results between ESWT receiving and ESWT free groups because of the difference in patient numbers but both groups showed improvements in treatment outcomes.

Study Limitations

The main limitation of our study is its retrospective quality. Although prospective studies would certainly produce more accurate results, there are not many studies assessing treatment modalities and treatment results in lower extremity lymphedema. Most patients in our study (72.7%) received a combination of compression bandaging, SMP and kinesiotape application. A more limited number of patients received ESWT in addition to SMP and compression bandaging. Because numbers in kinesiotaping and ESWT groups were far from equal, we could not compare their outcomes statistically, although all groups showed significant improvement with treatment. The lack of results from the maintenance phase of the CDT program

is another limitation of our study. After the completion of the intensive phase, all patients are continued to be followed up regularly but the heterogeneity in the number of control visits, number of measurements and follow-up intervals made it unfeasible to compare these data. We did not include the effect of treatment on quality of life because not all subjects in our patient group had been assessed regularly for changes in quality of life, which is another limitation of this study.

Conclusion

Although lower extremity lymphedema is more common than that of upper extremity, studies examining the effectiveness of treatment strategies focus more on upper extremity lymphedema, especially breast cancer related lymphedema. CDT has been proven to be effective in decreasing LVs in patients with cancer related lymphedema. In this retrospective analysis of treatment results from a tertiary lymphedema clinic, we have observed that primary lymphedema responds equally well to CDT as cancer related lymphedema. We have also detected similar volume reduction values with CDT in patients with chronic venous insufficiency, although differences in BMI and body composition may have an additional effect on treatment outcomes. Kinesiotaping is well tolerated and may be added to routine CDT program, but we did not have a large enough cohort to analyze its effectiveness in addition to compression bandaging.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no: 15-1.1/1, date: 29.06.2015).

Informed Consent: Since this study was retrospective, patient consent was not required.

Foonotes

Authorship Contributions

Concept: E.Ç., S.E., Design: E.Ç., S.E., Data Collection or Processing: E.Ç., B.N.A., E.Y.G., Analysis or Interpretation: E.Ç., S.E., B.N.A., E.Y.G., Literature Search: E.Ç., E.Y.G., Writing: E.Ç.

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Understanding Kinesiophobia in Chronic Mechanical Low Back Pain: An Analysis of Contributing Factors

Kronik Mekanik Bel Ağrısında Kinezyofobiyi Anlamak: Katkıda Bulunan Faktörlerin Analizi

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Abstract

Objective: This study aims to evaluate how kinesiophobia is related to demographics, pain intensity, functional status, and quality of life in patients with chronic mechanical low back pain.

Materials and Methods: We assessed 226 participants suffering from chronic mechanical low back pain for pain intensity (using the visual analog scale), neuropathic pain (with the douleur neuropathic 4 questionnaire, DN4), functional disability [(using the Oswestry disability index (ODI)], kinesiophobia [(using the Tampa kinesiophobia scale (TKS)], and quality of life [using the short form-36 (SF-36) quality of life index]. Patients were grouped and compared based on having a high (TKS ≥37) or a low (TKS <37) kinesiophobia.

Results: Most participants (69.4%) reported high levels of kinesiophobia. Mean scores: TKS=40.7±6.9; ODI=32.0±18.5; DN4=1.8±2.0. Kinesiophobia was significantly associated with female sex, activity-related pain, low education level, being a housewife, disability, and low quality of life. The multivariate model revealed that the individual SF-36 domain scores for limitations due to physical health, emotional well-being, and social function were significantly and independently correlated with distinguishing patients with high and low levels of kinesiophobia

Conclusion: Sex, activity-related pain, occupation, education level, disability, and quality of life are significant factors influencing kinesiophobia in chronic mechanical low back pain patients.

Keywords: Chronic low back pain, disability, kinesiophobia, quality of life

Öz

Amaç: Bu çalışmanın amacı, kronik mekanik bel ağrısı olan hastalarda kinezyofobinin demografik özellikler, ağrı şiddeti, fonksiyonel durum ve yaşam kalitesi ile nasıl ilişkili olduğunu değerlendirmektir.

Gereç ve Yöntem: Kronik mekanik bel ağrısı olan 226 katılımcının ağrı şiddeti görsel analog skala; nöropatik ağrı varlığı douleur nöropatik 4 (DN4) anketi, fonksiyonel engelliliği Oswestry engellilik indeksi (OEE); kinezyofobileri Tampa kinezyofobi ölçeği (TKÖ) ve yaşam kaliteleri kısa form-36 (SF-36) yaşam kalitesi indeksi kullanılarak değerlendirildi. Hastalar kinezyofobi skorlarına göre yüksek (TKÖ ≥37) ve düşük (TKÖ <37) olarak göre gruplandırıldı ve karşılaştırıldı.

Bulgular: Katılımcıların çoğu (%69,4) yüksek düzeyde kinezyofobi bildirmiştir. Ortalama kinezyofobi, fonksiyonel engellilik ve nöropatik ağrı puanları sırasıyla TKÖ=40,7±6,9; OEE=32,0 ±18,5; DN4=1,8±2 olarak saptandı. Kinezyofobi kadın cinsiyet, aktiviteye bağlı ağrı, düşük eğitim düzeyi, ev hanımı olma, engellilik ve düşük yaşam kalitesi ile anlamlı şekilde ilişkiliydi. Çok değişkenli model ile yapılan ileri analiz, fiziksel sağlık nedeniyle sınırlamalar, duygusal iyilik hali ve sosyal işlev alanlarındaki bireysel SF-36 skorlarının, yüksek ve düşük kinesiophobia seviyelerine sahip hastaları ayırt etme konusunda anlamlı ve bağımsız olarak korele olduğunu ortaya koydu.

Sonuç: Sonuç olarak, cinsiyet, aktivite ile ilişkili ağrı, meslek, eğitim düzeyi, engellilik ve yaşam kalitesi kronik mekanik bel ağrısı hastalarında kinezyofobiyi etkileyen önemli faktörlerdir.

Anahtar kelimeler: Kronik bel ağrısı, engellilik, kinezyofobi, yaşam kalitesi

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Introduction

Low back pain is one of the most important causes of disability worldwide, with its prevalence steadily increasing (1). Most low back pain develops due to mechanical reasons such as repetitive trauma and overuse, usually workplace injuries. Although many people experience acute low back pain at least once, this pain often becomes chronic. Symptoms of chronic low back pain are poorly correlated with pathology, and the persistence of symptoms cannot be explained by biological factors alone; Psychological and social factors also play an essential role (2).

Kinesiophobia and other psychological factors play crucial roles in the prognosis of chronic low back pain (3,4). Kinesiophobia is the tendency to reduce physical activity or avoid movement altogether due to fear or anxiety about pain and worsening of their current medical condition (3). Kinesiophobia is often reported as a crucial risk factor in the chronicity of low back pain and associated disability (4). Preoperative kinesiophobia is related to postoperative sedentary behavior and decreased physical activity in spine surgery patients (5). Kinesiophobia can significantly affect the pathway to recovery of physical function (6).

