SARCOSPA - Sarcopenia in spondyloarthritis patients

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ABSTRACT

Introduction: The loss of muscle mass (MM) is a serious problem which has been demonstrated in patients with rheumatoid arthritis. There are few studies about the loss of MM in patients with spondyloarthritis (SpA).
Objective: To assess muscle mass index (MMI) in a cohort of patients with SpA and compare it with a control group of healthy individuals; to verify if a higher risk of sarcopenia is related with disease activity, functional impairment, duration of the illness and radiological damage.
Methods: Case control study. Muscle mass index (MMI) was determined, from the value of MM, using Lee's equation, in a cohort of patients with spondyloarthritis and in a control group. Bath Ankylosing Spondylitis Disease Activity and Function Indexes (BASDAI and BASFI), Ankylosing Spondylitis Quality of Life (ASQoL) and Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) were assessed in a cohort of patients with axial SpA, as well as Health Assessment Questionnaire (HAQ) and Disease Activity Score 28 (DAS28) in patients with peripheral disease. Data were treated using SPSS version 17.0. Values of $p<0,05$ were considered with statistical significance.
Results: 60 patients were enrolled; 48.2% were males, mean age 45.5±13.4 years, mean disease duration 10.9±11.6 years; 36 had ankylosing spondylitis (AS) and 24 had psoriatic arthritis. 62% of patients had sarcopenia and there was a significant difference in mean MMI between patients and controls (7.65±0.98 vs 8.25±0.92; $p=0.001$, OR =5.23. In male patients, there was a statistically significant moderate negative correlation between MMI and BASDAI and BASFI ($p=-0.536$ and $p=-0.445$). No other significant correlations were identified.
Conclusion: Our study supports the hypothesis of a greater prevalence of sarcopenia in patients with SpA compared to healthy controls. Some limitations included the sample size, potential confounding factor such the bias of measurement and the use of a non-validated equation to Portuguese population to calculate MM.

Keywords: Sarcopenia; Muscle mass; Spondyloarthritis.

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INTRODUCTION

The loss of muscle mass is a serious problem, frequently associated to ageing or chronic diseases, which can have consequences in addition to the loss of muscle strength, like asthenia, greater predisposition to infections and premature death[1].

In recent years, new definitions of sarcopenia and cachexia have emerged. These are two conditions associated with loss of muscle mass, with different pathophysiological mechanisms. According to the latest definitions, sarcopenia is the loss of muscle mass associated with loss of strength or poor physical condition. Cachexia is a weight loss exceeding 5% in less than 12 months associated with other factors such as loss of muscle strength, fatigue, anorexia, low fat-free mass index or biochemical changes (increase in inflammatory markers, anemia, decreased albumin)[2]. In other words, the loss of muscle mass is called age-related sarcopenia, while the loss of muscle mass that occurs associated with chronic inflammatory diseases, is more often called cachexia. In clinical practice these two conditions are often undistinguishable and occur at the same time. There are different theories about the true pathogenesis associated with loss of muscle mass, but it is known that both in sarcopenia and cachexia, pro-inflammatory cytokines are involved, including tumor necrosis factor-α (TNF-α) and Interleukins (IL)-1 and 61.

In this sense, it is now recognized that certain chronic inflammatory diseases convey a greater risk of loss

of muscle mass. Several studies indicate that about two-thirds of patients with Rheumatoid Arthritis (RA) have associated loss of muscle mass, with stable or slightly increased fat mass, which is called rheumatoid cachexia[3]. In its pathogenesis a number of factors have been identified, such as: excessive production of cytokines and TNF-α, physical inactivity, concomitant therapy with glucocorticoids or reduction of peripheral insulin action. It is known that RA patients have high rates of protein degradation and it is thought that the TNF-α stimulates muscle catabolism, having been described as "sarcoactive", as well as IL-1β, IL-6, interferon and tumor growth factor β (TGF-β)[3-5].

