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SARCOPENIA IN RHEUMATOID ARTHRITIS WITH SPECIAL REFERENCE TO SERUM TNF-ALPHA

Rheumatology

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ABSTRACT

Background: A reduction of muscle mass that exceeds the physiological rate is considered the key factor responsible for the development of a geriatric syndrome called sarcopenia. Rheumatoid arthritis (RA) is an inflammatory rheumatic disease with progressive course affecting articular and extra-articular structures. Cytokines, particularly tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are believed to increase muscle loss. It is believed that the inflammatory cytokines TNF-α and interleukin-1β (IL-1β) play a pivotal role in pathogenesis of RA. **Methods:** It is a hospital based observational study including patients attending Assam Medical College and Hospital, Dibrugarh, Assam over a period of one year. 40 RA patients aged 12 years or above were included. ASM was measured by dual-energy x-ray absorptiometry (DEXA). Qualitative data were analyzed using Chi-square ($\chi 2$) test. Pearson's correlation coefficient (r) was used to measure correlation between quantitative variables. Significance was assessed at 5% level of significance ($p < 0.05$). **Results:** The mean value of ASM was 14.48±3.60 kg and 16.33±4.39 kg in cases and controls respectively. The mean value of ASM/Height2 was 5.99±1.13 kg/m2 in cases and 6.71±1.23 kg/m2 in controls. The mean TNF-α for cases with sarcopenia were 23.03±5.68 pg/ml and that of controls with sarcopenia was 17.30±2.32 pg/ml. **Conclusions:** ASM/height2 an indicator of sarcopenia, was significantly lower in patients with Rheumatoid Arthritis. It was seen that the high serum TNF-α significant statistically in patients with RA having sarcopenia.

KEYWORDS

Rheumatoid arthritis, Sarcopenia, tumor necrosis factor-α (TNF-α) dual-energy x-ray absorptiometry (DEXA).

1. INTRODUCTION

The loss of muscle mass and function with increasing age is a natural process. Muscle strength decreases by 20-40% in seventh to eighth decade of life.[1] A reduction of muscle mass that exceeds the physiological rate is considered the key factor responsible for the development of a geriatric syndrome called sarcopenia.[2] The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal mass, which can cause adverse consequences like physical disability, poor quality of life and death.[3]

The risk factors for the development of Sarcopenia are numerous. The most important being old age, age-related changes in hormone and cytokine levels.[4] However, energy shortage, lack of physical activity, poor diet, human immunodeficiency virus (HIV) infection, chronic inflammatory diseases (e.g., Rheumatoid Arthritis and other autoimmune disorder), insulin resistance, type II diabetes mellitus, and impaired tissue repair can lead to sarcopenia in younger individuals.[4,5]

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease with progressive course affecting articular and extra-articular structures leading to pain, disability and mortality. RA, a systemic disease also leads to a variety of extra-articular manifestations, including fatigue, subcutaneous nodules, lung involvement, peripheral neuropathy, pericarditis, vasculitis, and hematological abnormalities besides being associated with conditions like cardiovascular diseases, osteoporosis, hypoandrogenism.[6] Almost all patients with rheumatoid arthritis (RA) suffer from muscular weakness. Reduction in lean mass, extreme term "sarcopenia" and increased fat are an important indicators of poor health in the general population.[4]

Sarcopenia results from changes in hormonal and immunological phenomenon that occurs with aging. Cytokines, particularly tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are believed to increase muscle loss.[4] Studies have shown that chronic inflammatory diseases lead to sarcopenia. It is believed that the inflammatory cytokines TNF-α and interleukin-1β (IL-1β) play a pivotal role in pathogenesis of RA.[6] Given that TNF-α is elevated in RA, one could propose that RA may cause and accelerate the progression of sarcopenia.

