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Improvement in rheumatoid sarcopenia with biological therapy; muscle ultrasound study

Biyolojik terapi ile romatoid sarkopenide iyileşme; kas ultrason çalışması

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Abstract

Objective: The present research evaluated the use of muscle ultrasonography in individuals with rheumatoid arthritis (RAs) who were starting therapy with biologic disease-modifying antirheumatic drugs (b-DMARDs).

Methods: A total of 56 individuals diagnosed with RAs, who had not yet received b-DMARDs, were included in the current prospective study. The control and baseline muscular strength, physical performance tests, ultrasonographic muscle parameters, and disease activity scores were analyzed in a group of 40 patients under controlled conditions.

Results: Rectus abdominis muscle's thickness, rectus femoris (RF) muscle's cross-sectional area (RFCSA), external oblique muscle's thickness, and transverse abdominis muscle's thickness all showed substantial improvements. Additionally, Clinical Disease Activity Index scores showed significant associations with the percentage variations in RF muscle thickness, RFCSA, and gastrocnemius medialis muscle thickness in those who had achieved remission or had low disease activity.

Conclusion: Ultrasonographic muscle imaging can assist clinicians in monitoring both patients and disease activity scores during the treatment of RA.

Keywords: Rheumatoid arthritis, b-DMARDs, muscle, ultrasonography

Öz

Amaç: Bu çalışmada, biyolojik hastalığı modifiye eden antiromatizmal ilaçlar (b-DMARD) tedavisine başlayan romatoid artritli (RA) bireylerde kas ultrasonografisinin kullanımını araştırılmıştır.

Yöntem: RA tanısı almış ve henüz b-DMARD almamış toplam 56 kişi mevcut prospektif çalışmaya dahil edildi. Kontrol ve başlangıç kas gücü, fiziksel performans testleri, ultrasonografik kas parametreleri ve 40 hastadan oluşan bir grupta kontrollü koşullar altında hastalık aktivite skorları analiz edildi.

Bulgular: Rektus abdominis kasının kalınlığının, rektus femoris (RF) kasının kesit alanı (RFCSA), dış oblik kasının kalınlığı ve transvers abdominis kasının kalınlığı önemli iyileşmeler gösterdiği saptandı. Ek olarak, Klinik Hastalık Aktivitesi Indeksi puanları, remisyona ulaşan veya düşük hastalık aktivitesine sahip olanlarda RF kas kalınlığı, RFCSA ve gastrokinemius medialis kas kalınlığındaki yüzdelik değişimlerle istatiksel anlamlılık saptanmıştır.

Sonuç: Ultrasonografik kas görüntülemesi, RA hastalarının tedavisi sırasında klinisyene hastalık aktivite skorlarını izlemede yardımcı olabilir.

Anahtar Kelimeler: Romatoid artrit, b-DMARDs, kas, ultrasonografi

Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease that often leads to severe joint deterioration and dysfunction. Despite the efficacy of disease-modifying antirheumatic drugs and biological therapies, there is no curative treatment for RA.[1] Its average occurrence is reported to be 0.5%.[2] Patients with RA are more likely to experience a decline in muscle strength compared to the

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general population of the same age group. "Rheumatoid cachexia" is a well-known symptom of the disease, characterized by a decrease in muscle mass and an increase in intramuscular adipose mass. Tumor necrosis factor alpha (TNF-α) and several other cytokines, which are crucial in RA pathogenesis, catabolize muscle, which is the reason behind it. In this patient group, the loss of muscle mass is accompanied by a reduction in muscle strength and an increase in age-related sarcopenia.[3]

When the general literature was reviewed, it was discovered that there was considerable variation regarding the occurrence of sarcopenia, a condition marked by a reduction in athletic performance, muscle mass, and strength among RA patients. The frequency of sarcopenia, among RA patients, ranged widely from 1 to 56%, according to a review of the general literature.[4–7] It appears that the use of varying diagnostic techniques to identify sarcopenia and the incapacity to establish common diagnostic criteria are the reasons for the inconsistent prevalence results. In researchs investigating the impact of biologic disease-modifying anti-rheumatic drugs (b-DMARDs) on muscle mass in rheumatic diseases, conflicting results have been observed. Sarcopenia in inflammatory illnesses can be diagnosed using ultrasonography (USG) among other methods.[8,9]

The aim of this study was to evaluate the alterations in muscle strength and quantity, physical performance, in RA patients who were receiving b-DMARDs during the initial stages of treatment, as measured by USG.