The elevation of pro-inflammatory cytokines, particularly TNF-α, is also present in other rheumatic diseases, in particular in the group of Spondyloarthritis (SpA). So, it is predictable that loss of muscle mass may also occur in these patients. There are few studies about de loss of muscle mass in SpA and those that exist are inconsistent, partly due to different methodologies applied[6-8]. We didn't find any studies correlating radiological changes in SpA patients and the loss of muscle mass.

Therefore, the aims of this study were to evaluate muscle mass index (MMI) in a cohort of patients with SpA; verify if they have higher risk of sarcopenia and if the MMI is related with disease activity, functional impairment, duration of the illness and radiological damage.

MATERIAL AND METHODS

A case control study was run. Cases were patients diagnosed with ankylosing spondylitis (AS) (according to the modified New York Classification Criteria[9]) or psoriatic arthritis (according to the Classification Criteria for Psoriatic Arthritis – CASPAR criteria[10]); controls were individuals recruited from a primary healthcare center. Both cases and controls were aged between 18 and 75. Exclusion criteria were: immobilization for a period longer than 15 days in the last 6 months, palsy of any member and recent steroid therapy (over the last three months) with equivalent daily doses of prednisolone superior than 40 mg/day for longer than one week.

Analysed variables included, for both groups: sex, age, chronic medication and comorbidities potentially contributing to myopathy, and muscle mass. In the group of patients, variables related to the disease were also assessed: disease duration, activity indexes (DAS 28 for peripheral disease and BASDAI for axial disease), function indexes (HAQ and BASFI) and radiological damage (assessed by mSASSS).

Muscle mass (MM) was assessed using Lee's equation[11], which incorporates anthropometric parameters such as height and upper arm, thigh and calf girths, as well as variables such as sex, age and race:

MM = Ht x (0.00744 x CAG2 + 0.00088 x CTG2 + 0.00441 x CCG) + 2.4 x sex - 0.048 x age + race + 7.8

where Ht = height; CAG = skin-fold-corrected upper arm girth, CTG = skin-fold-corrected thigh girth, CCG = skin-fold-corrected calf girth; sex = 0 for female and 1 for male; age is in years; race = -2.0 for Asian, 1.1 for African American, and 0 for white and Hispanic.

The necessary measurements were made during outpatient visits.

Muscle mass index (MMI) can be obtained by a simple formula: muscle mass/height^2.

MMI value is considered normal if ≥10.75 in men and ≥6.75 in women; grade I sarcopenia is defined as 8.51<MMI<10.75 in males and 5.76<MMI<6.75 in females; grade II sarcopenia is defined as a MMI <8.51 in men and <5.76 in women.

Statistical analysis was performed using SPSS version 17.0. Kruskall-Wallis test was used to compare continuous variables among the two groups; Spearman's correlation was used to identify potential associations among continuous variables.

RESULTS

Both the patients and controls samples had 60 age-matched individuals. In the patients' group, 48.2% (n=29) were males versus 43.3% (n=26) in the controls' group and mean age was, respectively, 45.5±13.4 and 44.9±14.1 years (p=0.796) (Table I). All patients and controls were Caucasian.

As medical history, 11 patients had significant history of at least one possible muscle wasting disease (4 with thyroid disease, 6 with diabetes mellitus, 2 with knee osteoarthritis and 1 with rotator cuff tendonitis), while that number increased to 21 in controls group (7 with thyroid disease, 7 with diabetes mellitus, 8 with knee osteoarthritis and 2 with rotator cuff tendonitis) (Table I). Current treatment with statins was observed in 11 patients and in 18 controls, and 3 patients and 1 control were under corticosteroid treatment in low dose (<10mg/day).