Kinesiophobia in knee osteoarthritis is associated with pain and function (7). The term "low back-related leg pain" refers to both nerve root compression and referred leg pain without nerve involvement (3). Neuropathic pain in chronic low back pain ranges from 16% to 55% (2). Another common situation is sacroiliac joint dysfunction, which can be the main source of low back pain and is known to accompany other conditions (2,8). This complex nature of low back pain makes it increasingly complicated to treat.

Addressing kinesiophobia as one of the psychosocial factors in the low back pain treatment approach may increase the chances of success. Although clinical evidence is growing in this direction (5,9-11), the factors affecting fear of movement, especially in patients with chronic mechanical low back pain, are poorly defined. In this research, we aimed to contribute to the existing literature by exploring the link among kinesiophobia with demographic characteristics, pain severity, functional disability, and quality of life, as well as the relationship of kinesiophobia with sacroiliac dysfunction, leg pain, and neuropathic pain in patients with chronic mechanical low back pain.

Materials and Methods

This cross-sectional observational study was conducted following approval from the Health Sciences University Türkiye, Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (approval number: FSM EAH-KAEK 2023/47 date: 09/03/2023). This study was conducted per the principles of the Declaration of Helsinki. After a detailed investigation of the inclusion and exclusion criteria, all participants provided written voluntary informed consent for participation. Clinical trial records from this study were prospectively transmitted to a public database. Registration Number: NCT06190041.

The sample size was determined using G*Power software. As per the results of previous reference and preliminary studies, we determined an effect size of 0.5 (medium level effect; Cohen, 1988) for the between-group comparisons for low back-related leg pain score measured using a visual analog scale (VAS). Using this effect size value and a statistical significance coefficient of 0.05, the minimum sample size was calculated as 51 subjects to obtain 80% power. As per the study objectives, we intended to compare the characteristics of subjects with high and low levels of kinesiophobia; Accordingly, both groups were targeted to have 51 subjects each (n=102).

The study encompassed individuals aged 18 to 75 years who attended our physical medicine and rehabilitation (PMR) clinic and had chronic mechanical low back pain (pain duration of 3 months or more). To confirm their suitability, these participants were further assessed in detail by the PMR specialist based on anamnesis, physical examination, and imaging methods. All participants underwent two-directional X-ray and magnetic resonance imaging of the lumbar spine for diagnostic and differential diagnosis purposes. The individuals with inflammatory low back pain, those who had undergone lumbar spine, hip, or knee surgery, those with abnormal findings on hip and knee joint examinations, oncological conditions, suspected referred pain from internal organs, infections, pregnancy, recent trauma impacting the lumbar spine, and/or lumbar fractures were excluded.

Patient data regarding demographics and the presence of chronic diseases were recorded. The intensity of back pain at rest, activity, and night, as well as neuropathic pain, disability, kinesiophobia, and quality of life, were assessed by a blinded rater (a PMR physician). Sacroiliac dysfunction was evaluated by history and physical examination (8).

VAS is a unidimensional measure used to assess pain intensity and is frequently used in adult populations, including rheumatological patients (12). It comprises a 10-cm line (horizontal or vertical) on which the patient marks their pain; One end of the line indicates "no pain," and the other end is "most severe possible pain." The patient is asked to mark a point on the line that most accurately depicts the intensity of their back pain in the last week (12).

The DN4 is a scale developed to define neuropathic pain. A score of ≥4 suggests that the pain may be of neuropathic origin (13). DN4 was confirmed to be a reliable and accurate tool for assessing neuropathic pain in the Turkish population (14).

The ODI also comprises 10 questions evaluating disability. Disability can be classified into five categories (15): minimal (0%-20%), moderate (21%-40%), severe disability (41-60%), disabled (61%-80%), and bedridden (81%-100%). The validity and reliability of the ODI in the Turkish population have been established in a previous study (16).

The Turkish version of the TKS assessed fear of movement (17). The TKS consists of 17 questions that examine injury/reinjury and fear-avoidance parameters in work-related activities. The total score ranges between 17 and 68. Vlaeyen et al. (18) established that a TKS score of ≥37 indicates high kinesiophobia. This score (TKS ≥37) was used in the present study to classify patients into high and low kinesiophobia groups.

The short form-36 (SF-36), created in 1992 (19), is one of the most frequently used quality-of-life questionnaires. It comprises 36 questions about eight categories. The total score varies between 0 and 100, with higher scores indicating good health. The SF-36 has been proven valid and reliable in the Turkish population (20).

Statistical Analysis

All statistical analyses were conducted using SPSS (version 28.0). Descriptive statistics, including mean±standard deviation, median (range), and frequency (percentage), were used to summarize the data. The normality of the data distribution was evaluated with the Shapiro-Wilk test. The Mann-Whitney U test was used for independent quantitative data, while qualitative independent data were analyzed with the Chi-square test or Fisher's exact test, as appropriate. To identify potential predictors of kinesiophobia, both univariate and multivariate logistic regression analyses were performed. All tests with a p-value under 0.05 were deemed statistically significant.

Results

240 suitable participants were invited to participate, of which 230 agreed. Four patients (three of them had symptomatic knee osteoarthritis; One had symptomatic hip osteoarthritis) were excluded, and 226 patients were included in the study (Figure 1).

Table 1 summarizes the demographic data of the study participants. Most participants (68.1%) were females, among which 43.8% were housewives. The mean duration of pain was 48.2±71.8 months, and most participants reported high kinesiophobia (69.4%). The mean TKS, ODI, and DN4 scores of the entire cohort were 40.7±6.9, 32.0±18.5, and 1.8±2.0, respectively. A summary of the participants' clinical features is shown in Table 2. More than half (58.4%) of participants had

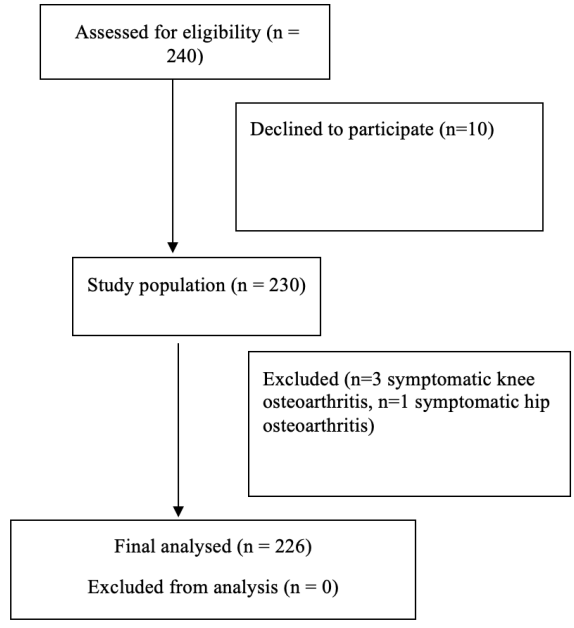

Figure 1. Flow diagram of participation

Table 1. Demographic parameters of participants

		Min-max	Median	Mean±SD/n%	
Age		18.0-75.0	52.0	51.5±13.7	
Sex	Female			154	68.1%
	Male			72	31.9%
BMI		17.2 - 43.0	28.1	28.5±4.8	
HT				73	32.3%
DM				43	19.0%
CAD				27	11.9%
Education	Illiterate			21	9.3%
	Primary school			97	42.9%
	Secondary school			18	8.0%
	High school			44	19.5%
	University			46	20.4%

