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Predictive Factors for Muscle Weakness in Rheumatoid Arthritis

Romatoid Artritte Kas Güçsüzlüğü İçin Öngördürücü Faktörler

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ABSTRACT Objective: We aimed to determine muscle strength in patients with rheumatoid arthritis (RA) and several factors including structural joint damage that may affect decrease in muscle strength. The relations between muscle strength and quality of life and functional disability were examined. **Material and Methods:** Seventy five RA patients and 51 controls were involved. Demographic characteristics, body mass index, waist circumference, 25-hydroxy vitamin D, and patient global assessments of disease activity (PGA) were documented. Disease Activity Score-28 (DAS28), Visual Analog Scale-Pain (VAS-pain), Health Assessment Questionnaire (HAQ) and the Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) were calculated. Radiographs of the hands were evaluated by van der Heijde modified Sharp score (vdHSS). Grip strength of both hands was measured by Jamar dynamometer. **Results:** Demographics (age, gender) were not different between RA patients and control group. Grip strength of patients with RA (22.79±18.58) was lower than control group (26.00±11.25, p=0.04). There was a significant correlation with grip strength and disease duration, tender joint count, VAS-pain, PGA, DAS28, HAQ, RAQoL, erosion and narrowing score (p<0.05). DAS28 and erosion score were associated with grip strength in multivariate analyses p<0.05). **Conclusion:** This study showed that RA obtains decreased muscle strength, impaired function and quality of life. Joint space narrowing and disease activity are the main parameters that affect muscle strength.

Keywords: Muscle strength; body mass index; quality of life

ÖZET Amaç: Romatoid artritli (RA) hastalarda, kas kuvvetini değerlendirmeyi ve kas kuvvetindeki azalmayı etkileyebilecek yapısal eklem hasarı dâhil çeşitli faktörleri belirlemeyi amaçladık. Bu çalışmada, kas gücü ile yaşam kalitesi ve fonksiyonel yetersizlik arasındaki ilişki incelenmiştir. **Gereç ve Yöntemler:** Yetmiş beş RA hastası ve 51 kontrol alındı. Demografik özellikler, beden kitle indeksi, bel çevresi, 25-hidroksi vitamin D, hastanın hastalık aktivitesinin küresel değerlendirmesi [patient global assessments of disease activity (PGA)] kaydedildi. Hastalık Aktivite Skoru-28 [Disease Activity Score-28 (DAS28)], Görsel Analog Skala [Visual Analog Scale (VAS)]-ağrı Sağlık Değerlendirme Anketi [Health Assessment Questionnaire (HAQ)] ve Romatoid Artrit Yaşam Kalitesi Anketi [Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)] hesaplandı. El radyografileri van der Heijde modifiye Sharp skoru [van der Heijde modified Sharp score (vdHSS)] ile değerlendirildi. Jamar dinamometre ile her iki elin kavrama gücü ölçüldü. **Bulgular:** Demografik özellikler (yaş, cinsiyet) RA hastaları ve kontrol grubu arasında farklı değildi. RA'lı hastaların kavrama gücü (22,79±18,58) kontrol grubundan düşüktü (26,00±11,25; p=0,04). Kavrama gücü ile hastalık süresi, "tender joint count", VAS-ağrı, PGA, DAS28, HAQ, RAQoL, erozyon ve daralma skoru arasında anlamlı korelasyon vardı (p<0,05). Çok değişkenli analizlerde DAS28 ve erozyon skoru kavrama gücü ile ilişkili bulundu (p<0,05). **Sonuç:** Bu çalışma, RA'nın kas gücünü azalttığını ve fonksiyonel yetersizliğe ve yaşam kalitesinde bozulmaya neden olduğunu göstermiştir. Eklem aralığı ve hastalık aktivitesi kas gücünü etkileyen ana parametrelerdir.