Amongst patients, 36 had ankylosing spondylitis (21

TABLE I. DESCRIPTION OF PATIENTS AND CONTROLS

	Patients	Controls	
M:F	29:31	26:34	p=0.796
Mean age (years)	45.5±13.4	44.9±14.1	
Comorbidities	11	21	
Thyroid disease	4	7	
Diabetes	6	7	
Knee osteoarthritis	2	8	
Rotator cuff tendonitis	1	2	
Disease duration (years)	10.9±11.6		
Diagnosis			
AS	36		
Axial	22		
Axial + Peripheral	14		
PsA	24		
Axial	1		
Peripheral	18		
Axial + Peripheral	5		
Axial disease (n=42)			
Mean BASDAI	3.47±2.67		
Mean BASFI	3.24±2.69		
Mean mSASSS	8.48±12.06		
Peripheral disease (n=37)			
Mean DAS28	2.78±1.16		
Mean HAQ	0.42±0.58		

TABLE II. MMI IN PATIENTS AND CONTROLS (MALES AND FEMALES)

	MMI	p
Patients	7.65±0.98	0.001
Controls	8.25±0.92	
Male patients	7.79±0.94	0.016
Male controls	8.84±1.00	
Female patients	7.52±1.00	0.012
Female controls	8.11±0.83	

TABLE III. SARCOPENIA IN PATIENTS AND CONTROLS

	Patients	Controls	OR
Normal	12	34	5.23
Sarcopenia	48	26	
Grade 1 sarcopenia	23	12	
Grade 2 sarcopenia	25	14	

with axial disease, 14 with axial and peripheral involvement and 1 with axial and enthesopatic disease) and 24 had psoriatic arthritis (1 with axial disease, 18 with peripheral involvement, 5 with both axial and peripheral disease; enthesopathy was present in 2 patients). Mean disease duration was 10.9±11.6 years.

In patients with axial disease, mean BASDAI was 3.47±2.67, mean BASFI was 3.24±2.69 and mean mSASSS was 8.48±12.06. In peripheral disease, mean DAS28 was 2.78±1.16 and mean HAQ was 0.42±0.58 (Table I).

Mean MMI was significantly different in both groups: 7.65±0.98 in the cases group (7.79±0.94 in males and 7.52±1.00 in females) and 8.25±0.92 in control group (8.84±1.00 in males and 8.11±0.83 in females) (p=0.001). This statistically significant difference was also observed when males and females were analysed separately (Table II).

Sarcopenia was more common among patients comparing to controls (61.7% *vs* 43.3%), as shown in table II, with an odds ratio (OR) of 5.23 (p <0.01) (Table III).

However, the adjusted OR for the presence of comorbidities is not statisticaly significant (p= 0.055).

There was no significant difference in MMI between patients with ankylosing spondylitis and psoriatic arthritis (p=0.323) nor between patients with axial, peripheral or both types of involvement (p=0.894). These findings were reproducible in the subsets of male and female patients.

MMI didn't significantly correlate with disease duration (ρ= -0.220, p>0.05).

In patients with axial disease, no significant correlation was found between MMI and BASDAI, BASFI or mSASSS (ρ= -0.111, p>0.05; ρ= 0,131, p>0.05 and ρ= -0.130, p>0.05, respectively); when separate analysis by sex was made, in male patients the MMI showed a statistically significant moderate negative correlation both with BASDAI and BASFI (p=-0.536 and p=-0.445, respectively). (Table IV)

In patients with peripheral disease, no significant correlation was found between MMI and DAS28 or HAQ (Table V).

Concomitant possible muscle wasting medication didn't influence MMI neither in the patients group (p=0.708) nor in the control group (p=0.908).

DISCUSSION

As noted above, the scarcity of studies focusing on sar-

TABLE IV. CORRELATION BETWEEN MMI AND BASDAI, BASFI AND MSASSS, IN SPA PATIENTS WITH AXIAL DISEASE, DEFINED BY SPEARMAN'S COEFFICIENT

	MMI (Males, n= 20)	p	MMI (Females, n=22)	p	MMI (Total= 42)	p
BASDAI	ρ= -0.536	0.015	ρ= 0.183	0.415	ρ= -0.111	0.482
BASFI	ρ= -0.445	0.049	ρ= 0.104	0.654	ρ= -0.131	0.413
mSASSS	ρ= -0.265	0.458	ρ= 0.033	0.373	ρ= -0.130	0.250