The prevalence of sarcopenia varies across populations and according to the definitions and cut-offs used, prevalence of 3% to 24% have been reported in individuals older than 65 years. Another study from Japan stated that the prevalence of sarcopenia was 37.1% , with 49.0% classified as having low muscle mass among the patient with Rheumatoid Arthritis.[7] The present study will assess sarcopenia and serum TNF-alpha in patients with Rheumatoid Arthritis attending outpatient department or getting admitted in Department of Medicine, Assam Medical College & Hospital and study the correlation of serum TNF-alpha with disease activity.

2. METHODOLOGY

AIM:

To assess sarcopenia and serum TNF-alpha in patient with Rheumatoid Arthritis.

OBJECTIVES

1. To assess sarcopenia by DEXA Scan
2. To assess TNF-alpha via the sandwich ELISA principle
3. To study the correlation of serum TNF-alpha level with disease activity and sarcopenia.

Inclusion Criteria:

1. Patients with Rheumatoid Arthritis as per 2010 revised American college of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria.
2. The patients of age 12 years and above.
3. The patients with informed consent.

Exclusion Criteria

1. Patients with co-morbidities like Diabetes Mellitus, Chronic Kidney Disease, Chronic Liver Disease, Human Immunodeficiency Virus infection, Malignancy, Tuberculosis, Chronic Pancreatitis and Chronic Obstructive Pulmonary Disease and Cognitive dysfunction
2. Pregnancy
3. Current arthritis or deformity in dominant hand joints

Study Design :
Hospital Based Comparative Observational Study

Place of Study :
Assam Medical College and Hospital, Dibrugarh

Duration of Study :
The study was conducted over a period of one year from 1st June, 2020 to 31st May, 2021

Study Population:
All the patients with Rheumatoid Arthritis, aged 12 years or above, diagnosed by the 2010 American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria attending Medicine and Rheumatology OPD or admitted in the Department of Medicine in Assam Medical College, Dibrugarh satisfying the inclusion criteria.

Sample Size:
Considering 95% Confidence Interval with a power of 90% and proportion of sarcopenia in rheumatoid arthritis and in healthy individual to be 43.3 and 10 % respectively[5], the sample size was calculated and rounded off to be 40 in each group.

Method Of Collection Of Data:
Data was collected from patients of rheumatoid arthritis admitted in AMCH after written informed consent. All RA patients were diagnosed by the 2010 American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) Classification fulfilling the inclusion and exclusion criteria were taken up for the study. A proforma was prepared which included detailed history, clinical examination and requisite investigations available in our hospital. A detailed clinical history, thorough general and systemic examination with required investigations were done.

Diagnostic Criteria For Sarcopenia
- Asian Working Group For sarcopenia (2019)
- ASM/height^2 -- Men-7 kg/m^2, Women-5.4 kg/m^2
- Appendicular skeletal mass (ASM) was obtained from DEXA scan

Appendicular Skeletal Mass (ASM) measurement:
ASM was measured by dual-energy x-ray absorptiometry (DEXA). Dual energy X-ray absorptiometry is a technique which can distinguish different body structures by using two X ray beams of different energy levels. It is the modality of choice for measuring bone mineral density and total body composition.

Principle of DEXA:
It is a fast, reliable, noninvasive technique with little radiation exposure and is considered as gold standard for diagnosis of osteoporosis. It is based on variable absorption of x-ray by different body components and uses high & low energy x-ray photons. It acts by two mechanisms depending on the equipment used:
- Generator emitting alternating high (140) kvp & low (70-100) kvp.
- Generator emitting a constant beam where a rare-earth filter separate high from low energy photons.

Procedure:
ASM along with BMD was measured by Dual-Energy X-ray Absorptiometry (DEXA) installed in Department of Medicine. Then they were advised to remove all the metallic belongings including ornaments or any electronic gazettes and were advised to wear loose clothes then properly placed on the DEXA machine The patient lied supine with arm by the side. A full body scanning was done for each subject and the results obtained for each subject were duly recorded and were expressed as:
(a) Appendicular Skeletal Mass in kg
(b) Total Body Bone Mineral Density (TB-BMD) as T-score

Measurement of Serum TNF-α:
TNF α estimated by ELISA method. 2 ml of venous sample was collected in clot activated vial and allowed to clot for 1 hour at room temperature and centrifuged for 20 minutes at 1000×g at 2-8°C. Sera with particles were cleared by low-speed centrifugation (<1000 RPM). Samples were collected in clean, dry and empty tubes. After separation of serum, Samples were stored -80°C. Hemolyzed or turbid or lipemic samples were avoided.

