The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5492-5498

Evaluation of Insulin-like Growth Factor-1 as a Potential Biomarker for Sarcopenia among Elderly Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Sarcopenia denotes progressive age-related reduction in skeletal muscle mass and strength. In rheumatoid arthritis (RA), chronic synovial inflammation and metabolic dysregulation can accelerate its development.
Objective: To assess insulin-like growth factor-1 (IGF-1) as a potential biomarker for sarcopenia in elderly RA cases.
Patients and Methods: Ninety participants were stratified into three groups (30 each): Group A-RA with sarcopenia, Group B-RA without sarcopenia, and Group C-age- and sex-matched controls. All underwent clinical evaluation, including body mass index (BMI), hand-grip strength (HGS), mid-arm circumference (MAC), and 4-meter walk test (4MWT). Laboratory tests included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor(RF), anti-citrullinated peptide antibodies (ACPA), and serum IGF-1. **Results:** Females predominated across all groups. Group A showed the lowest MAC (19.04 ± 2.26 cm), reduced HGS (11.77 ± 6.81 kg), and slowest 4MWT (9.93 ± 1.55 s). Mean IGF-1 levels were lower in Group A (26.53 ± 16.69 ng/mL) than Group B (35.67 ± 7.80 ng/mL) and Group C (63.25 ± 11.28 ng/mL). IGF-1 correlated negatively with disease activity score involving 28 joints for ESR (DAS28-ESR) ($r_s = –0.318$, $p = 0.013$), Disease Activity Score(DAS28-CRP) ($r_s = –0.367$, $p = 0.004$), and 4MWT ($r_s = –0.676$, $p < 0.001$), and positively with MAC ($r_s = 0.715$, $p < 0.001$) and HGS ($r_s = 0.611$, $p < 0.001$). **Conclusion:** Lower IGF-1 levels in RA cases with sarcopenia indicate its potential utility as a biomarker for early detection and monitoring of muscle loss and disease activity.
Keywords: Insulin Growth Factor-1, Sarcopenia, Rheumatoid Arthritis, Elderly.

INTRODUCTION

Aging is an inherent biological phenomenon which is correlated with buildup of senescent cells that release pro-inflammatory factors. Worldwide, the rising proportion of older individuals has led to a greater number of elderly people experiencing extended life spans [1]. In Egypt, demographic changes are evident, with the population aged 60 years and above projected to more than double, from 8.4 million in 2020 to 22 million by 2050, representing roughly 14% of the total population [2].

Age-related alterations in the neuromuscular system involve progressive reductions in muscle mass and strength, coupled with decreased anabolic responsiveness, which together contribute to impaired protein synthesis [3]. At the same time, protein breakdown increases, a process closely linked to chronic, low-grade inflammation [4]. Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by ongoing synovial inflammation and progressive joint erosion, frequently accompanied by systemic features. Worldwide, it contributes substantially to morbidity, disability, and diminished quality of life. The immune-mediated nature of RA often manifests as symmetrical polyarthritis and can extend to extra-articular organs, particularly the pulmonary, cardiac, and ocular systems [5, 6].

Sarcopenia, marked by a progressive decline in skeletal muscle mass and strength, leads to increased vulnerability to falls, fractures, and physical disability in the elderly. Chronic systemic inflammation and the overproduction of cytokines and myokines play pivotal roles in initiating and sustaining this process [7].

Insulin-like growth factor 1 (IGF-1) is crucial for maintaining muscle protein balance and supporting regeneration, and its decline with age is closely tied to sarcopenia onset [8]. IGF-1 also improves muscle quality by reducing fat infiltration (myosteatosis) and oxidative stress, both of which hamper muscle contraction. Within RA, IGF-1 has gained attention for its anti-inflammatory properties and its role in tissue regeneration [9, 10].

This study explored IGF-1 as a biomarker of sarcopenia in elderly RA patients and its association with muscle strength and physical function.