Materials and Method

Investigation Design

A prospective investigation was carried out at a university hospital. Patients were evaluated at their first examination before starting biological treatment and at their 3rd or 6th-month follow-up examinations.

Study Population

The study comprised 56 patients who had never used b-DMARDs. Patients under 18 years old and over 80 years old were not included in our study. Patients with previous rheumatoid cachexia, active malignancy, and active infection, patients with disability, and patients with prosthesis were also not included in the study. Patients with active RA [Disease Activity Score 28 (DAS28) >5.1 or expert judgment)] were administered b-DMARDs. There were forty patients at the third or sixth-month follow-up. The clinical assessment included information on previous therapies, current b-DMARDs, and demographic data.

Disease Activity Assessments

The data were obtained from the TReasure database. The TReasure database was previously described concisely as the collection of data at the start of therapy and during the initial follow-up session.[10] The Clinical Disease Activity Index (CDAI)[11], Simplified Disease Activity Index (SDAI)[1]. DAS-28[12], visual analog scale (VAS) global-physician assessment[13], VAS global-patient assessment[13], VAS for global pain[13], VAS fatigue[13], Health Assessment Questionnaire-Disability Index (HAQ-DI)[14], and EuroQol Group (EQ5D)[15] prior to treatment initiation and at the initial visit were noted.

Anthropometric Parameters

Anthropometric characteristics such as body mass index (BMI), hip, and waist circumference were assessed. In our study, all muscle ultrasound measurements at baseline and in the controls were performed by a single experienced physician for the reliability and standardization of the evaluations. The anterior superior iliac spine was used to measure the hip circumference, while the umbilicus was used to measure the waist circumference.

Assessment of Muscle Strength and Physical Performance

To evaluate muscle strength, the sit-stand test (SST) and the handgrip strength test (HGST) were executed. To evaluate physical performance, the timed up and go test (TUG), gait speed, and the 4-meter walking test were used. The presence of sarcopenia was assessed using the SARC-F test. HGST was applied while the elbow was at a 90-degree angle using a hand dynamometer.[9] The SST is conducted with the patient's arms crossed in front of their torso. They are required to sit and stand at a rate of five times their maximum capacity.[9] By measuring the average walking speed of four meters, the gait speed was computed.[9] The TUG test was assessed by observing the individual's performance of standing up, walking a distance of 3 meters, turning around, and sitting back down.[16] The patient was asked to complete the SARC-F exam, indicating that they had trouble walking around the room, getting out of a chair, climbing ten flights of stairs, and having experienced a fall during the previous year, in addition to having trouble carrying a weight of five kilograms. Each response was assigned a score between 0 and 2 (0=none, 2=a lot, use aides, or be unable). Scores of 4 or higher were deemed positive for sarcopenia screening.[17,18]

Ultrasonographic Measurements

Rectus abdominis (RA) muscle thickness, transverse abdominis (TA) muscle thickness, internal oblique (IO)

muscle thickness, external oblique (EO) muscle thickness, gastrocnemius medialis (GM) muscle thickness, GM pennation angle, GM fascicle length, rectus femoris (RF) muscle thickness, and RF cross-sectional area (RFCSA) were all evaluated using USG. A linear instrument with a 5 cm width and an operating frequency of 8-10 MHz was employed (LOG IQ 200 PRO, General Electric's Medical Systems). Transversal images were obtained to measure the thickness of the muscle at the broadest distance between the superficial and deep fascia. For both GM in the prone position and the RF thickness in the supine position, the largest region of the medial head is located midway between the anterior superior iliac spine and the upper edge of the patella. Longitudinal images were used to determine the pennation angle (PA) of the GM muscle, which is the angle between the muscle fibers and the deep fascia of the muscle. The distance between the superficial and deep aponeuroses was quantified to determine fascicle length (FL). The RFCSA was defined as the cross-sectional area of the RF muscle that is perpendicular to its longitudinal axis. While the patient was in a supine position, the images of the abdominal muscles were obtained at the conclusion of a typical expiration. The RA is located 2 cm lateral to the umbilicus, while the EO, IO, and TA are located at the midpoint between the iliac crest and the 12th costal cartilage. [19-21] Intraclass correlation coefficients (ICC) were evaluated using two images taken at 15-minute intervals of 10 healthy participants to evaluate interobserver reliability. The ICCs for muscle thickness of the GM, RF, and RA were 0.94, 0.92, and 0.96, respectively, and 0.94 for RFCSA.