Statistical Analysis
Descriptive statistical analysis has been carried out in the present study. Quantitative data were expressed as mean ± standard deviation (S.D). Qualitative data were expressed as number and percentage. Qualitative data were analyzed using Chi-square ($\chi 2$) test. Pearson's correlation coefficient (r) was used to measure correlation between quantitative variables. Significance was assessed at 5% level of significance ($p < 0.05$). The statistical analysis of all the data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 20.0 Chicago, SPSS Inc.) and Microsoft Excel 2010.

3. RESULTS

Table 1: Age distribution of the study participants

Age (in years)	Cases		Controls	
	N	%	n	%
13-25	3	7.5	1	2.5
26-35	5	12.5	5	12.5
36-45	18	45	14	35
46-55	10	25	14	35
56-65	4	10	6	15
TOTAL	40	100	40	100
Age: Mean ± SD	44.25±10.67		45.36±10.20	

Table 2: Sex distribution of the study participants

Gender	Cases		Controls	
	N	%	n	%
Male	10	25	9	22.5
Female	30	75	31	77.5
Total	40	100	40	100

Table 3: Comparison of baseline parameters in cases and controls

Comparison Of Baseline Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
ASM (kg)	14.48	3.60	16.33	4.39	0.041
ASM/Height2 (kg/m2)	5.99	1.13	6.71	1.23	0.008

Table 4: Distribution of Sarcopenia in Cases and Control

Sarcopenia	Cases		Control		Odd Ratio	p value
	N	%	n	%		
Present	18	45	5	12.5	5.727	0.002
Absent	22	55	35	87.5		
Total	40	100	40	100		

p value is calculated using Chi Square Test.

Table 5: Duration of Disease in RA patient with and without sarcopenia

Variables	With Sarcopenia	Without Sarcopenia	p value
Duration of Disease in cases (in years)	14.78(±6.61)	6.77(±2.22)	<0.001

- All values are presented as Mean (±SD).
- p value is calculated using independent t test

Table 6: Disease activity (DAS28 ESR score) in RA patient with and without sarcopenia

Variables	With Sarcopenia	Without Sarcopenia	p value
DAS28 ESR	4.32±1.17	3.64±0.99	<0.056

- All values are presented as Mean±SD
- p value is calculated using Independent t test

Table 7: TNF-alpha in cases and controls

Variable	Cases	Controls	p value
TNF-α (pg/ml)	20.13±14.89	15.97±2.82	<0.001

- All values are presented as Mean±SD.
- p value is calculated using independent t test.

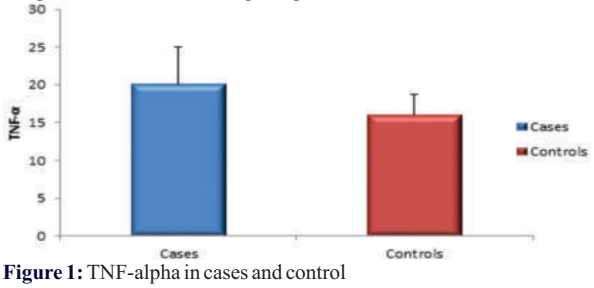

Figure 1: TNF-alpha in cases and control

Table 8: TNF-alpha in RA cases with and without sarcopenia

Variable	RA with sarcopenia	RA without sarcopenia	p value
TNF-α (pg/ml)	23.04±5.68	17.75±2.25	<0.001

- All values are presented as Mean ±SD.
- p value is calculated using independent t test.