PATIENTS AND METHODS

In this prospective observational investigation, 90 subjects aged 60 years or older were enrolled from the Geriatric and Rheumatology Outpatient Clinics at Alexandria Main University Hospital

Subjects were stratified into three equal groups: Group A consisted of RA patients accompanied by sarcopenia; Group B included RA patients without sarcopenia; and Group C comprised healthy control subjects matched for age and sex.

Exclusion criteria Any autoimmune disease other than RA, malignancy, thyroid disease, end stage renal disease and severe liver impairment.

The following data were obtained from each case:

1. **Proper full medical history** taken from patient or his caregiver which included (age, sex, occupation, marital

Received: 25/05/2025
Accepted: 29/07/2025

status, special habits as well as history of RA and history of physical activity).

2.Full clinical assessment.

A. Body mass index (BMI) Assessment

The BMI of each subject was calculated using the established standard formula:

BMI= Weight (kg)/ [Height (m)]^2 In elderly individuals (>60 years), BMI is interpreted cautiously due to age-related changes in body composition, such as loss of height from vertebral compression and increased fat mass despite stable weight. Conventional adult BMI thresholds may not accurately represent nutritional risk or the presence of sarcopenic obesity among older individuals.

WHO criteria for older adults define underweight as BMI < 22 kg/m², normal weight as 22–27 kg/m², and overweight/obesity as >27 kg/m². These ranges better align with health outcomes and mortality risks in the elderly [11].

B. Assessment of sarcopenia

1- Mid-arm circumference (MAC) for muscle mass.

A flexible, non-stretchable tape was used to measure MAC on the non-dominant arm to the nearest 0.1 cm, positioned midway between the acromion and olecranon landmarks while the arm was relaxed alongside the body.

MAC is a simple, inexpensive, and validated anthropometric measure used to estimate muscle mass and nutritional status, particularly in elderly individuals, where body composition assessments (e.g., DXA) are often unavailable. MAC has been demonstrated to correlate with appendicular skeletal muscle mass, particularly among community-dwelling older adults [12].

In this study, MAC was used as a surrogate marker for sarcopenia and was interpreted according to age-specific cut-off points suggested by recent literature. The following thresholds were applied:

- Men: MAC < 23 cm indicates low muscle mass
- Women: MAC < 22 cm indicates low muscle mass

The adopted cut-off values conform to the EWGSOP2 criteria and have been supported by recent research validating their applicability in older adult populations [13].

2- Assessment of hand grip strength (HGS) for muscle strength.

HGS was used as a primary indicator of muscle strength, in accordance with the EWGSOP2 criteria for sarcopenia diagnosis in older adults [14]. It was assessed using a hydraulic hand dynamometer (Camry Model, Yueqing Leqi Instrument Co, China).), a standardized and reliable method frequently employed in clinical and research settings.

- Measurement protocol:

With the shoulder adducted and neutrally rotated, elbow at 90° flexion, forearm neutral, and wrist extended 0°–30°, participants performed three dominant-hand trials separated by ≥30 s rest. The highest force value (kg) was included in the analysis.

- Interpretation in elderly:

According to updated EWGSOP2 recommendations and validated studies from 2022–2024; low muscle strength is defined as < 27 kg for men and < 16 kg for women. These thresholds reflect poor functional reserve and are strongly associated with increased risk of mobility limitations, falls, hospitalization, and mortality in individuals over 60 years of age [15-17].

3- The 4 meters walking test for assessment of physical performance.

Physical performance was evaluated using the 4-Meter Walking Speed Test (4MWT), a widely accepted and validated tool for assessing functional mobility and predicting disability, frailty, and mortality among elderly individuals.

Each participant completed a 4-meter walk test on a level, unobstructed path while wearing customary footwear and walking at a usual pace. The stopwatch was started at the first foot movement and stopped as the second foot passed the 4-meter mark. Two trials were conducted, and the better (faster) time, expressed in meters per second, was used for analysis.