Statistical Analysis

A statistical analysis was conducted using SPSS software version 25. Analysis of histograms, probability graphs, and analytical procedures was conducted to assess the normality of the variables. Descriptive information was presented as the mean ± standard deviation for normally distributed data and the median (Inter Quartile Range) for non-normally distributed variables. A comparison was made between variables using the Wilcoxon test and the paired sample Student's t-test. The variations between baseline and control data were used to illustrate the changes in muscular strength, physical performance assessments, and USG measurements. To assess the variations between disease activity scores, physical performance assessments, and muscle measurements, percent changes were shown. To explore the relationships between baseline disease activity ratings and physical parameters, muscular strength, and physical performance tests, partial correlation analyses were adjusted based on baseline BMI. A comparison of therapy responses based on CDAI scores, percent improvements in muscular strength and physical performance test assessments, and ultrasonographic measurements was made. The statistical significance was inferred at a 5% type-1 error level. Using G-power analysis, the sample size was determined to be 55 when the effect size was accepted as 0.45 with a 0.05 (alpha) margin of error and a 95% power.

The study was approved by the Hacettepe University Clinical Research Ethics Committee [decision no: 2022/20-08 (KA-21151), date: 22.11.2022] and Turkish Medicines and Medical Devices Agency. Informed consent form was obtained from all participants in the study.

Patient Characteristics

Control visits were conducted for 40 (71.4%) of the 56 patients who were incorporated into the research. The median disease duration was 5.1 years, with a range of 1 to 8. The duration of observation at the midpoint of the study was 4.2 months (range, 3-6). 46 (82.1%) of the study population were female, and the median age was 52 (19-76) years. The demographic parameters and disease activity scores of the patients were reported in Table 1. The control visit was attended by a greater number of seropositive RA patients [31 (81.6%) compared to 7 (46.7%), p=0.01].

Variations in Disease Activity and Laboratory Parameters Pre and Post b-DMARDs Treatment

At the follow-up visit, there were substantial modifications in the comprehensive evaluation of disease activity and functional status in comparison to the patients' baseline values: Median [minimum-maximum (min-max) CDAI 24 (12; 66) vs. 8 (0; 2.5), p<0.001; SDAI 27 (12.3; 73.6) vs. 10 (0.19; 60.4), p<0.001; DAS-28 5.1 (2; 7.7) vs. 2.5 (0; 7.9), p<0.001; VAS global physician 60 (30; 100) vs. 30 (0; 100), p<0.001; VAS global patient 70 (40; 100) vs. 40 (0; 100), p<0.001; VAS pain 70 (30; 100) vs. 45 (0; 100), p<0.001; VAS fatigue 70 (10; 100) vs. 40 (0; 100), p<0.001; HAQ-DI 0.95 (0.1; 4.6) vs. 0.35 (0 ;7.9), p<0.001; EQ5D 11 (5; 13) vs. 6 (0; 15), p<0.001]. Erythrocyte sedimentation rate (ESR) [median (min-max)] [20 (4-72) mm/h vs. 12.5 (3-98) mm/h, p=0.002] was significantly different. The C-reactive protein levels [median (min-max)] were not statistically different [0.67(0.14-9.96) mg/dL vs. 0.88 (0.11-14.5) mg/dL, p=0.11].

Anthropometric Measurements Prior to and Following b-DMARDs Treatment

The baseline BMI of 40 patients was 26.9 kg/m² [median (min-max)], with a waist circumference of 96 cm (70-126) and a hip circumference of 101.5 cm (78-135). The only significant increase observed during the control visits was in BMI, with a median value of [cm] (p=0.008).