low back pain-related leg pain. The high and low kinesiophobia groups were statistically comparable in terms of participants' age, body mass index (BMI), the incidence of comorbidities (as well as the individual rates of hypertension, diabetes mellitus, coronary artery disease), occupation (civil servants, workers, retirees, or students), and alcohol use and smoking status ($p>0.05$; Table 3). In contrast, the high kinesiophobia group exhibited a markedly greater proportion of female patients,

Table 1. Continued

		Min-max	Median	Mean±SD/n%	
Occupation	Housewife			99	43.8%
	Civil servant			22	9.7%
	Worker			59	26.1%
	Retired			42	18.6%
	Student			4	1.8%
Smoking	Never smoking			130	57.5%
	Previous smoking			35	15.5%
	Smoking			61	27.0%
Alcohol use	None			199	88.1%
	Less than once a month			27	11.9%
VAS score					
Rest		0.0-10.0	5.0	4.3±2.7	
Activity		0.0-10.0	8.0	7.4±2.2	
Night		0.0-10.0	4.0	3.9±3.6	

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, VAS: Visual analog scale, SD: Standard deviation, Min-max: Minimum-maximum

Table 2. Clinical features of participants

		Min-max	Median	Mean±SD/n%	
Low back-related leg pain	**Yes**			**132**	**58.4%**
	No			**94**	**41.6%**
Pain duration		1.0-360.0	12.0	48.2±71.8	
DN4 score		0.0-8.0	1.0	1.8±2.0	
TKS score		20.0-61.0	41.0	40.7±6.9	
ODI score		2.0-90.0	28.8	32.0±18.5	
ODI classification	Minimal disability			72	31.9%
	Moderate disability			86	38.1%
	Severe disability			51	22.6%
	Disabled			13	5.8%
	Bedridden			4	1.8%
SF-36 scale					
Physical functioning		0.0-100.0	60.0	56.2±24.1	
Role limitations due to physical health		0.0-100.0	25.0	34.3±38.0	
Role limitations due to emotional problems		0.0-100.0	33.3	37.2±40.0	
Energy		0.0-90.0	45.0	41.3±20.2	
Emotional well-being		10.0-100.0	52.0	52.9±19.0	
Social function		0.0-100.0	62.5	56.4±25.2	
Pain		0.0-90.0	35.0	38.0±20.6	
General health		0.0-90.0	45.0	44.9±19.6	

DN4: Douleur neuropathic 4 questions, TKS: Tampa kinesiophobia scale, ODI: Oswestry disability index, SF-36: Short form-36, Min-max: Minimum-maximum

lower education levels, and a higher incidence of housewives (p=0.013, p=0.012, p=0.007, respectively).

Regarding clinical features, both the high and low kinesiophobia groups had statistically comparable VAS scores for resting pain, night pain, low back-related leg pain, and pain duration (p>0.05); However, activity-related pain was higher in the high kinesiophobia group (p=0.002). The high kinesiophobia group had more patients diagnosed with sacroiliac dysfunction as compared to the low kinesiophobia group (p<0.05). The DN4 score for neuropathic pain was also statistically similar in both groups (p>0.05). In terms of functional status, the high kinesiophobia group had a notably higher ODI score (p=0.001) than the low kinesiophobia group (Table 4). Lastly, the high kinesiophobia group had notably higher scores on all eight domains of the SF-36 when juxtaposed with the low kinesiophobia group (p<0.001; Table 5).

Sex, VAS score for activity-related pain, educational status, disability score, and the SF-36 score (all domains) were significant indicators that can be used to distinguish patients with high and low kinesiophobia levels (p=0.014, p=0.005, p=0.013, p=0.008, p<0.001 respectively). The multivariate model revealed that the individual SF-36 domain scores for limitations due to physical health, emotional well-being, and social function were significantly and independently correlated (p=0.006, p=0.001, p=0.018 respectively) with classifying patients based on high and low levels of kinesiophobia (Table 6).

Discussion

In this study, the majority of participants (69.4%) reported high levels of kinesiophobia, consistent with existing literature (11,12). The findings of our research indicated that kinesiophobia

Table 3. Distribution of kinesiophobia according to demographic characteristics of the participants

		Low-level kinesiophobia n=69			High-level kinesiophobia n=157			p-value
		Mean±SD/n%		Median	Mean±SD/n%		Median	
Age		50.0±15.6		53.0	52.2±12.8		52.0	0.382[m]
Sex	Female	39	56.5%		115	73.2%		0.013[x2]
	Male	30	43.5%		42	26.8%		
BMI		27.8±4.8		27.3	28.8±4.8		28.4	0.171[m]
HT		17	24.6%		56	35.7%		0.102[x2]
DM		15	21.7%		28	17.8%		0.491[x2]
CAD		8	11.6%		19	12.1%		0.914[x2]
Education								
Illiterate		5	7.2%		16	10.2%		0.012 [x2]
Primary school		25	36.2%		72	45.9%		
Secondary school		3	4.3%		15	9.6%		
High school		12	17.4%		32	20.4%		
University		24	34.8%		22	14.0%		
Occupation								
Housewife		21	30.4%		78	49.7%		0.007[x2]
Civil servant		10	14.5%		12	7.6%		0.110[x2]
Worker		18	26.1%		41	26.1%		0.997[x2]
Retire		17	24.6%		25	15.9%		0.121[x2]
Student		3	4.3%		1	0.6%		0.086[x2]
Smoking	Never smoking	42	60.9%		88	56.1%		0.691[x2]
	Previously smoking	11	15.9%		24	15.3%		
	Smoking	16	23.2%		45	28.7%		
Alcohol use	None	62	89.9%		137	87.3%		0.580[x2]
	Less than once a month	7	10.1%		20	12.7%		

[m]Mann-Whitney U test, x²Chi-square test
BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, SD: Standard deviation, CAD: Coronary artery disease, Min-max: Minimum-maximum

was associated with female gender, being a housewife, lower educational level, disability, poor quality of life, and the presence of sacroiliac dysfunction.