Anahtar Kelimeler: Kas gücü; beden kitle indeksi; yaşam kalitesi

Rheumatoid arthritis (RA) is a well-known autoimmune inflammatory disease that influences articular, periarticular structures and synovial membrane. The connective tissue inflammation induces progressive disability. The most frequently affected components in RA are hands. Progressive hand dysfunction causes various limitations in patients' daily life activities, functions, and quality of life likewise social aspects of life.[1]

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Sarcopenia is characterized as the reduction of muscle mass and strength. The diagnosis, is identified by the European Working Group on Sarcopenia in Older People, includes dual energy X-ray absorptiometry, walking speed and handgrip strength measurements. Handgrip strength that can be measured by a dynamometer is usually accepted as sarcopenia scanning method and it is correlated with muscle strength in other body parts.[2-4]

Chronic inflammation can stimulate metabolic changes; protein catabolism and whole-body protein break down. Therefore, patients with RA have changes in their muscle mass and fat mass components. The loss of muscle mass is named as rheumatoid cachexia and can be associated with an increase in fat mass. Weight loss may accompany increased or stable fat mass. Muscle weakness and loss of muscle mass as well as joint damage are notable features in these patients.[5-8] Lower muscle mass, increased intramuscular fat content, physical inactivity due to the pain and joint deformities enhance muscle weakness in patients with RA. On the other side, decreased muscle strength leads more physical inactivity, disability and deterioration in quality of life.[9-12]

Disease activity, joint deformities, age, and physical inactivity are considered to play a role in muscle weakness except for the body-fat distribution.[5-12] In the current report, we aimed to assess muscle strength in RA patients and the association between functional disability, quality of life and muscle strength. Moreover, we purposed to examine several factors including structural joint damage that may affect the muscle weakness.

MATERIAL AND METHODS

Our cross-sectional trial was planned in a physical medicine and rehabilitation outpatient clinic. Written informed consent has been received from all of the patients and controls. The study was approved by Ankara Numune Training and Research Hospital Scientific and Medical Research Ethics Committee (Decision no/date: 2014-727/3.1.2014). The study agreed with the World Medical Association's Declaration of Helsinki.

Seventy-five RA patients who met the American College of Rheumatology and European League Against Rheumatology 2010 classification criteria for RA and 51 controls that were similar in terms of gender distribution and age were involved in the study.[13] Exclusion criteria were: <18-year-old, trauma, fracture or upper extremity nerve damage affecting hand functions, severe cognitive and neurological problems (stroke, multiple sclerosis, amyotrophic lateral sclerosis etc.), active cancer, and receiving any antidepressant medication in the last one year.

Demographic characteristics, body mass index (BMI), waist circumference, duration of disease and morning stiffness, tender joint count (TJC) and swollen joint count, erythrocyte sedimentation rates, C-reactive protein, 25 hydroxi vitamin D [25(OH)D] patient global assessments of disease activity (PGA) were documented. Receiving disease modifying antirheumatic drugs (DMARD) was recorded.

Disease Activity Score-28 (DAS28) and 10 cm Visual Analog Scale-Pain (VAS-pain) were used to specify disease activity and pain severity.[14,15] Health Assessment Questionnaire (HAQ) and Rheumatoid arthritis Quality of Life Questionnaire (RAQoL) results recorded to assess functional status and the health-related quality of life.[13,16,17]

Van der Heijde modified Sharp score (vdHSS) was considered to evaluate the changes in posteroanterior hand X-rays, joint space narrowing and erosion score were determined.[18]

Grip strength of both hands measured by Jamar dynamometer in the sitting position, and the shoulder was in neutral rotation and adduction, the elbow was in 90 ° flexion, the wrist in the neutral position. In the test procedure, three measurements were made with a minute interval between each measurement for hand grip strength and averages were recorded.[19]

Normality was tested with Shapiro-Wilk test. General descriptive statistics are summarized as mean, standard deviation, median, minimum-maximum, number and frequencies. Independent samples t-test or Mann-Whitney U test were used to compare groups. Homogeneity of the distributions of categorical variables was determined using chi-square tests. Spearman correlation coefficient was used and the correlation coefficient ranges in value from -1 to +1. Coefficients determined negligible, weak, moderate,

strong, and very strong correlation (0-0.10; 0.10-0.39; 0.40-0.69; 0.70-0.89; 0.90-1.00 respectively).[20] Significant predictors for grip strength were evaluated with univariate analyses and at least moderately significant variables were selected for multivariate linear regression analyses. Backward method is used in the selection of variables. A value of $p<0.05$ was considered statistically significant. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp. software was used for all these analyses.