Table 1. Baseline characteristics of participants

Characteristics	All participants (n=56)	Patients with control visits (n=40)	Patients without control visits (n=16)	p
Age [median (minimum-maximum)]	52 (19;76)	54 (19;76)	50 (32;68)	0.97
Female gender [n (%)]	46 (82.1)	33 (82.5)	13 (81.3)	0.91
Disease duration [median (minimum-maximum)]	5 (1-38)	6 (1-38)	3 (2-31)	0.36
Seropositive rheumatoid arthritis [n (%)]	38 (71.7)	31 (81.6)	7 (46.7)	0.01
Previous or current cs-DMARDs treatments [n (%)]				
Sulfasalazine	19 (33.9)	16 (40)	3 (18)	0.12
Methotrexate	45 (80.4)	33 (82.5)	12 (75)	0.52
Leflunomide	41 (73.2)	28 (70)	13 (81.3)	0.39
Plaquenil	45 (80.4)	33 (82.5)	12 (75)	0.52
Steroıds	55 (98.2)	39 (97.59)	16 (100)	1.00
b-DMARDs treatments [n (%)]				
Anti-TNF				
Adalimumab	18 (32.1)	13 (32.5)	5 (31.3)	0.92
Certolizumab	5 (8.9)	3 (7.5)	2 (12.5)	0.61
Etanercept	1 (1.8)	0	1 (6.3)	0.28
Infliximab	1 (1.8)	1 (2.5)	0	1.00
Janus kinase inhibitors				
Baricitinib	10 (17.9)	6 (15)	4 (25)	0.37
Tofacitinib	14 (25.0)	10 (25)	4 (25)	1.00
Anti CD20 monoclonal antibody				
Rituximab	10 (17.9)	9 (22.5)	1 (6.3)	0.15
T-cell inhibitor				
Abatacept	4 (7.1)	4 (10)	0 (0)	0.31
Disease activity parameters [median (minimum-maximum)]				
CDAI	22 (8; 66)	24 (12; 66)	18 (8; 65)	0.08
SDAI	24.4 (9; 73.6)	26.9 (12.3; 73.6)	18.3 (9; 68.5)	0.08
DAS-28	5.1 (1.9; 8.2)	5.1 (2; 7.7)	4.2 (1.9; 8.2)	0.36
VAS global physician	60 (10; 100)	60 (30; 100)	50 (10; 90)	0.33
VAS global patient	70 (20; 100)	70 (40; 100)	70 (20; 100)	0.81
VAS pain	70 (30; 100)	70 (30; 100)	80 (30; 100)	0.93
VAS fatigue	70 (10; 100)	70 (10; 100)	65 (10; 100)	0.95
HAQ-DI	1 (0.1; 4.6)	0.9 (0.1; 4.6)	1.3 (0.2; 3)	0.14
EQ5D	11 (5; 14)	11 (5; 13)	11 (7; 14)	0.52

b-DMARDs: Biologic disease-modifying antirheumatic drugs, CDAI: Clinical disease activity ındex, cs-DMARDs: Conventional synthetic disease-modifying antirheumatic drugs, DAS-28: Disease activity score 28, EQ5D: EuroQol group EQ-5D-3L, HAQ-DI: Health assessment questionnaire-disability ındex, SDAI: Simple disease activity ındex, TNF: Tumor necrosis factor, VAS: Visual analog scale

Evaluation of Muscular Strength, Physical Performance Tests, and Muscle Alterations Before and After Therapy with b-DMARDs

The SARC-F test, locomotor speed, and 4-m walking test exhibited no statistically significant differences (p=0.87, p=0.76, and p=0.22, respectively). The scores of the HGST, TUG, and SST differed significantly (p=0.008, p=0.087, and p=0.012, respectively). Significant differences were observed in the thickness of the RA muscle, the TA muscle, the EO muscle, and the RFCSA (Table 2).

Associations Between Initial Disease Activity Scores, Physical Parameters, Physical Performance Tests, and Muscular Strength

The scores of CDAI (r=0.338), SDAI (r=0.326), DAS-28 (r=0.329), VAS global patient (r=0.314), VAS pain (r=0.378), HAQ-DI scores (r=0.641), and EQ5D (r=0.426) were all correlated with the SARC-F score. The SST score had a correlation with the following variables: DAS-28 (r=0.303), VAS global patient (r=0.311), VAS fatigue (r=0.419), HAQ-DI scores (r=0.47), and EQ5D (r=0.311). The TUG score was correlated with the following variables: CDAI (r=0.372), SDAI (r=0.367), DAS-28 (r=0.357), VAS global physician (r=0.322), VAS global patient (r=0.342), VAS pain (r=0.325), VAS fatigue (r=0.346), HAQ-DI scores (r=0.523), and EQ5D (r=0.451). The DAS-28 (r=-0.358) and HAQ-DI

Table 2. Baseline and control muscle strength and physical performance tests and ultrasonographic parameters in patients with control visit