Walking speed is a strong indicator of lower-extremity function and overall health in the elderly. Based on updated international geriatric and sarcopenia guidelines:

- Normal performance: ≥ 0.8 m/s
- Low physical performance (sarcopenic): < 0.8 m/s

The 4-meter test was chosen due to its high feasibility and strong correlation especially in frail or mobility-limited populations, such as elderly patients with RA [18, 19].

C - Disease activity score-28 for RA (DAS28).

The disease activity score involving 28 joints (DAS28) is an integrated assessment instrument designed to gauge RA activity by examining: The count of tender joints (TJC28), The count of swollen joints (SJC28) The patients overall health rating (Visual Analogue Scale) and Inflammatory markers as ESR or CRP.

DAS28 scores are interpreted according to the following ranges:

- Above 5.1: Indicates high disease activity.
- Between 3.2 and 5.1: Indicates moderate disease activity.
- Between 2.6 and 3.2: Indicates low disease activity
- Below 2.6: indicates remission [20].

3. Laboratory Investigations:

Venous blood was drawn from all participants for subsequent laboratory analysis. The following

investigations were performed: Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), C-reactive Protein (CRP), thyroid Stimulating Hormone (TSH), serum creatinine, alanine transferase (ALT), aspartate transferase (AST), haemoglobin A1c, rheumatoid factor (RF), and anti-citrullinated protein antibody (ACPA). Serum IGF-1 levels were determined using an ELISA kit. The reaction was stopped with a stop solution that converted the colour from blue to yellow, and absorbance was read at 450 nm using a spectrophotometer. IGF-1 concentrations were calculated by comparing the optical density (O.D.) of samples to a standard calibration curve generated from known IGF-1 standards assayed concurrently.

Ethical considerations

The study was approved by the Institutional Review Board of the Faculty of Medicine, Alexandria University (IRB NO: 00012098). All participants provided written informed consent prior to enrollment after receiving a full explanation of the study objectives and procedures. Confidentiality and anonymity of participants were strictly maintained, and data were used solely for research purposes. The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki for research involving human subjects.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 20.0 (Armonk, NY, USA: IBM Corp.). The Chi-square test was used for categorical variables, applying Fisher's Exact or Monte Carlo corrections when >20% of expected counts were <5. Qualitative data were summarized as frequencies and percentages, and quantitative data as range, mean ± SD, median, and IQR. Normally distributed data were compared using one-way ANOVA test with Tukey's post hoc test, whereas non-normally distributed variables were analyzed using Kruskal–Wallis tests with Dunn's post hoc correction when needed. Statistical significance was set at $p < 0.05$.

RESULTS

The study demonstrated a female predominance across all groups, representing 80% in Groups A and C and 70% in Group B. Statistical analysis showed no marked variation among groups regarding gender distribution. In contrast, a highly substantial variation was detected in BMI, with Group A recording the lowest mean value (19.02 ± 0.82 kg/m²), consistent with the expected phenotype of sarcopenic cases with RA (**Table 1)**.

Table (1): Socio-demographic and clinical data of studied groups

	Group A (n = 30)		Group B (n = 30)		Group C (n = 30)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	6	20.0	9	30.0	6	20.0	χ^2= 1.118	0.572
Female	24	80.0	21	70.0	24	80.0		
Age (Years)								
Min. – Max.	60.0 – 70.0		61.0 – 70.0		61.0 – 69.0		F= 0.156	0.856
Mean ± SD.	64.40 ± 3.10		64.60 ± 2.37		64.23 ± 2.05			
Median (IQR)	64.0 (62.0 – 67.0)		64.0 (63.0 – 66.0)		64.0 (63.0 – 65.0)			
Marital status								
Married	25	83.3	26	86.7	26	86.7	χ^2= 9.185*	MCp= 0.026*
Divorced	0	0.0	4	13.3	1	3.3		
Widow	5	16.7	0	0.0	3	10.0		
Smoking	5	16.7	8	26.7	0	0.0	χ^2=9.974*	MCp=0.006*
Diabetes Mellitus	8	26.7	4	13.3	8	26.7	χ^2=2.057	0.358
Hypertension	15	50.0	5	16.7	5	16.7	χ^2=11.077*	0.004*
P between groups	p_1<0.001*, p_2<0.001*, p_3<0.001*							
Body mass index (kg/m²)								
Min. – Max.	16.95–20.28		18.60 – 24.70		25.60 – 29.90		F= 356.871*	<0.001*
Mean ± SD.	19.02 ± 0.82		21.98 ± 2.02		27.61 ± 1.50			
Median (IQR)	19.10 (18.5–19.54)		22.0 (20.10 – 23.80)		27.85(26.10 – 29.0)			
P between groups	p_1<0.001*, p_2<0.001*, p_3<0.001*							