RESULTS

Seventy-five RA patients with a mean age of 51.96±12.82 years and 51 controls with a mean age of 54.84±10.16 were recorded for the study. Gender distribution and mean age were not different between RA and control groups ($p>0.05$). In RA group, waist circumference and BMI measurements were higher and 25(OH)D levels were lower than controls. Grip strength of healthy controls was higher than RA patients (Table 1).

All of the patients with RA continued to follow-up visit regularly at least one year. Duration of disease was 24-420 months. 56 (74.66%) patients were using conventional DMARD, 9 (12%) patients were using biological DMARD and 10 patients were using corticosteroids and/or analgesics. DAS28 results indicated that 32 (42.7%) RA patients were in remission, 7 (9.3%) had low disease activity, 28 (37.3%) had moderate disease activity and 8 (10.7%) had severe disease activity, and 28 (37.33%) RA patients had no pain on their joints. Disease activity parameters, vdHSS, HAQ and RAQoL results of patients with RA were summarized in Table 2.

The handgrip strength differences between medication types (corticosteroid users, biological and conventional DMARD) were analyzed. Handgrip strength was 37.01±40.42 and 34.05±33,05 in corticosteroid users; 32.22±12.01 and 36.11±15.76 in biological DMARD users; 30.33±19.43 and 29.91±19.59 in conventional DMARD users (right- and left-hand measures respectively) The difference was not significant between medication types ($p=0.687$; $p=0.654$ right and left hand respectively)

Relationships between grip strength and clinical variables were analyzed. There were significant correlation with disease duration, TJC, VAS-pain, PGA, DAS28, HAQ, RAQoL, erosion and narrowing score (Table 3).

TABLE 1: Demographic and clinical features of rheumatoid arthritis patients and controls.

	Rheumatoid arthritis n=75	Controls n=51	p value
Age (years, mean±SD)	51.96±12.82	54.84±10.16	0.174
Gender, n (%)			
Female	56 (74.7)	40 (78.4)	0.626
Male	19 (25.3)	11 (21.6)	
Body mass index			
(kg/m^2, mean±SD)	28.85±6.45	26.14±4.12	0.029*
Waist circumference (cm, mean±SD)	95.73±15.72	87.05±18.79	0.041*
25(OH) D			
(ng/mL, mean±SD)	11.72±7.63	17.58±10.48	
Median (minimum-maximum)	10.87 (3-35.40)	14.48 (4.17-44)	0.003*
Grip strength, right			
(Kg, mean±SD)	24.19±20.85	26.60±11.12	
Median (min-max)	20 (2-40)	25 (10-60)	0.031*
Grip strength, left			
(Kg, mean±SD)	22.79±18.58	26.00±11.25	
Median (minimum-maximum)	20 (2-40)	25 (10-60)	0.039*

*p<0.05; SD: Standard deviation; 25(OH)D: 25 hydroxi vitamin D.

TABLE 2: Disease activity, functional assessment and quality of life in patients with rheumatoid arthritis.

	Patients with rheumatoid arthritis n=75
Disease duration (months, mean±SD)	133.72±91.02
Median (minimum-maximum)	120 (24-420)
Erythrocyte sedimentation rate (mm/h, mean±SD)	20.54±12.31
Median (minimum-maximum)	20 (2-57)
C-reactive protein (mg/L, mean±SD)	11.77±15.20
Median (minimum-maximum)	6.67 (0.20-72.72)
Pain-VAS (mm, mean±SD)	3.56±2.91
Median (minimum-maximum)	3 (0-10)
PGA-VAS (mm, mean±SD)	3.04±2.85
Median (minimum-maximum)	3 (0-9)
Tender joint count (mean±SD)	10.48±14.11
Median (minimum-maximum)	4 (0-28)
Swollen joint count (mean±SD)	0.52±1.33
Median (minimum-maximum)	0 (0-8)
DAS28 (mean±SD)	3.21±1.37
Antirheumatic drugs n (%)	
Conventional DMARD	56 (74.66)
Biologic DMARD	9 (12)
Corticosteroids (only)	7 (9.33)
None	3 (4)
HAQ (mean±SD)	0.92±0.79
Median (minimum-maximum)	0.75 (0-2.75)
RAQoL (mean±SD)	12.10±10.43
Median (minimum-maximum)	11 (0-29)
vdHSS (erosion)	6.77±12.07
Median (minimum-maximum)	2 (0-62)
vdHSS (narrowing)	16.82±11.71
Median (minimum-maximum)	14 (0-61)