	Baseline	Control	p
Muscle strength and physical performance tests [median (minimum-maximum)]			
HGST (kg)	15.4 (5; 51.2)	20.1 (5; 0.6)	0.008
4-m walking test (sec)	3.8 (2.5; 6.1)	4 (2.2; 9.9)	0.87
Gait speed (m/sec)	1 (0.6; 1.5)	1 (0.4; 1.8)	0.76
TUG (sec)	8.5 (5.7; 13.6)	7.5 (3; 18.7)	0.087
SST (sec)	14.1 (5.8; 24.3)	11.9 (7; 33.5)	0.012
SARC-F	4 (0; 8)	4 (0; 7)	0.22
Ultrasonographic parameters [median (minimum-maximum)]			
GM MT (mm)	16 (8.3; 42.2)	16 (9.2; 54.3)	0.34
GM FL (mm)	29.9 (6.3; 38)	29.7 (8.6; 53.8)	0.19
GM PA (°)	24.5 (13; 37)	24.5 (16; 45.3)	0.14
RF MT (mm)	15.7 (9.4; 23.1)	15.8 (3.8; 22.7)	0.68
RFCSA (mm^2)	5.6 (2.5; 12.5)	6.8 (3.8; 12)	0.025
RA MT (mm)	7.5 (3.9; 14.1)	8.2 (4.5; 11.7)	0.038
TA MT (mm)	2.9 (1.6; 8.8)	3.5 (1.7; 6.7)	0.01
IO MT (mm)	6.3 (3.3; 9.4)	6.7 (1.9; 10.6)	0.72
EO MT (mm)	3.1 (1.6; 7)	4 (2; 12.2)	0.021

EO MT: External oblique muscle thickness, GM MT: Gastrocnemius medialis muscle thickness, GM FL: Gastrocnemius medialis fascicle length, GM PA: Gastrocnemius medialis pennation angle, HGST: Hand Grip Strength test, IO MT: Internal oblique muscle thickness, RA MT: Rectus abdominis muscle thickness, RF MT: Rectus femoris muscle thickness, RFCSA: Rectus femoris cross sectional area, SST:Sit-to-stand test, TA MT: Transverse abdominis muscle thickness, TUG: Time up and go

scores (r=-0.431) were correlated with the gait speed score. EQ5D (r=0.351), CDAI (r=0.346), SDAI (r=0.339), DAS-28 (r=0.44), and HAQ-DI scores (r=0.523) were all correlated with the 4-m walking test score. The CDAI (r=-0.296), SDAI (r=-0.296), and DAS-28 (r=-0.321) were all correlated with the TUG score.

Comparison of Percentage Changes and Discrepancies in Muscular Strength and Physical Performance Test Evaluations, Ultrasonographic Measures, and Treatment Responses Based on CDAI Scores

When patients were categorized according to their control CDAI scores as remission or low disease activity and moderate or high disease activity, no distinction was observed, with the exception of the TUG percent change in assessments of muscular strength and physical performance. In the remission or low disease activity group, the percentage changes in GM MT, RFCSA, and RF MT were significantly higher in ultrasonographic measurements (Table 3).

Discussion

In this observational study, we found that the thickness of the RA muscle, RFCSA, TA muscle, and EO muscle all

Table 3. Comparison of percent changes of muscle strength and physical performance tests assessments, ultrasonographic measurements and treatment responses according to CDAI scores

	Disease activity regarding to CDAI score					
	Remission and/or low disease activity regarding to CDAI score (<10.1) (n=26)		Moderate and/or high disease activity regarding to CDAI score (>10) (n=14)			
	Percent changes of muscle strength and physical performance tests assessments [median (minimum-maximum)]	Muscle strength and physical performance tests differences [median (minimum-maximum)]	Percent changes of muscle strength and physical performance tests assessments [median (minimum-maximum)]	Muscle strength and physical performance tests differences [median (minimum-maximum)]	p1	p2
HGST (kg)	20.9 (-46.3; 132.4)	5.1 (-9.6; 15.1)	7.6 (-52.2; 135.2)	1.5 (-8.3; 11.7)	0.34	0.36
4-m walking test (sec)	-0.4 (-31.2; 85.9)	-0.01 (-1.4; 4)	7.5 (-34.4; 102.4)	0.2 (-2.1; 5)	0.63	0.63
Gait Speed (m/sec)	0.94 (-47; 44.9)	0.01 (-0.6; 0.5)	2.2 (-50.6; 53.8)	0.01 (-0.5; 0.3)	0.77	0.70
TUG (sec)	-100 (-100; -89.1)	-0.4 (-6.6; 9.4)	-100 (-100; 19.9)	-1.1 (-4; 5.1)	0.02	0.67
SST (sec)	-15.2 (-47.8; 94.1)	-1.8 (-8.9; 16.2)	-11.6 (-38.4; 35.7)	-1.9 (-7.4; 5)	0.91	0.82
SARC-f	0 (-100; 300)	0 (-4; 3)	-31.2 (-100; 100)	-1 (-4; 3)	0.69	0.64
	Percent changes of muscle measurements [median (minimum-maximum)]	Muscle measurements differences (median [median (minimum-maximum)]	Percent changes of muscle measurements [median (minimum-maximum)]	Muscle measurements differences [median (minimum-maximum)]		
GM MT (mm)	10.9 (-24.8; 229.1)	1.6 (-5.5; 37.1)	-6.1 (-50.7; 57)	-1 (-21.4; 9.7)	0.02	0.01
GM FL (mm)	3.9 (-76.8; 433.3)	1.2 (-28.8; 27.3)	0 (-18.1; 94)	0 (-6.4; 14.1)	0.75	0.60
GM PA (°)	4.6 (-35; 126)	1 (-12; 25.5)	18.8 (-29; 87.9)	3.5 (-9; 11.7)	0.44	0.53
RF MT (mm)	4.5 (-67.8; 57.6)	0.6 (-8.1; 8.3)	-6.1 (-52.8; 39)	-1 (-12.2; 5)	0.03	0.04
RFCSA (mm^2)	29.5 (-43.5; 122.1)	1.3 (-4.9; 6.2)	-6.3 (-62.2; 90.4)	-0.3 (-7.8; 3.9)	0.02	0.01
RA MT (mm)	5.7 (-38.1; 51.2)	0.4 (-3.7; 2.8)	11.5 (-45.7; 53.5)	0.8 (-3.8; 3)	0.81	0.80
TA MT (mm)	19.1 (-49.1; 235)	0.5 (-4.1; 4.7)	23.6 (-60.5; 121)	0.7 (-4.6; 2.3)	0.60	0.45
IO MT (mm)	2.5 (-39.7; 49.1)	0.1 (-3.3; 3)	2.3 (-59.5; 121.2)	0.1 (-3.4; 5.8)	0.85	0.85
EO MT (mm)	11.7 (-57.1; 351.8)	0.4 (-4; 9.5)	20.3 (-24.2; 68.7)	0.6 (-0.8; 1.8)	0.78	1.0