F: F-value for one-way ANOVA test, χ^2: Chi-square test; MC: Monte Carlo test; p: p-value for comparison among the three studied groups; p_1: p-value for comparison between Group A and Group B; p_2: p-value for comparison between Group A and Group C; p_3: p-value for comparison between Group B and Group C; * indicates statistical significant difference at $p \leq 0.05$. Group A: RA with sarcopenia; Group B: RA without sarcopenia; Group C: control group.

Clinical assessments for sarcopenia including MAC, HGS and 4MWT were done to the whole subjects included in the current study and revealed highly substantial variations across groups. Group A demonstrated the lowest mean MAC (19.04 ± 2.26 cm), consistent with marked muscle wasting in sarcopenic patients. Also, Group A had profoundly reduced grip strength (11.77 ± 6.81 kg) highlighting the severe functional impairment in sarcopenic RA patients. Meanwhile, regarding 4MWT, which assesses gait speed and mobility, Group A showed the slowest walking time (9.93 ± 1.55 seconds) (**Table 2)**.

Table (2): Clinical measures of sarcopenia among studied groups

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	H	p
MAC					
Min. – Max.	17.10 – 26.50	16.0 – 29.0	22.30 – 33.60		
Mean ± SD.	19.04 ± 2.26	21.65 ± 2.07	26.43 ± 3.29	59.778*	<0.001*
Median (IQR)	18.55(17.60 –19.40)	21.80(20.70 –22.50)	25.70(23.60 –28.60)		
P between groups.	p_1=0.001*,p_2<0.001*,p_3<0.001*				
HGS					
Min. – Max.	5.0 – 29.0	10.0 – 29.0	17.0 – 45.0		
Mean ± SD.	11.77 ± 6.81	18.53 ± 5.26	36.33 ± 6.19	63.037*	<0.001*
Median (IQR)	9.0 (6.0 – 15.0)	17.50 (15.0 – 22.0)	36.50 (34.0 – 41.0)		
P between groups.	p_1=0.005*,p_2<0.001*,p_3<0.001*				
4MWT					
Min. – Max.	6.0 – 12.0	5.0 – 9.0	3.0 – 6.0		
Mean ± SD.	9.93 ± 1.55	6.60 ± 1.22	4.40 ± 0.77	71.216*	<0.001*
Median (IQR)	10.0 (9.0 – 11.0)	6.0 (6.0 – 7.0)	4.0 (4.0 – 5.0)		
P between groups	p_1<0.001*,p_2<0.001*,p_3<0.001*				

MAC: Mid arm circumference; HGS: Hand grip strength ;4MWT: 4-meter walking test; IQR: **Inter quartile range**; SD: **Standard deviation**; H: H for **Kruskal Wallis test,** pairwise comparison bet. each 2 groups were done using **Post Hoc Test (Dunn's for multiple comparisons test)** p: p value for comparing between the three studied groups; p_1: p value for comparing between Group A and Group B; p_2: p value for comparing between Group A and Group C; p_3: p value for comparing between Group B and Group C; *: Statistically significant at p ≤ 0.05; **Group A:** Rheumatoid arthritis and Sarcopenia; Group **B:** Rheumatoid arthritis; Group **C:** Control group.