SD: Standard deviation; VAS: Visual Analog Scale; PGA: Patient global assessments of disease activity; DAS28: Disease Activity Score-28; DMARD: Disease modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; RAQoL: Rheumatoid arthritis Quality of Life Questionnaire; vdHSS: van der Heijde modified Sharp score.

We determined significant predictors for grip strength with using multivariate analyses. Only two variables, DAS28 and erosion score were associated with grip strength. Results were shown in Table 4.

DISCUSSION

In the current report, we aimed to explore hand grip strength in RA patients and healthy participants and to analyze the predictors for decreased muscle strength in RA. Our results supported that RA patients had decreased muscle strength and the most important factors of muscle weakness were joint space narrowing and disease activity.

Muscle dysfunctions are frequently observed problems in RA, and these dysfunctions are associated with pain, atrophy, reflex inhibition, myopathy, and psychological factors. The decrease in the level of physical activity leads to morphological changes such as muscle strength loss and increase in muscle fiber length, decrease in capillary density and increase in intramuscular connective tissue.[21] In addition, tumor necrosis factor alpha (TNF-α) and other inflammatory cytokines also act as catabolic mediators. Schaap et al. showed that TNF-α and its soluble mediators were related with muscle weakness and muscle mass in elderly.[22] Secondary sarcopenia can be seen frequently in patients with RA due to active cytokines, oxidative stress, chronic inflammation, and physical inactivity.[23] Patients with RA have higher protein destruction and sarcopenia that were

TABLE 3: Correlations between grip strength and clinical variables.

	Grip strength rho	Grip strength p value
Age	-0.71	0.542
Body mass index (kg/m^2)	-0.16	0.151
Waist circumference (cm)	-0.13	0.262
Disease duration	-0.22	0.044*
ESR	-0.09	0.443
CRP	-0.13	0.248
25(OH)D ng/mL	0.12	0.333
TJC	-0.26	0.024*
SJC	-0.12	0.268
Morning stiffness	-0.22	0.052
VAS pain	-0.23	0.044*
PGA	-0.31	0.002*
DAS28	-0.33	0.006*
HAQ	-0.41	0.005*
RAQoL	-0.41	<0.001*
vdHSS (erosion)	-0.31	0.018*
vdHSS (narrowing)	-0.38	0.003*

*p<0.05; ESR: Erythrocyte sedimentation rates; CRP: C-reactive protein; 25(OH)D: 25 hydroxi vitamin D; TJC: Tender joint count; SJC: Swollen joint count; VAS: Visual Analog Scale; PGA: Patient Global Assessment; DAS28: Disease Activity Score-28; HAQ: Health Assessment Questionnaire; RAQoL: Rheumatoid arthritis Quality of Life Questionnaire; vdHSS: van der Heijde modified Sharp score.

TABLE 4: Relationship between clinical predictors and grip strength.