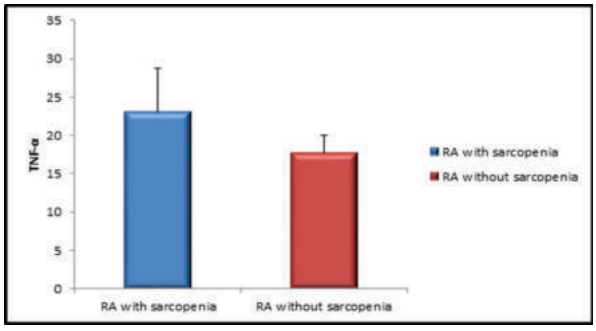

Figure 2: TNF-alpha in RA cases with and without sarcopenia

The mean TNF-alpha for RA cases with sarcopenia was 23.04±5.68 pg/ml and that of RA cases without sarcopenia was 17.75±2.25 pg/ml (p <0.001).

Table 9: Correlation between Das-28 ESR & TNF-α in RA cases with Sarcopenia

Variable	TNF-α	
	r value	p value
DAS28 ESR	0.858	<0.001

r value calculated by Pearson correlation

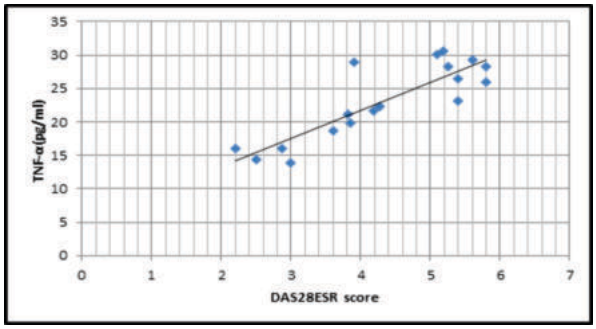

Figure 3: Correlation between Das-28 ESR & TNF-α in RA cases with Sarcopenia

Table 10: Correlation between Das-28 ESR & TNF-α in RA cases without Sarcopenia

Variable	TNF-α	
	r value	p value
DAS28 ESR	0.184	0.411

r value calculated by Pearson correlation.

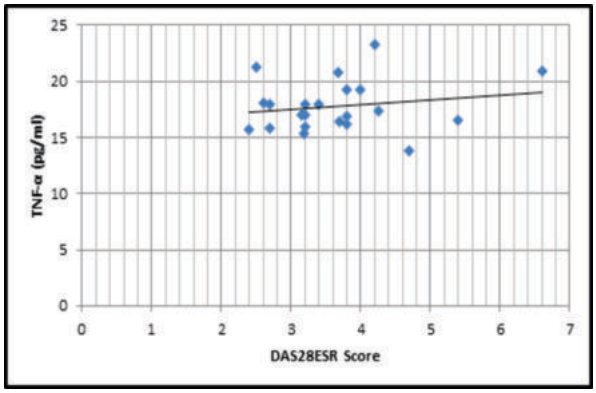

Figure 4: Correlation between Das-28 ESR & TNF-α in RA cases without Sarcopenia

4. DISCUSSION

In the study population of 40 cases and 40 controls, the mean age of cases and controls were 44.25±10.67 and 45±10.20 years respectively. Majority (45%) of cases belonged to 36-45 years of age. Doğan SC et al, Barone M et al and Giles J T et al also found similar results with a mean age of 47.70 ±5.49, 56.5±8.8, 59.9±8.4 years respectively.[4,8,9] Female preponderance was seen in our study (75%), as was also found in studies by Vlietstra L et al., Tekgoz E et al.[10,11]

In our study, the mean value of ASM was 14.48(±3.60) kg and 16.33±4.39 kg in cases and controls respectively. The mean value of ASM/Height^2 was 5.96±1.13 in cases and 6.71±1.23 in controls. The difference was statistically significant with p value <0.005.

We found that 45% of the patients with RA had sarcopenia and the same was 12.5% in control group. Among the men with RA, 80% had sarcopenia while in control it was 20% whereas among females with RA, 33.33% had sarcopenia and among controls without RA it was 9.68%. This finding was similar to the below mentioned studies.