Elevated CRP levels were observed in Group A (mean = 42.89 ± 26.88 mg/L) when compared with Group B (mean = 22.80 ± 23.54 mg/L) and Group C (mean = 4.03 ± 2.00 mg/L), with a highly variation among groups. These results demonstrate a graded escalation in inflammatory markers, increasing from healthy individuals to RA patients without sarcopenia and reaching a maximum in those with both RA and sarcopenia. Likewise, ESR was higher in Group A (mean = 54.60 ± 26.42 mm/hr) than in Group B (mean = 34.83 ± 18.91 mm/hr) and Group C (mean = 13.03 ± 6.44 mm/hr), with statistically significant difference.

A key component of the investigation hypothesis was to evaluate the correlation of IGF-1 with sarcopenia and RA in the elderly. Analysis revealed a highly substantial intergroup variation in IGF-1 concentrations, highlighting its value in differentiating disease and muscle status categories. Group A exhibited the lowest mean IGF-1 level (26.53 ± 16.69 ng/mL), Group B demonstrated intermediate values (35.67 ± 7.80 ng/mL), and Group C showed the highest level (63.25 ± 11.28 ng/mL), as illustrated in **Figure 1**. These results substantiate the concept that declining IGF-1 levels are closely correlated with both sarcopenia and chronic inflammation in RA, with their coexistence producing a synergistic reduction.

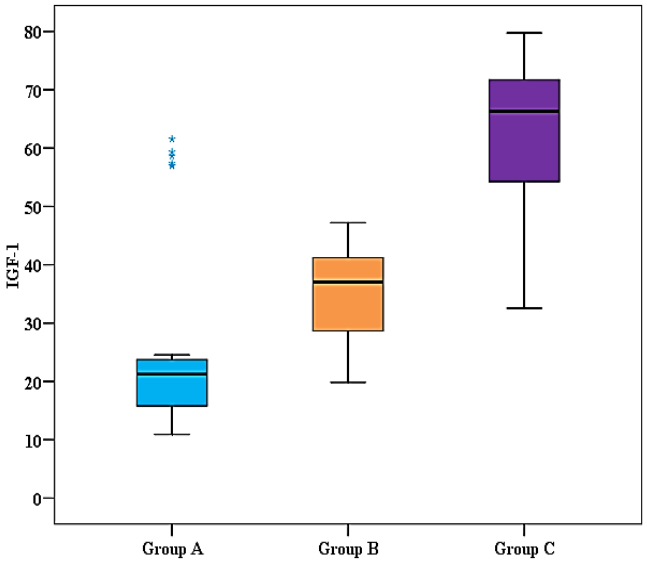

Figure (1): Box- plot figure showing IGF-1 levels among the three studied groups.

ROC curve analysis was applied to evaluate the ability of serum IGF-1 levels to discriminate between RA

cases with and without sarcopenia **(Figure 2)**. The AUC was 0.782, indicating good overall discriminatory performance. At an optimal threshold of ≤27.66 ng/mL, IGF-1 demonstrated a 80.0% sensitivity and a 76.67% specificity, with corresponding PPV and NPV values of 77.4% and 79.3%, respectively. This well-balanced performance underscores the clinical relevance of IGF-1 measurement for distinguishing sarcopenic status among cases with RA.