		B	SE	p value	95% CI	
Grip strength	**DAS28**	-5.28	2.47	0.036	-10.25	-0.31
	vdHSS joint space narrowing					
	(R^2=0.29 F=7.07)	-0.67	0.20	<0.005	-1.08	-0.27

DAS28: Disease Activity Score-28; vdHSS: van der Heijde modified Sharp score; R^2: Coefficient of determination; B: Regression coefficient; SE: Standard error; CI: Confidence interval.

affected by cytokines like TNF-α and interleukin 6.[24] In this sense, blocking TNF-α and interleukin 6 with biological DMARD may provide the protein catabolism. Although glucocorticoid use is known to be a risk for sarcopenia with its known myopathy side effect and its impact on muscle and adipose tissue distribution, anti-inflammatory effects will prevent protein catabolism caused by cytokines.[23] Muscle strength in patients with RA has been found lower than healthy controls and decrease in muscle strength can be seen from the early stages of this disease.[25] Our results confirm that RA patients have decreased muscle strength which was evaluated by hand dynamometer. In our study, no relationship was found between the medications used in patients with RA and hand grip strength. Similarly, the lack of a causal relationship between glucocorticoid use and sarcopenia in the study of Torii et al. supports the contradictory effects of steroids on the sarcopenia mechanism.[23]

Muscle mass is important for patients because it is the main protein source of body and, supports the adaptation to metabolic stress. Body composition, especially fat and mass composition, may change in RA patients. This disease may lead a complex metabolic syndrome which is accompanied with muscle loss without weight loss.[7] Our findings referred that RA patients had higher BMI and waist circumference than healthy controls although they had decreased muscle strength. This result supports that RA changes body fat and muscle composition, and has an effect on increasing fat/muscle ratio.

It is known that vitamin D has effects on preadipocyte differentiation and may affect muscle-fat tissue distribution. In addition, it has been suggested that vitamin D supplementation causes an increase in muscle strength and muscle mass, and may be beneficial in the prevention of sarcopenia.[26] This study did not reveal a causal relationship between sarcopenia and vitamin D deficiency in patients with RA. It was thought that the low level of vitamin D in patients in general may be a factor on these results.

Hand grip strength is crucial for many of the daily living activities and informs about the patients' functionality. Dysfunction of hands, which are the most frequently and seriously affected joints in RA, and this is the main reason of disability.[27] Bodur et al. determined that pinch measurements, grip strength, disease activity indicators were associated with hand disability. They reported that there was a stronger relationship between grip strength and hand function.[28] Several studies argued that grips strength was related with functional impairment and disability in RA patients.[21,27] Similarly in the present study, grip strength was negatively correlated with functionality. Moreover, our outcomes demonstrated an association among the grip strength and, VAS pain, disease duration quality of life, PGA, TJC, disease activity, and structural damage. It is naturally expected that the pain parameters associated with muscle strength and longer disease duration may lead more physical inactivity and more severe structural damage which decrease muscle strength. On the other hand, multivariate regression analyses showed that only 2 parameters have an effect on muscle strength. These parameters were DAS28 and joint space narrowing score. In these outcomes, increased protein catabolism of the active disease with TNF pathway appears to be effective rather than being associated with pain or disease duration. Erol et al., findings supported the effect of disease activity on muscle strength. In their study, grip strength was significantly associated with bone edema and tenosynovitis score on magnetic resonance imaging.[12] RA is a chronic disease that induces decrease in the quality of life as a result of

several factors. These factors, which are closely related to each other, also appear to involve muscle weakness.

According to our knowledge, this is the first study that explored the relationship with grip strength and vdHSS. We found that joint space narrowing has a notable influence on muscle strength. Various studies determined that decrease in hand joints' range of motion was related with muscle strength.[21,27] It is thought that the joint space narrowing seen in the direct graphs, joint damage, and limitation of movement may cause a decrease in muscle strength.

Limitations of our report were: The cross-sectional plan, which does not enable for appreciation of the temporal changes due to disease. Systemic parameters (such as cardiac, bone mineral densitometry) that may be associated with sarcopenia were not included. Hand grip strength, which is a very good predictor of sarcopenia, was measured, but sarcopenia was not classified according to the European Working Group on Sarcopenia in Older People criteria. Therefore, longitudinal studies in larger samples are required to corroborate our preliminary findings.

CONCLUSION

Our study supported that RA obtains decreased muscle strength, impaired functionality and quality of life. Joint space narrowing and disease activity are the main parameters that affect muscle strength. Muscle loss may lead impaired functionality and quality of life for RA patients.

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