Previous studies have identified high kinesiophobia in elderly adults with chronic low back pain (9,21); Our research did not find a significant link between age and kinesiophobia, possibly due to the younger age of our sample compared to studies like Tiaho et al. (22). Regarding sex differences, the literature presents varying results. Tiaho et al. (22). found no association; John et al. (9) reported higher rates in males. In contrast, our study observed significantly higher levels of kinesiophobia in females, similar to the results of Manoj and Gaurav (23), possibly due to lower muscle mass and higher pain perception among women. However, further research with larger samples is needed to validate these findings. In line with previous research (9,22), our study revealed no notable correlation between BMI and kinesiophobia. Unlike Tiaho et al. (22), we did not observe a notable connection regarding pain duration and kinesiophobia, aligning with the findings of Altuğ et al. (10).

Table 4. Distribution of kinesiophobia according to clinical characteristics of the participants

	Low-level kinesiophobia			High-level kinesiophobia			p-value
	Min-max/n-%		Median	Min-max/n-%		Median	
VAS score							
Rest	0-10		5.0	0-10		5.0	0.167[m]
Activity	2-10		6.0	0-10		8.0	**0.002[m]**
Night	0-10		3.0	0-10		4.0	0.127[m]
Low back-related leg pain							
Yes	41	59.4%		91	58.0%		0.838[x²]
No	28	40.6%		66	42.0%		
Sacroiliac disfunction	4	5.8%		24	15.3%		0.046[x²]
Pain duration	3-360		12.0	3-360		12.0	0.547[m]
DN4 score	0-8		2.0	0-8		1.0	0.153[m]
ODI score	2-86		22.0	2-90		31.0	0.001[m]
ODI Classification							
Minimal Disability	33	47.8%		39	24.8%		**0.001**[x2]
Moderate disability	21	30.4%		65	41.4%		
Severe disability	10	14.5%		41	26.1%		
Disabled	4	5.8%		9	5.7%		
Bedridden	1	1.4%		3	1.9%		

mMann-Whitney U test, [x²]Chi-square test, DN4: Douleur neuropathic 4 Questions, ODI: Oswestry disability index, VAS:Visual analog scale, Min-max: Minimum-maximum

Tablo 5. Distribution of kinesiophobia according to participants' quality of life

	Low-level kinesiophobia		High-level kinesiophobia		p-value
	Min-max	Median	Min-max	Median	
SF-36 scale					
Physical functioning	0-100	70.0	0-100	55.0	**0.000**[m]
Role limitations due to physical health	0-100	50.0	0-100	0.0	**0.000**[m]
Role limitations due to emotional problems	0-100	66.7	0-100	25.0	**0.000**[m]
Energy	0-85	50.0	0-90	35.0	**0.000**[m]
Emotional well-being	16-100	60.0	10-96	48.0	**0.000**[m]
Social function	12.5-100	75.0	0-100	50.0	**0.000**[m]
Pain	0-90	45.0	0-87.5	35.0	**0.000**[m]
General health	15-90	55.0	0-90	40.0	**0.000**[m]

[m] Mann-Whitney U test, SF-36: Short form-36, Min-max: Minimum-maximum

Table 6. Predictors of kinesiophobia according to regression analysis

	Univariate modal			Multivariable modal		
	OR	**95% CI**	**p-value**			
Sex	0.475	0.262-0.859	**0.014**			
Pain activity	1,210	1.060-1,381	**0.005**			
Education	0.481	0.270-0.855	**0.013**			
Oswestry	1,024	1,006-1,041	**0.008**			
Sacroiliac disfuncton	1,431	0.992-2.065	0.055			
SF-36 scale						
Physical functioning	0.976	0.963-0.989	**0.000**	OR	95% CI	p-value
Role limitations due to physical health	0.983	0.975-0.990	**0.000**	0.988	0.980-0.997	**0.006**
Role limitations due to emotional problems	0.985	0.978-0.992	**0.000**			
Energy	0.973	0.959-0.988	**0.000**			
Emotional well-being	0.959	0.943-0.976	**0.000**	0.970	0.953-0.988	**0.001**
Social function	0.968	0.955-0.981	**0.000**	0.982	0.968-0.997	**0.018**
Pain	0.972	0.957-0.986	**0.000**			
General Health	0.965	0.949-0.981	**0.000**			
Lojistik regresyon (forward LR)						

SF-36: Short form-36, LR: Likelihood ratio, OR: Odds ratio, CI: Confidence interval

Our study also revealed a marked inverse link with education level and kinesiophobia; While John et al. (9) found no such relationship, Knapik et al. (24) reported a positive correlation. The negative correlation in our study may be due to the high proportion of primary school graduates among our participants, emphasizing the role of education in reducing movement fear. Public health initiatives and educational interventions promoting physical activity benefits could help reduce kinesiophobia in populations with limited exercise habits (25).

The relationship between kinesiophobia and pain intensity remains debated. Some studies show a connection (9,22) while our research found only activity-related pain intensity to be significantly correlated with kinesiophobia, suggesting that patients with high kinesiophobia avoid activity to prevent pain. Núñez-Cortés et al. (3) did not observe a notable link involving kinesiophobia and the leeds assessment of neuropathic symptoms and sign neuropathic pain scale but stated that high kinesiophobia was associated with impaired motor control in patients with low back leg pain. Similarly, in the present study, we did not find an association between neuropathic pain, low back leg pain, and kinesiophobia; Instead, we concluded that activity-related pain may better predict kinesiophobia. On the other hand, Baranidharan et al. (26) suggest that the available scales may not reliably identify the neuropathic component in low back pain and that a system to identify neuropathic pain in chronic low back pain is needed.

Chronic low back pain's clinical symptoms are often poor correlate with pathology and symptoms (2). Psychological factors such as kinesiophobia play crucial roles in prognosis (10). Our study confirmed significant links among kinesiophobia, disability, and quality of life, aligning with previous research findings (4,10,11,22).

Researches indicate that fear avoidance can delay recovery and lead to chronicity, and that interventions to address kinesiophobia in the acute phase can improve treatment outcomes and prevent chronicity (27). People with chronic low back pain have lower quality of life and physical activity levels than healthy individuals, and kinesiophobia negatively affects quality of life (2,10,22). Our study found strong negative correlations between kinesiophobia and all SF-36 domains, with physical health limitations, emotional well-being, and social function as independent predictors. Emotional well-being is impacted by anxiety and depression, which worsen kinesiophobia (4). Social function limitations contribute to social withdrawal, reinforcing avoidance behaviors and exacerbating kinesiophobia. Reduced social engagement further hinders physical activity, which is crucial for chronic pain management. The bio-psycho-social model highlights that disability in chronic musculoskeletal pain arises from both pain intensity and biomedical-psychological factors (2). Therefore, rehabilitation should incorporate cognitive-behavioral therapy to address kinesiophobia (21) and consider the patient's emotional well-being and social function as well as physical condition.

Study Limitations

Our study's limitations include its cross-sectional design, which prevents causality determination, and its single-center scope, limiting generalizability. Although emotional status was evaluated in SF-36, the depression scale could also be used.