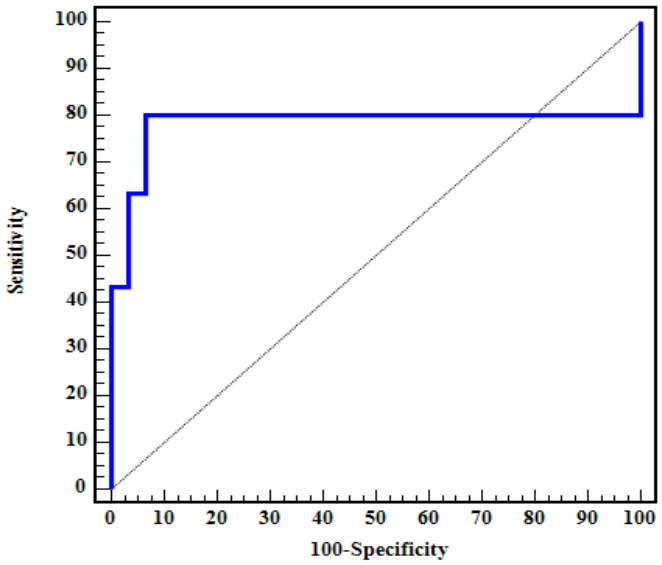

Figure (2): ROC curve for IGF-1 to discriminate Group A (n = 30) from Group B (n = 30).

Correlation analysis demonstrated marked inverse associations between IGF-1 and RA disease activity, as measured by DAS28-ESR (rs = –0.318) and DAS28-CRP (rs = –0.367). In contrast, IGF-1 exhibited strong positive correlations with muscle-related and nutritional parameters, including MAC (rs = 0.715), HGS (rs = 0.611), and BMI (rs = 0.746). Moreover, IGF-1 correlated negatively with 4MWT (rs = –0.676), indicating that lower IGF-1 concentrations are linked to slower gait speed and reduced functional capacity **(Table 3)**.

Table (3): Correlation between IGF-1 and different parameters in the total sample of the studied groups

	N	IGF-1	
		r_s	p
DAS28 (ESR)	**60**	-0.318*	0.013*
DAS28 (CRP)	**60**	-0.367*	0.004*
ESR	**90**	-0.636	<0.001*
CRP	**90**	-0.592	<0.001*
MAC	**90**	0.715*	<0.001*
HGS	**90**	0.611*	<0.001*
4MWT	**90**	-0.676*	<0.001*
BMI (kg/m²)	**90**	0.746	<0.001*

r_s: Spearman coefficient, ***:** Statistically significant at p ≤ 0.05.

DISCUSSION

Sarcopenia, a condition predominantly affecting older adults, is influenced by nutritional deficiencies and persistent low-grade inflammation in individuals with RA, sarcopenia risk is amplified by ongoing systemic inflammation, decreased mobility, and catabolic consequences of chronic disease progression. Although sarcopenia is increasingly acknowledged as a comorbidity in RA, its early diagnosis continues to pose clinical difficulties [21].

IGF-1 plays a pivotal role in muscle anabolic pathways, regulating protein synthesis, regeneration, and metabolic activity. Its reduction, commonly observed in aging and chronic inflammatory conditions, may represent a key pathophysiological mechanism contributing to sarcopenia [22, 23]. Research addressing the prognostic utility of IGF-1 as a marker for sarcopenia in elderly RA populations remains scarce. In response, the current study sought to evaluate the predictive and diagnostic potential of IGF-1 for sarcopenia in older adults with RA.

Within the framework of this study, the sarcopenic group exhibited the lowest average BMI among the 3 groups. These findings underscore the significant decline in BMI observed in sarcopenic cases relative to non-sarcopenic and healthy individuals, aligning with the muscle mass loss that defines sarcopenia. Similarly, **Moschou *et al.*** [24] examined 32 postmenopausal women with RA, both with and without sarcopenia, and reported that those with sarcopenia had a significantly lower average BMI (27.1 kg/m²) compared to their non-sarcopenic counterparts (30.5 kg/m²; p = 0.008). In contrast, **Ngeuleu *et al.*** [25] evaluated 123 RA cases with sarcopenia and reported that most had a normal BMI but an increased waist circumference, with the majority aged between 41 and 50 years.

Both CRP and ESR levels were significantly elevated among RA cases with sarcopenia compared with other study groups. These findings demonstrate that the presence of sarcopenia in RA is accompanied by a pronounced systemic inflammatory response, surpassing that of RA cases without sarcopenia. Similar outcomes were documented by **Lian *et al.*** [26], who reported significantly elevated disease activity (DAS28, CRP, and ESR) among those with sarcopenia.