P1: Comparison of percent changes of muscle strength and physical performance tests and muscle measurements

P2: Comparison of muscle strength and physical performance tests and muscle measurements differences

CDAI: Clinical disease activity ındex, EO MT: External oblique muscle thickness, IO MT: Internal oblique muscle thickness, HGST: Hand grip strength test, GM MT: Gastrocnemius medialis muscle thickness, GM FL: Gastrocnemius medialis fascicle length, GM PA: Gastrocnemius medialis pennation angle, RF MT: Rectus femoris muscle thickness, RA MT: Rectus abdominis muscle thickness, RFCSA: Rectus femoris cross sectional area, SST:Sit-to-stand test, TUG: Time up and go, TA MT: Transverse abdominis muscle thickness

increased substantially during the initial stages of treatment. Furthermore, the disease activity scores, HGST, SST, and TUG scores improved significantly during treatment. The correlation between the change in VAS global physician, EQ5D scores and the change in SST scores, as well as the correlation between the change in VAS pain scores and the change in HGST scores, was identified. We found that the treatment-responsive group exhibited superior percentage changes in RF muscle thickness, RFCSA, and GM muscle thickness when the treatment response was assessed using the CDAI scores.

Sarcopenia is defined as a condition characterized by low muscle mass, low skeletal muscle strength, and/or poor physical performance, as per the criteria of the European Working Group on Sarcopenia in Older People.[9] It has been demonstrated that sarcopenia is not exclusively associated with age; it can also be the result of inflammation and is linked to an undesirable prognosis and an elevated risk of mortality.[22] In a straightforward regression analysis, Ange Ngeuleu et al. demonstrated that sarcopenia was associated with DAS 28, ESR, waist circumference, and HAQ.[23] In accordance with this, Wanruchada et al.[24] demonstrated that sarcopenia was correlated with elevated disease activity.

Previous research has demonstrated that appendicular lean mass in the limbs is a more accurate indicator of skeletal muscle than total lean mass, as the extremities contain over half of the total muscle mass.[25] A more rational approach may involve assessing total muscle mass through regional measurements administered with USG.

The most valuable imaging methods for evaluating muscle mass are magnetic resonance, computed tomography, bioelectrical impedance analysis, and dual energy X-ray absorptiometry (DXA). However, these methods require experienced personnel, are costly, lack portability, depend on the patient's hydration level, and the presence of metallic devices. There is also the possibility that the results of various DXA devices may differ.[26-28] USG is preferable to other methods of muscle evaluation due to its lack of radiation exposure.[29] Muscle USG can offer objective and consistent quantitative and qualitative measurements of the muscle and can also be employed at the bedside.