TABLE V. CORRELATION BETWEEN MMI AND HAQ, AND BETWEEN MMI AND DAS28, IN PATIENTS WITH PERIPHERAL DISEASE, DEFINED BY SPEARMAN'S COEFFICIENT

	MMI (Males, n=19)	p	MMI (Females, n=18)	p	MMI (Total, n=37)	p
DAS28	ρ= -0.434	0.158	ρ= -0.048	0.876	ρ= -0.224	0.282
HAQ	ρ= -0.149	0.662	ρ= -0.180	0.555	ρ= -0.168	0.434

copenia in patients with spondyloarthritis is striking if compared to patients with other inflammatory joint diseases such as rheumatoid arthritis.

Even though our cohorts were small, there was an unequivocal difference on MMI in both groups. Patients with spondyloarthritis had a decreased MMI compared to controls, and no significant difference on MMI was found between ankylosing spondylitis (AS) or psoriatic arthritis patients. Notably, except for the case of BASDAI and BASFI in males with axial involvement, MMI didn't correlate with disease activity, function or radiological indexes. A longer history of disease didn't seem to condition a greater loss of MM. Eventually, a greater sample of patients could provide different conclusions.

The results obtained in our study are in agreement with those from Marcora et al[6], in whose study the loss of muscle mass was evaluated by dual-energy X-ray absorptiometry (DXA) in a group of patients with long-standing AS and radiological changes. They found a significant reduction of appendicular lean mass (6Kg), as well as in functional strength test scores. Other studies found no differences in body composition of patients with AS[7,8]. These discordant results may be related to different criteria for inclusion in the study. For example, Toussirot *et al*.[7] only included patients with early disease; and Dos Santos *et al*[8] excluded patients with syndesmophytes. Our study included patients with early and long standing disease. However, and once again, duration and activity of the disease didn't seem to correlate with reduced MMI. Moreover, not only the heterogeneity in patients' characteristics, but also the size of the cohorts may lead to different conclusions, with greater samples warranting an empowerment of the analysis. In fact, the samples of both patients and cohorts ranged from 19 patients/controls in the study from Marcora *et al*[6] to 71 in the study from Toussirot *et al*[7]. Besides that, the different methods of evaluating lean body mass might account for the conflicting results.

The main limitations of the study were the small number of individuals enrolled and the use of an equation not validated for European individuals. The most precise way to determine body composition is (DXA); some studies have been run in order to evaluate the performance of the existent equations used to determine muscle mass, using DXA values as reference. Des pite the fact that Lee's equation is not an exact method of measuring MM, it has shown to be the one that best correlates with DXA determinations[12-13].

Many questions remain unanswered about sarcopenia in patients with chronic inflammatory joint diseases. One of them relates to the underlying mechanisms: inflammation plays a role of upmost importance, but since different cytokines profiles underlie different diseases, the role of some singular inflammatory mediators is still unknown. Another relevant question is: is muscle loss a consequence or a contributive factor to the disease in spondyloarthritis? Cooper *et al.* pointed that paraspinal muscle fibrosis might be a specific pathological component of ankylosing spondylitis[14]; Hopkins *et al* showed similar findings in peripheral muscle biopsies, and both authors suggest that these muscle changes may account for some of the clinical features of the disease[15]. Besides that, it is also yet a matter of discussion if different the-

rapies may improve patient's muscle mass and strength; some studies have reported an increase in body weight, fat mass and lean mass in RA, psoriasis and spondylarthritis patients treated with anti--TNF[16-18]. However, the effect of some other traditional disease modifying anti-rheumatic drugs on sarcopenia in patients with inflammatory joint disease is still unknown.

CONCLUSION

In our small cohort, patients with spondylaoarthritis showed a decreased MMI compared to sex and age-match control individuals and a double risk of sarcopenia.

The existing studies are scarce and with small numbers of patients. Even though a correlation between sarcopenia and spondyloarthritis may be suspected, the role of muscle in the disease remains unknown – is sarcopenia a consequence or a part of the physiopathology?

The authors intend to highlight the need of further studies to elucidate the meaning of the muscle mass loss in spondyloarthritis.

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