Conclusion

Our results revealed that sex, occupation, education level, activity-related pain, disability, and quality of life significantly influence kinesiophobia in chronic mechanical low back pain patients. Further studies are required to confirm these findings. Rehabilitation should address psychosocial factors and possible kinesiophobia, while patient education should emphasize the importance of physical activity and the harmful effects of kinesiophobia.

Ethics

Ethics Committee Approval: It was carried out after the approval received from the Clinical Research Ethics Committee of the Fatih Sultan Mehmet Training and Research Hospital, University of Health Sciences (approval number: FSM EAH-KAEK 2023/47 date: 09/03/2023).

Informed Consent: After a detailed investigation of the inclusion and exclusion criteria, all participants provided written voluntary informed consent for participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Ş.K., S.Y.E.D, F.A.B., Concept: D.Ş.K., G.Ö. Design: D.Ş.K., F.Ü.Ö., İ.A. Data Collection or Processing: G.Ö., M.Y.K., Analysis or Interpretation: Y.E.D, F.A.B., M.Y.K, P.A. Literature Search: D.Ş.K, Y.E.D., G.Ö., M.Y.K., P.A. Writing: D.Ş.K., P.A., F.Ü.Ö., İ.A.

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Multiple Myeloma in a Male Patient with Inadequate Response to Osteoporosis Treatment: A Case Report

Osteoporoz Tedavisine Yetersiz Yanıt Veren Erkek Hastada Multipl Miyelom: Olgu Sunumu

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Abstract

Secondary causes of osteoporosis are more common in males compared to females, and multiple myeloma is a scarce cause in men. This case report emphasizes the necessity of exploring the reasons for secondary osteoporosis in menwho have inadequate responses to osteoporosis therapies.

Keywords: Multiple myeloma, osteoporosis, treatment failure

Öz

Osteoporozun ikincil nedenleri erkeklerde kadınlara göre daha sık görülür ve multipl miyelom erkeklerde nadir görülen bir nedendir. Bu olgu sunumunda, osteoporoz tedavisine yetersiz yanıt veren erkek hastalarda sekonder osteoporozun nedenlerinin araştırılmasının önemi vurgulanmaktadır.

Anahtar kelimeler: Multipl miyelom, osteoporoz, tedavi başarısızlığı

Introduction

Osteoporosis typically goes unnoticed in men as it presents no symptoms unless a fracture occurs. Even though males experience higher rates of mortality and morbidity from osteoporosis, they tend to be assessed less frequently for osteoporosis (1). The occurrence of secondary factors leading to osteoporosis is higher in males compared to females (1,2). Among the infrequent causes of osteoporosis in men is multiple myeloma (MM). This case report highlights the significance of examining the reasons for secondary osteoporosis in a male individual experiencing treatment failure to osteoporosis therapy.

Case Report

A man aged 66 came in complaining of pain in his chest and şank a year prior. The individual experienced discomfort that began during a playful engagement with his three-year-old grandson and persisted for two days. Upon careful examination, the thoracic region was found to be devoid of any swelling, bruising, or crepitus. The radiological assessment conducted for the patient revealed no evidence of rib fractures; However, a notable reduction in the height of the lower thoracic vertebrae was observed (Figure 1). A request was made for bone

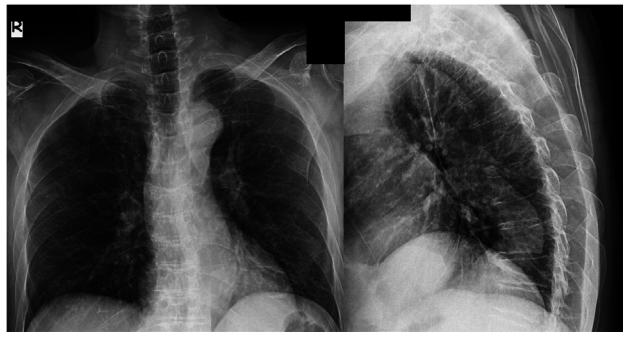

Figure 1. The radiologic imaging shows vertebral body height loss in the patient's lower thoracic vertebrae

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mineral density (BMD) measurements and various laboratory analyses. Results from laboratory tests indicated a hemoglobin level of 12.6 g/dL, an mean corpuscular volume of 96, an erythrocyte sedimentation rate (ESR) of 62 mm/h, a vitamin B12 concentration of 126 pg/mL, and an elevated leukocyte count in the urine. The findings from the comprehensive laboratory assessments, encompassing total protein, albumin, serum calcium and phosphorus, uric acid, liver function tests, kidney function tests, thyroid function tests, parathormone, free testosterone, gonadotropin, prolactin, prostate-specific antigen, and C-reactive protein, were all determined to be within normal limits. Additionally, the concentration of 25-hydroxyvitamin D was measured at 34.30 ng/mL. The results of the bone mineral densitometry assessment were as follows: the total T score for the L1-L4 region was -3.1, with a BMD of 0.750 g/cm². For the femur, the total T score was -1.5, corresponding to a BMD of 0.802 g/cm². The femoral neck presented a t-score of -1.1 and a BMD of 0.774 g/cm². Alongside antibiotic therapy and vitamin B-12 replacement, a plan was set to include intravenous zoledronic acid at a dosage of 5 mg, as well as treatments with calcium carbonate and cholecalciferol. It was mentioned that there would be a follow-up examination in 1 to 3 months. After a gap of 11 months since his initial visit, the patient came back to our facility with a complaint of pain in his flank. In the results from the control laboratory tests, the total protein concentration was recorded at 8.2 g/dL, while the ESR indicated a significant elevation of 106 mm/h. The hemoglobin level was measured at 11.7 g/dL, and the platelet count was noted as 141000. The parathormone level was determined to be 9.2 pg/dL, with magnesium levels at 1.7 mg/dL. Additionally, serum calcium and phosphorus levels, uric acid, liver function tests, kidney function tests, thyroid function tests, free testosterone, gonadotropin, prolactin, prostate-specific antigen, C-reactive protein, 25-hydroxyvitamin D, and albumin values were all within the normal reference intervals. He had no complaints such as weight loss, fever, or night sweats. The results from the bone density evaluation showed that the total t-score for the L1-L4 region was -3.7, with a BMD of 0.680 g/cm². The femur's total t-score was -1.4, indicating a BMD of 0.819 g/cm², and the femoral neck had a t-score of -1.0 with a BMD of 0.790 g/cm². Computed tomography of the vertebral column revealed degenerative changes in the vertebral bodies (osteophytes, increased sclerosis), approximately 25% loss of height in the T10 vertebral body, and a sclerotic lesion in the T3 vertebral body (Figure 2). A thorough evaluation was performed, including serum and urine electrophoresis, as well as immunofixation. Protein and creatinine levels were measured in both spot and 24-hour urine samples. The analysis included assessments of immunoglobulins IgA, IgG, IgM, and both kappa and lambda light chains. The patient was referred to the hematology clinic due to the observed elevation in IgA and kappa light chains. Finally, the diagnosis of MM was confirmed with bone marrow aspirate findings showing 39% plasma cells. After the chemotherapy, the patient underwent autologous stem cell transplantation. A written informed consent was obtained from the patient.