In RA, sarcopenia may be caused by a variety of factors. The total muscle mass and stamina may be adversely affected by the increased production of cytokines, including TNFα, interleukin (IL)-1β, and IL-6, which inhibit muscle metabolism. Also, the risk of muscle atrophy is elevated in RA patients due to the prevalence of physical inactivity, which is caused by functional impairment.[30,31] It has been demonstrated that b-DMARDs can result in an increase in muscle mass in approximately 50% of RA patients.[32] In a single study, RA patients who were administered anti-TNF showed a substantial increase in their HGST and 6-minute walk test scores.[33] During therapy, no notable enhancement was reported in HGST, gait speed, or SST in RA patients in another study.[34] In a study conducted on RA patients who were taking b-DMARDs, no significant change was observed in HGST.[35] Significant improvements were observed in the HGST, TUG, and SST assays in our investigation. The gait speed, SARC-F, and 4-minute walk test did not exhibit any significant differences. Despite the improvements in HGST and SST tests detected after treatment, no improvement was detected in SARC-F, gait speed, 4-m walking tests, which have similar results to the literature. It can be explained by suggesting that a longer treatment and follow-up period may be required to make a more definitive interpretation of the improvement in these tests.

The majority of the literature on this topic pertains to muscle quantity measurement. The increase in appendicular skeletal mass and fat-free mass index in RA patients with minimal disease activity was enhanced by b-DMARDs, as demonstrated by a study.[35] Lemmey et al.[36], in contrast, reported that RA patients with minimal disease activity have a higher total fat mass and a lower TLM compared to healthy controls. The relationship between sarcopenia results and disease activity after treatment in RA patients was not investigated, as demonstrated by a meta-analysis.[32] Also, skeletal mass index and muscle strength were not examined. Our research demonstrated a negative correlation between the change in VAS global physician, EQ5D scores, and SST scores. Significant increases in the percentage changes of GM muscle thickness, RFCSA, and RF muscle thickness were observed in patients in the remission or reduced activity group when evaluated according to CDAI responses. The study's assets are the concurrent evaluation of three sarcopenia-related metrics, namely muscle mass, muscle strength, and physical performance, as well as the examination of the correlation between these values and disease activity scores. To date, no studies in the literature have demonstrated the use of ultrasound to measure muscle size in RA patients undergoing treatment with b-DMARDs.

Study Limitations

Lack of a control group is the study's primary limitation. Additionally, due to the ongoing coronavirus disease 2019 pandemic at the time of our investigation, certain patients were unable to attend for control visit. Although the c-DMARD treatments used by the patients before biological treatment are given in detail in Table 1, the fact that we do not have records of their characteristics such as basic and

daily physical activity level and nutritional status is one of the limitations of our study. The fact that the proportion of female patients is higher than that of male patients in our study is not a limitation of our study but rather due to the fact that RA is a disease more common in women. Another limitation of our study is that sarcopenia could not be evaluated comprehensively due to the lack of data on muscle quality of the patients in our study.

Conclusion

In inflammatory disorders such as RA, muscle assessment is essential for guiding patient management and contributing disease activity scores to the evaluation of treatment efficacy. It also provides prognostic insights for diseases. This could be accomplished using a non-invasive technique such as USG, similar to our investigation. A larger patient population and extended follow-up periods are still necessary for the investigation of this topic.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Clinical Research Ethics Committee [decision no: 2022/20-08 (KA-21151), date: 22.11.2022] and Turkish Medicines and Medical Devices Agency.

Informed Consent: Informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practies: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Concept: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Design: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Data Collection or Processing: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Analysis or Interpretation: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Literature Search: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Writing: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H.