Tekgoz E et al in a study, the prevalence of sarcopenia was in RA cases to be 35% and 9% in in controls.[11] Doğan SC et al 2015, reported a prevalence of sarcopenia 43.3% in female RA cases and 10% in controls.[4] Gilies J T et al 2008, reported a prevalence of sarcopenia in RA females to be 21.4% and that in female controls without RA to be 7.7%.The prevalence of sarcopenia in RA males and that in male controls without RA was 33.3% and 16% respectively.[9] Ngeuleu1 A et al 2017, reported 39.8% (out of 49 subjects) of RA cases to be suffering from sarcopenia. Of 49 subjects, 40 were female.[12] Manzano W et al 2021, mentioned 31% prevalence of sarcopenia in rheumatic disease.[13]

In this study majority of the patient (27.78%) having sarcopenia had disease duration of 16-20 years. The mean disease duration in RA patients with and without sarcopenia was 14.78(±6.61) years and 6.77(±2.22) years (p-value=<0.001). The findings were similar to Barone M et al 2018 who found the mean disease duration in RA patients with and without sarcopenia to be 13.4±9.8 and 10.9±7.7 respectively.

In the study, the mean TNF-α was 20.13±14.89 pg/ml in cases and 15.97±2.82 pg/ml in controls (p<0.001). The mean TNF-α for cases with sarcopenia were 23.04±5.68 pg/ml and that of controls with sarcopenia was 17.30±2.32 pg/ml (p=0.040). The mean TNF-α for RA cases without sarcopenia was 17.75±2.25 pg/ml.

Thilagar et al, found the mean TNF-α to be 17.9 ± 3.6 in RA group when compared to control (5.5 ± 3.3).[14] Gunaydin R et al 2014, also found TNF- α level was higher in RA patients (37.16±25.76 pg/mL) when compared with control (25.27±11.52 pg/mL).[15]

A statistically significant positive correlation was found between DAS28 ESR score and serum TNF-α level in RA cases with sarcopenia (r=0.858, p<0.001). However, although a positive correlation was found between DAS28 ESR score and serum TNF-α level in RA cases without sarcopenia, it was statistically insignificant. (r=0.184, p=0.411)

Visser M et al 2013, showed that higher plasma concentrations of IL-6 and TNF-α are associated with lower muscle mass and lower muscle strength in well-functioning older men and women.[16] Ngeuleu A et al 2017, found a significant relationship between DAS 28 ESR and sarcopenia in men(p value =0.03) but not in women(p value=0.74).[12]

5. Limitations Of The Study

There were certain limitations in the present study such as small study population, shorter duration of the study and missing out on some of the eligible cases because of limited human resources and time constraints. Further large-scale studies are required to validate our study. The effect of drug was not included in the study because of high variability of drug combination, duration and dosage among the patient. The correlation of drug compliance and physiotherapy with sarcopenia also may have provided us some valuable insight into the disease which we plan to include in future assessments. Patient with active arthritis were excluded from the study.

6. CONCLUSION

The science of Rheumatoid Arthritis has taken major leaps forward by illuminating new disease related genes, environmental interactions and a remarkable improvement in its outcomes. The crippling arthritis of year's past is encountered much less frequently today. Our study showed that ASM/height^2, which is a indicator of sarcopenia, were significantly lower in patient with Rheumatoid Arthritis. Hence, the patients with Rheumatoid Arthritis are at an increased risk of Sarcopenia.

There is significant correlation between Rheumatoid Arthritis and sarcopenia in terms of duration of disease, disease activity, ESR, malnutrition, bone mineral density and TNF-α. It was seen that the serum TNF-α correlated positively in patients with increasing disease activity in RA patient with and without sarcopenia however it was significant statistically in patient with RA having sarcopenia.

Further studies are needed for better understanding of sarcopenia to clarify its role in Rheumatoid Arthritis and to develop therapeutic strategies.

7. Conflicts Of Interest: Nil

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