Discussion and Conclusion

Malignancy should always be considered a reason for osteoporosis and fractures (3). MM is classified as a hematologic malignancy characterized by the abnormal proliferation of clonal plasma cells. This disorder is associated with various severe complications, including the formation of destructive bone lesions, renal dysfunction, anemia, and elevated calcium levels in the blood (2,4-8). The loss of bone in MM is attributed to an increase in the resorption of bone by osteoclasts, coupled with a decrease in the formation of new bone structures (5-9). Bone disorders associated with MM may result in various severe issues, including fractures, spinal cord compression, and hypercalcemia. These complications significantly diminish patients' quality of life, contributing to severe pain, psychological challenges, loss of independence, and an elevated risk of mortality (2,7,8). In a study to define

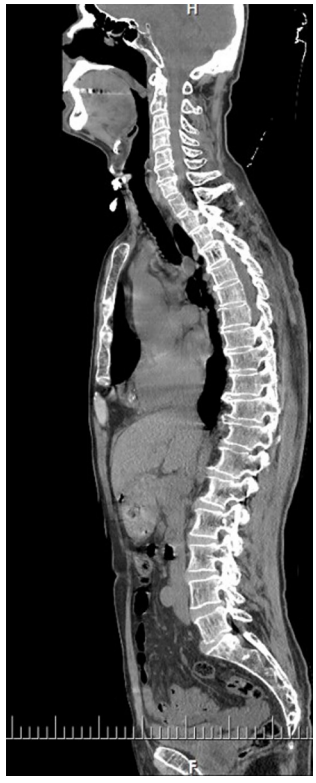

Figure 2. Degenerative changes in the vertebral bodies (osteophytes, increased sclerosis), approximately 25% loss of height in the T10 vertebral body, and a sclerotic lesion in the T3 vertebral body in computed tomography of the vertebral column

and investigatethe diagnostic process of patients with MM from the rare and undiagnosed diseases cohort study, Vijjhalwar et al. (10) found that 52% of participants had received a diagnosis other than MM, with musculoskeletal diseases including osteoporosis, costochondritis, or muscle strains. The initial symptoms reported with the highest frequency comprised back pain and fractures in the vertebrae, with subsequent presentations including chest pain, shoulder pain, rib pain, and fatigue. MM is a crucial medical condition that should be considered in the differential diagnosis for individuals experiencing treatment failure for osteoporosis therapy. Measuring serum protein electrophoresis and immunofixation is essential for evaluating elderly osteoporosis patients, especially those with unexplained fragility fractures, as this could indicate an underlying plasma cell disorder needing monitoring and potential treatment (9).

Mumford et al. (11) reported a case of severe osteoporosis and IgA myeloma combined with multiple vertebral fractures. IgA myeloma was detected in this patient during an examination for persistent pain in the spine and hips that did not improve within the expected time. The patient, who initially had a vertebral fracture at L3, experienced deterioration in BMD, acute fractures in the vertebrae at T9, T11, and T12, and sustained loss of heightat L3 despite bisphosphonate treatment during the six-month interval that has transpired. In this period, serum electrophoresis showed no monoclonal bands, and the urine Bence-Jones protein test was negative. The administration of teriparatide commenced ten months subsequent to the occurrence of the initial fracture. However, investigating ongoing intense pain in the thoracic region and hip 12 months after the first vertebral fracture, revealed the presence of Bence-Jones protein, and the findings from the serum immunofixation analysis have substantiated the presence of IgA kappa paraprotein. Also, multiple lytic lesions were detected and then bone marrow aspirate provided definitive confirmation of the diagnosis of MM (11).

Pain is the most common symptom of MM, while weight loss and anemia are other common findings (6). Anemia, thrombocytopenia, elevated ESR, hypercalcemia, hyperuricemia, renal dysfunction and reversal of albumin-globulin ratio may occur. Unusual serum electrophoresis warns the physicians that myeloma may be present. Radiologically, lytic bone lesions can be observed, particularly in the proximal regions of the spine and limbs, and pathological fractures may ensue (6,7). The patient initially had macrocytic anemia with B-12 deficiency and an elevated ESR of 62 mm/h. furthermore, an elevated count of leukocytes was detected in the urine, while all other laboratory assessments showed normal findings. Imaging revealed height loss in the patient's lower thoracic vertebrae without lytic lesions. Since there were no accompanying findings such as hypercalcemia, hyperuricemia, renal dysfunction, and reversal of the albumin-globulin ratio, we did not initially suspect MM and therefore did not request electrophoresis. Anti-osteoporotic treatment was initiated after the diagnosis of osteoporosis was confirmed through bone densitometry results. When he applied again 11 months later with şank pain, electrophoresis was requested due to inadequate response to osteoporosis treatment, anemia, increased ESR, and increased total protein. Findings suggestive of myeloma were detected on electrophoresis. After the bone marrow biopsy, the diagnosis of MM was established for the patient.

MM represents a critical condition that warrants careful consideration when evaluating skeletal system pain and osteoporosis, even if typical findings cannot be detected at first. Managing osteoporosis in patients with MM requires a multidisciplinary approach. Treatment for MM, such as chemotherapy and steroids, might deteriorate bone density and worsen osteoporosis. Individualized treatment plans and close monitoring are essential to optimizing outcomes and reducing the risk of skeletal complications.

MM should be considered for cases experiencing treatment failure to osteoporosis therapy, particularly older individuals with high ESR and acute fractures. Our case report highlights the importance of considering the possibility of MM and requesting appropriate tests for OP patients without waiting for treatment failure.

Ethics

Informed Consent: A written informed consent was obtained from the patient.

Footnotes

Financial Disclosure: The author declared that this study has received no financial support.