In the current study, MAC and HGS were markedly lower in sarcopenic group relative to both the non-sarcopenic group and controls, also sarcopenic patients recorded the longest time in the 4MWT at 9.93 ± 1.55 seconds, reflecting slower gait speed, these results validate a reduction in muscular strength, muscle mass, and physical function among sarcopenic patients.

Similarly, **Akar *et al.*** [27] studied 25 women with RA and 25 healthy women, reporting a higher prevalence of sarcopenia and significantly poorer outcomes in

skeletal muscle mass ($p = 0.004$), skeletal muscle mass index ($p = 0.011$), grip strength in both hands ($p = 0.001$), knee extension strength on both sides ($p = 0.001$), and 4-meter gait speed test performance ($p = 0.001$) among sarcopenic cases relative to controls. Furthermore, **Moschou *et al.*** [24] examined 32 postmenopausal women with RA and reported a significant reduction in handgrip strength among those with sarcopenia compared to their non-sarcopenic counterparts along with lower BMI, muscle mass, and physical activity levels.

Among our cohort, RA cases with sarcopenia exhibited the lowest average IGF-1 levels (26.53 ± 16.69 ng/mL), significantly lower than those observed in non-sarcopenic patients (35.67 ± 7.80 ng/mL; $p = 0.015$) and healthy controls (63.25 ± 11.28 ng/mL; $p < 0.001$). These results suggest a gradual reduction in IGF-1 levels, highlighting its possible involvement in maintaining muscle health and its contribution to the development of sarcopenia. Similarly, **Moschou *et al***. [24] studied 32 postmenopausal women with RA and reported significantly lower IGF-1 levels in sarcopenic patients relative to their non-sarcopenic counterparts. Additionally, **Zhao *et al***. [28] reported that serum IGF-1 levels were significantly lower in RA patients relative to controls (SMD = –0.936, $p < 0.001$).

This study demonstrated statistically substantial positive correlations between IGF-1 levels and markers of muscle and nutritional status, including MAC, HGS, and BMI. Conversely, IGF-1 exhibited significant negative correlations with inflammatory and functional parameters such as CRP, ESR, and the 4MWT. These findings indicate that higher IGF-1 concentrations are associated with better nutritional status, greater muscle strength, and enhanced physical performance, whereas lower levels correspond to increased inflammation and impaired functional capacity.

Similarly, **Baker *et al.*** [29] found in a study of 50 RA cases that individuals with IGF-1 levels below age- and sex-specific norms exhibited reduced appendicular lean mass index (ALMI) and smaller leg muscle cross-sectional area, with IGF-1 levels inversely correlating with disease activity and CRP. Consistent with this, **Bian *et al.*** [15] studied 420 elderly sarcopenic patients and 2,856 non-sarcopenic individuals and reported a positive correlation between IGF-1 levels and both BMI and HGS. Conversely, in a cohort of 80 RA patients**, Lee *et al.*** [30] observed no substantial association between serum IGF-1 and ESR or CRP, although IGF-1 levels varied in relation to DAS28-CRP disease activity.

This investigation is limited by being conducted at a single center and by the modest sample size, potentially affecting the generalizability of its conclusions. Muscle mass was assessed using MAC rather than imaging-based techniques like DXA or BIA, which may have influenced diagnostic precision. IGF-1 was measured at a single time point, and longitudinal variations were not examined. In addition, dietary, physical activity, and medication-related confounders were not fully addressed. Therefore, validation of the IGF-1 cutoff in larger, multicenter studies is recommended before clinical adoption.

CONCLUSION

In summary, the significantly reduced IGF-1 levels observed in RA patients with sarcopenia indicate its potential utility as a biomarker for early detection of individuals at risk. The correlations identified between IGF-1 and both muscle strength and disease activity emphasize its relevance to musculoskeletal integrity and inflammatory status. Evaluating IGF-1 in elderly RA patients may therefore facilitate risk stratification, prevention, and early management of sarcopenia, a frequently overlooked yet clinically important comorbidity.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

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