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References

1. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244-57.
2. Amaya-Amaya J, Botello-Corzo D, Calixto OJ, et al. Usefulness of patients-re- ported outcomes in rheumatoid arthritis focus group. Arthritis. 2012;2012:935187.
3. Santo RCE, Fernandes KZ, Lora PS, et al. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2018;9: 816-25.
4. Yu S, Appleton S, Adams R, et al. The impact of low muscle mass definition on the prevalence of sarcopenia in older Australians. Biomed Res Int. 2014:2014:361790.
5. Brown JC, Harhay MO, Harhay MN. Sarcopenia and mortality among a population- based sample of community-dwelling older adults. Journal of Cachexia Sarcopenia and Muscle 2016;7:290-8.
6. Hugo M, Mehsen-Cetre N, Pierreisnard A, et al. Energy expenditure and nutritional complications of metabolic syndrome and rheumatoid cachexia in rheumatoid arthritis: an observational study using calorimetry and actimetry. Rheumatology (Oxford). 2016;55:1202-9.
7. El Maghraoui A, Sadni S, Rezqi A, et al. Does rheumatoid cachexia predispose patients with rheumatoid arthritis to osteoporosis and vertebral fractures? J Rheumatol. 2015;42:1556-62.
8. van Bokhorst-de van der Schueren MA, Konijn NP, Bultink IE, et al. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. Clin Nutr. 2012;31:1008-10.
9. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16-31.
10. Kalyoncu U, Taşcılar EK, Ertenli Aİ, et al. Methodology of a new inflammatory arthritis registry: TReasure. Turk J Med Sci. 2018;48:856-61.
11. Singh H, Kumar H, Handa R, et al. Use of clinical disease activity index score for assessment of disease activity in rheumatoid arthritis patients: an Indian experience. Arthritis. 2011:2011:146398.
12. Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Ann Rheum Dis. 2008;67:1360-4.
13. Miller MD, Ferris DG. Measurement of subjective phenomena in primary care research: the visual analogue scale. Fam Pract Res J. 1993;13:15-24.
14. Küçükdeveci AA, Sahin H, Ataman S,et al. Issues in cross-cultural validity: Example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. Arthritis Rheum. 2004;51:14-9.
15. Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Quality Life Res. 2010;19:887-97.
16. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal Am Geriatr Soc. 1999;39:142-8.
17. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14:531-2.
18. Bahat G, Yilmaz O, Kilic C, et al. Performance of SARC-F in regard to sarcopenia definitions, muscle mass and functional measures. J Nutr Health Aging. 2018;22:898-903.
19. Kara M, Kaymak B, Ata AM, et al. STAR-sonographic thigh adjustment ratio: a golden formula for the diagnosis of sarcopenia. Am J Phys Med Rehabil. 2020;99:902-98.

20. Deniz O, Cruz-Jentoft A, Sengul Aycicek G, et al. Role of ultrasonography in estimating muscle mass in sarcopenic obesity. JPEN J Parenter Enteral Nutr. 2020;44:1398-406.

21. Esme M, Karcıoglu O, Oncel A, et al. Ultrasound assessment of sarcopenia in patients with sarcoidosis. J Ultrasound Med. 2022;41:951-9.

22. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology. 2004;43:1219-23.

23. Ngeuleu A, Allali F, Medrare L, et al. Sarcopenia in rheumatoid arthritis: prevalence, influence of disease activity and associated factors. Rheumatol Int. 2017;37:1015-20.

24. Katchamart W, Kieattisaksopon S, Narongroeknawin P, et al. Risk factors for sarcopenia in THAI patients with rheumatoid arthritis. Discov Med. 2023;35:436-43.

25. Kim J, Wang Z, Heymsfield SB, et al. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr. 2002:76:378-83.

26. Gallagher D, Song M-Y. Evaluation of body composition: practical guidelines. Prim Care. 2003;30:249-65.

27. Bolanowski M, Nilsson BE. Assessment of human body composition using dual-energy x-ray absorptiometry and bioelectrical impedance analysis. Med Sci Monit. 2001;7:1029-33.

28. Buckinx F, Landi F, Cesari M, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle. 2018;9:269-78.

29. Perkisas S, Baudry S, Bauer J, et al. Application of ultrasound for muscle assessment in sarcopenia: towards standardized measurements. Eur Geriatr Med. 2018;9:739-57.

30. Pistilli EE, Jackson JR, Alway SE. Death receptor-associated pro-apoptotic signaling in aged skeletal muscle. Apoptosis. 2006;11:2115-26.

31. Sokka T, Häkkinen A, Kautiainen H, et al. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis Rheum. 2008:59:42-50.

32. Tekaya AB, Mehmli T, Ben Sassi M, et al. Effects of biologic and target synthetic disease-modifying anti-rheumatic drugs on sarcopenia in spondyloarthritis and rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2023;42:979-97.

33. Vial G, Lambert C, Pereira B, et al. The effect of tnf and non-tnf-targeted biologics on body composition in rheumatoid arthritis. J Clin Med. 2021;10:487.

34. Marcora SM, Chester KR, Mittal G, et al. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006;84:1463-72.

35. Santo RC, Silva JM, Lora PS, et al. Cachexia in patients with rheumatoid arthritis: a cohort study. Clin Rheumatol. 2020;39:3603-13.

36. Lemmey AB, Wilkinson TJ, Clayton RJ, et al. Tight control of disease activity fails to improve body com- position or physical function in rheumatoid arthritis patients. Rheumatology (Oxford). 2006: 55:1736-45.