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Bilateral Shoulder Osteoarthritis After COVID-19 in a Patient with Hereditary Spastic Paraplegia: A Case Report

Herediter Spastik Paraplejili Bir Hastada COVID-19 Sonrası Bilateral Omuz Osteoartriti: Olgu Sunumu

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Abstract

The study, the first to report such a relationship to date, presents a patient with accelerated osteoarthritis (OA) in weight-bearing shoulder joints after Coronavirus disease-2019 (COVID-19). A 61-year-old man with hereditary spastic paraplegia was diagnosed with bilateral shoulder OA after presenting with bilateral shoulder pain and restricted range of motion. Laboratory tests and X-rays showed no pathology in the pelvis, hands, or knees. However, shoulder X-rays revealed narrowed joint space, subchondral sclerosis, and signs of aging in the capitulum humeri; Unlike the X-ray taken three years ago (before COVID-19). Magnetic resonance imaging revealed bilateral OA and bicipital tendinitis. Further research is needed on COVID-19's impact on joints.
Keywords: Cartilage, COVID-19, glenohumeral osteoarthritis, hereditary spastic paraplegia, osteoarthritis

Öz

Burada daha önce literatürde rastlamadığımız, Koronavirüs hastalığı-2019'dan (COVID-19) sonra ağırlık taşıyan omuz eklemlerinde hızlı gelişen osteoartrit (OA) olan bir hasta sunulmaktadır. Herediter spastik paraplejisi olan 61 yaşında bir erkek hasta, bilateral omuz ağrısı ve eklem hareket kısıtlılığı ile başvurduğunda bilateral omuz OA teşhisi aldı. Laboratuvar testleri ve pelvis, el ve diz direkt grafileri normaldi. Ancak omuz direkt grafisinde, üç yıl önce (COVID-19'dan önce) çekilen grafinin aksine, daralmış eklem aralığı, subkondral skleroz, kapitulum humeri yaşlanma belirtileri gösterdi. Manyetik rezonans görüntüleme, bilateral OA ve biseps tendinitini ortaya koydu. COVID-19'un eklemler üzerindeki etkisi hakkında daha fazla araştırmaya ihtiyaç var.
Anahtar kelimeler: Kıkırdak, COVID-19, glenohumeral osteoartrit, herediter spastik parapleji, osteoartrit

Introduction

Osteoarthritis (OA) is the world's most common joint disease and there is currently no cure. Glenohumeral OA (GHOA) accounts for an estimated 5-17% of patients with shoulder complaints. The etiology of GHOA is multifactorial. These can be divided into nonspecific and specific factors as well as systemic and local factors. Joint damage develops from the interplay between these factors, where local or systemic factors, or non-specific or specific factors, may dominate (1). Current knowledge is lacking about the impact of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) on cartilage degeneration and synovial inflammation. This case represents accelerated OA in the weight-bearing shoulder joints after Coronavirus disease-2019 (COVID-19). Symmetrical shoulder OA is rare, late-onset disease is usually seen in early age groups in rheumatologic disorders (2). Early age presentations can be triggered by increased systemic inflammation such as COVID-19.

Case Report

A 61-year-old male was admitted to the rehabilitation unit with the impairment of walking and bilateral shoulder pain with limited range of motion. His past medical history included hereditary spastic paraplegia (HSP), hypertension, diabetes, benign prostatic hyperplasia, and a confirmed COVID-19 diagnosis 3 years ago. He gave a family history of a son and daughter who were diagnosed with HSP. He was unable to walk without a walker. He reports the pain in both shoulders has been present for the last 3 years. On examination, upper extremity muscle strength

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was evaluated as 5/5. Symmetrical lower limb weakness was predominantly distal and respectively graded in extensor hallucis longus as 1/5, ankle dorsi-flexors as 2/5, hip flexors as 3/5, knee extensors as 3/5, ankle plantar flexors as 5/5. Pain-free flexion and abduction range were respectively 145 and 150 degrees in the right shoulder; Both flexion and abduction range of the left shoulder were 160 degrees with a mechanical pain and crepitation sense during the movements of both shoulders. There was significant spasticity in the hip flexors, hip adductors, and hamstrings respectively scored as 2, 3, 2 using the Modified Ashworth Scale (MAS) (3).

Laboratory investigations and the X-ray imaging of the pelvis, hands, and knees did not show any pathology considering ankylosing spondylitis, rheumatoid arthritis, or other rheumatic disease. A plain X-ray of the shoulders showed narrowed joint space, subchondral sclerosis, marginal osteophyte formation, subchondral cyst formation, and aging signs of caput humeri Kellgren-Lawrence graded as 4 which did not exist in the X-ray taken three years ago (Figures 1A,1B). Magnetic resonance imaging of both shoulders performed for differential diagnosis showed bilateral OA and bicipital tendinitis. Prior chest computed tomography revealed post-COVID-19 pulmonary fibrotic-like changes.

In the rehabilitation program, active assistive range of motion exercises, strengthening and stretching of both upper and lower extremities, balance training, and an unweighted treadmill for ambulation have been administrated. The botulinum toxin applied to both hip adductor and gastrocnemius muscles improved one point on the five-point MAS following ten days post injections. On the bilateral shoulder conventional transcutaneous electrical nerve stimulation, with a frequency of 50 Hz, a current transition time of 100 microseconds, and an amplitude density that does not cause contractions or excessive discomfort was performed for 30 minutes. The shoulder joint positions improved from 145° to 165° in flexion and from 150° to 165° in abduction on the right, improved from 160° to 175° in flexion and abduction on the left. His participation in daily living activities was increased with a 60% decreased shoulder pain on the visual analog scale. The Functional Independence measure score improved from 102 to 110.

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for participation and publication was obtained from the patient.

Discussion

OA is a painful condition caused by a combination of biomechanical and metabolic features resulting in changes in articular cartilage and bone (4). GHOA is less common than OA of the weight-

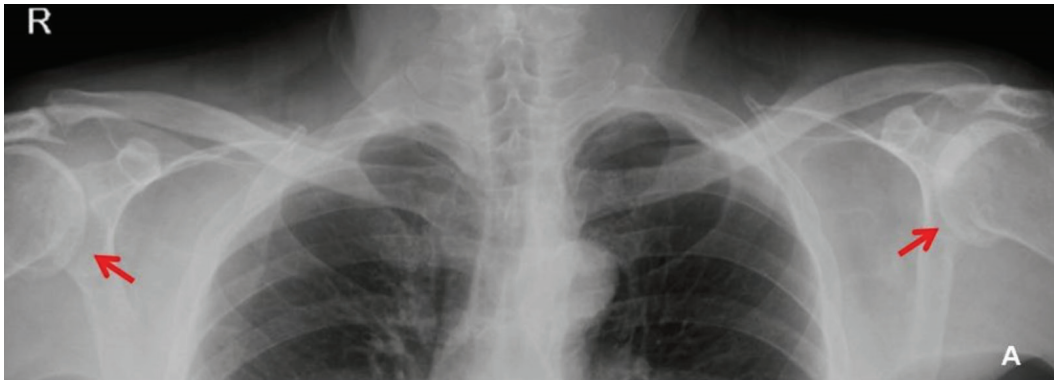

Figure 1A. X-ray of shoulders before COVID-19. A plain X-ray of the shoulders showed a normal joint space

COVID-19: Coronavirus disease-2019

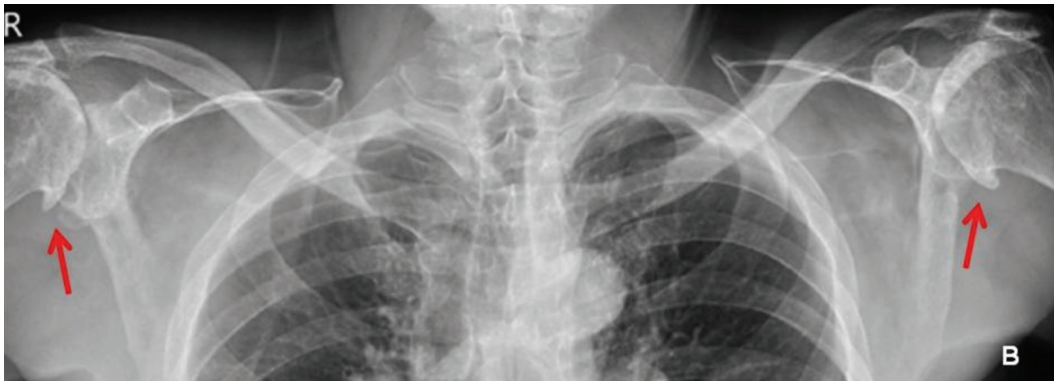

Figure 1B. X-ray of shoulders post-COVID-19. A plain X-ray of the shoulders showed narrowed joint space, subchondral sclerosis, marginal osteophyte formation, and subchondral cyst formation

COVID-19: Coronavirus disease-2019

bearing joints but is a painful condition that can severely affect independence by limiting the pain-free range of motion about the shoulder (1).

In this case report, a 61-year-old male patient presented with bilateral GHOA, complicated by HSP. The patient, who had to rely on his arms to walk, naturally put a load on his arms, which may have contributed to the development of OA, with the additional contribution of systemic inflammation such as SARS-CoV-2.

HSP is a clinical picture consisting of symmetrical spasticity and weakness in lower limbs that progresses very slowly, impairment of walking, increased tendon reflexes, and Babinski's sign. There is axonal degeneration prominently in the distal parts of corticospinal tracts and occasionally in the posterior cords. Numbness in the distal lower extremities and impaired vibration sense may be present. While only these symptoms are seen in uncomplicated forms, epileptic seizures, dementia, muscle atrophies, extrapyramidal findings, peripheral neuropathy, and cataracts may be seen in complicated forms. Although the inheritance of HSP is heterogeneous, the dominant form is more common. The prevalence ranges from 0.1 to 9.6 per 100,000 around the world (5).

In patients with HSP, spasticity in lower limbs requires them to use an assistance device to walk, and the weight-bearing shoulder may be at risk of developing OA. A study comparing the rate of shoulder OA between the control group who did not undergo surgery and the group after hip arthroplasty requiring to use of arm support did not find a significant difference (6). Environmental factors such as weight-bearing might lead to the development of the early OA-like phenotype without a viral presence in the joint. The binding of SARS-CoV-2 to angiotensin converting enzyme-2 (ACE-2) is assumed to initiate the endothelial and adipose dysfunction subsequently OA-like phenotype. The overstimulation of immune response in COVID-19 induces OA-like changes similar to metabolic syndrome leading to endothelial and adipose tissue dysfunction. In contrast to the disruption of the renin-angiotensin system pathway via ACE-2 receptors, the nicotinic cholinergic system as the anti-inflammatory pathway stimulates chondrocyte and osteoblast proliferation and restores subchondral bone (7).

Au et al. (8) show damage to the knee joint following in vivo infection with wild-type, Delta, and Omicron variants of SARS-CoV-2. Two patients with post-COVID OA experienced rapid joint damage with cystic lesions at the osteochondral junction, which was replicated in a golden Syrian hamster model. Viral spike proteins leaked into the subchondral bone as a result of increased vascular permeability brought on by SARS-CoV-2-activated endothelin-1 signaling. Histological confirmation of osteoclast activation, chondrocyte dropout, and cyst formation was obtained (8).

Conclusion

HSP is a progressive disease and causes struggle in walking and balance over time, resulting in the need for an assistive walking device. Our case emphasizes the contribution of COVID-19 to the early aging of unusual joints of disabled individuals who need an assistive device.

Ethics

Informed Consent: Written informed consent for participation and publication was obtained from the patient.

Foonotes

Authorship Contributions

Surgical and Medical Practices: B.S., Ö.Z.K., Concept: B.S., Ş.A., H.D., Design: Y.T., Ö.Z.K., Data Collection or Processing: B.S., Ş.A., H.D., Analysis or Interpretation: B.S., Y.T., Ö.Z.K., Literature Search: B.S., Ş.A., H.D., Writing: B.S., Y.T., Ö.Z.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Do it Without Steroids, Even if it is Incidental

Tesadüfi Olsa Bile, Steroid Kullanmadan Yapın

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Keywords: Complication, osteoporotic fracture, sympathetic ganglion, lymphedema, osteoporosis, steroids
Anahtar kelimeler: Komplikasyon, osteoporotik kırık, sempatik ganglion, lenfödem, osteoporoz, steroidler

Dear Editor,

We express our appreciation to Dr. Uğur Ertem for his interest in our research (1). The comments made by him enable us to highlight certain aspects.

Firstly, our patient had several comorbidities including cancer, medications used in cancer treatment, osteoporosis (OP), and senility, and these conditions are among the independent risk factors for the development of osteoporotic fracture in the patient (2,3). These risk factors play an important role in the development of OP and we are aware that a significant association with osteoporotic fracture can be established. In light of this, we agree with Ertem's comment.

Secondly, research investigating the correlation between epidural steroid injection (ESI) and bone mineral density (BMD) has revealed that cumulative dosages of methylprednisolone reaching 200 mg within one year and 400 mg within three years were linked to substantial reductions in BMD (4), nevertheless, we lack data regarding the appropriate dosage of steroids to administer during the ESI process when these risk factors of OP are present. As we stated in our article, to our knowledge, no studies have been conducted investigating the connection between lumbar sympathetic ganglion block (LSGB) and OP. Thus, we are unable to provide definitive evidence regarding the safe dosage or any correlation between LSGB and OP. Nevertheless, we believe that our recommendation in this case is valuable in a scenario that could lead to serious complications including spinal vertebral fracture, even if it may be an incidental finding.

Thirdly, the LSGB using only local anesthetic, without the use of steroids can be performed, but it remains a topic of controversy (5). Thus, given the already severe risk factors for osteoporotic fracture and the need for repeat procedures, performing LSGB procedures without steroids may be a rational option in this high-risk patient group. Therefore, as mentioned in the original article, when conducting sympathetic blocks, it is preferable to either avoid using steroids completely or administer them at the minimum dosage in patients with these risk factors.

Finally, based on this knowledge, we suggest that LSGB should be performed without steroids in patients with cancer-related lymphedema due to serious complications.

We hope that we have adequately addressed all issues. Once again, we are grateful to Dr. Uğur Ertem for his valuable and thoughtful comments.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.I., Ş.A., Concept: R.I., S.Ş., Design: S.Ş., O.H.G., Data Collection or Processing: R.I., Ş.A., Analysis or Interpretation: R.I., S.Ş., O.H.G., Literature Search: R.I., S.Ş., Writing: R.I., S.A., S.Ş., O.H.G.

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