

Original Article

Application of current sarcopenia definitions in spinal cord injury

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Abstract

Objective: Little is known about how appropriate the working definitions of sarcopenia are in subjects with spinal cord injury (SCI). This study aimed to evaluate the application of current sarcopenia definitions in SCI. **Methods:** We compared 31 complete SCI men with 33 able-bodied age matched subjects. All were examined by whole body DXA (Norland XR 36, USA) regarding muscle and fat mass and by peripheral quantitative computed tomography (pQCT XCT-3000, Germany) in 66% of tibia's length (muscle cross sectional area, (CSA) in mm²). Low muscle mass was defined by skeletal muscle index, (SMI= appendicular lean mass (aLM)/height² in Kg/m²) and by the residual method: relative aLM, 20th percentile of the distribution of residuals as the cutoff point, (RASM), respectively. CSA is a surrogate for force. **Results:** We found lower values on RASM (p<0.001), and SMI (p<0.001) compared to controls in SCI and difference in the rate of sarcopenia according to sarcopenia definitions. CSA was significantly decreased in SCI (p<0.001) and correlation with duration of paralysis was weak. **Conclusion:** Current functional definitions of sarcopenia classify different individuals as sarcopenic. Sarcopenia was more prevalent in SCI. The sensitivity and specificity of using these measurements in SCI remain unclear.

Keywords: Sarcopenia, Spinal Cord Injury, Cross Sectional Muscle Area, pQCT, Whole Body DXA

Introduction

Spinal cord injury (SCI) causes suddenly an immobilisation associated with regional profound changes in the body composition including mainly loss of lean tissue mass (LM) and bone but gain in fat mass (FM)^{1,2}. Sarcopenia, an agerelated loss of muscle mass and power has recently been recognized as a disease and since September 2016 received code ICD 10: M62.84³. The European Working Group on Sarcopenia in Older People (EWGSOP) developed a definition and consensus diagnostic criteria for age-related sarcopenia

using both low muscle mass and low muscle function (strength or performance). The EWGSOP categorized sarcopenia according to the cause, in primary-age related and secondary sarcopenia. The secondary has further been subdivided in: related to physical activity (e.g. after prolonged bed rest, low physical activity, sedentary life style), related to some diseases (e.g. advanced organ failure, inflammatory diseases, malignancy, endocrinopathy, etc.) and lastly, related to nutrition (e.g. insufficient diet, malabsorption, gastrointestinal disorders, and drug induced anorexia)⁴.

The pathophysiology of sarcopenia in SCI is complicated⁵. Deconditioning occurs in any muscle that is not moved daily and thus, the presence of a physical disability can set the occasion for deconditioning; SCI causes inactivation and, consequently, unloading of affected skeletal muscle. The danger of decline in capacity for physical activity begins immediately after the injury. Disuse, spasticity and microvascular damage, contribute to the induction of the marked morphological and enzyme histochemical changes seen in the paralyzed skeletal muscle leading to altered functional properties

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| Table 1. Anthropometric values and measured parameters of study's population. All values are mean \pm SD. BMI, body mass index; CSA, |
|--|
| cross-sectional area; SMI (aLM (Kg) /ht (m)²); kg, kilograms; m, meters. |

| Measured pa | arameters | mean | SD | p-value |
|-------------------------|------------|---------|-------|--------------|
| Age (years) | Paraplegic | 39,23 | 15,76 | 0.504 |
| | Control | 36,88 | 18,97 | 0.594 |
| Height (m) | Paraplegic | 1,76 | ,08 | 0.700 |
| | Control | 1,77 | ,07 | 0.700 |
| Weight (Kg) | Paraplegic | 74,19 | 13,09 | 0.034 |
| | Control | 81,36 | 13,32 | 0.034 |
| BMI (Kg/m²) | Paraplegic | 23,87 | 3,02 | 0.030 |
| | Control | 26,12 | 4,38 | 0.020 |
| SMI (aLM (Kg) /ht (m)²) | Paraplegic | 5.53 | 0.84 | 10.001 |
| | Control | 8.40 | 1.29 | <0.001 |
| CSA (mm²) | Paraplegic | 5327.31 | 1640 | 40.001 |
| | Control | 8028.7 | 1136 | <0.001 |
| Total Lean Mass (Kg) | Paraplegic | 42.2 | 6.5 | <0.001 |
| | Control | 56.6 | 8.8 | |
| Total Fat Mass (Kg) | Paraplegic | 23 | 9.4 | <0.05 |
| | Control | 19 | 6.5 | NO.05 |

and atrophy. Motoneuron death and muscle denervation must contribute to the severe atrophy that is measured in muscles after SCI. Malabsorption leads to protein deficits and muscle catabolism. Hormonal disturbances of the thyroid, hypercortisolism and insulin resistance lead to sarcopenia resulting from protein deficiency^{6.7}.

Muscle cross-sectional area (CSA) declines from 1 to 17 months after injury and thereafter reaches nadir. Conversion to type II fibers has been suggested to occur between 4 months and 2 years after SCI, resulting in even slow-twitch muscle becoming predominantly fast twitch thereafter. However, these changes may not apply for upper extremity muscles in paraplegic patients⁸.

Diagnostic assessment of muscle mass means specific anthropometric, biological, densitometry and imaging studies. Whole body dual-energy X-ray absorptiometry (DXA) measurement remains the gold standard for muscle mass measurements. DXA allows a valid quantitative assessment of the skeletal muscular mass of the four limbs called appendicular skeletal muscle mass (ASM). Sarcopenia is then defined with ASM/height² or skeletal muscle mass index (SMI) in weight per meter² (kg/m²). In the New Mexico Aging Process study, sex specific cut points for kg/m² were defined as values that were two standard deviations (SDs) below the mean of a healthy young adult population, like the method used to define osteoporosis9.

However, to define sarcopenia in older subjects' muscle strength or physical performance assessment are also needed, in example measurements such as hand grip strength or gait speed, Short Physical Performance Battery test (SPPB) etc. Although muscle mass does not predict muscle strength or physical performance, is significantly correlated

with these parameters and is contributed to disability and frailty in old people^{10,11}.

An alternative validated measurement of force in SCI would be muscle cross-sectional area (CSA). It has been proposed as a surrogate for muscle effectiveness or loading (force)¹². Bone mass responds to the forces placed upon it, it has become common to use mass- or size-based surrogates of muscle force capacity¹³. Cross-sectional muscle area (CSA) derived from peripheral quantitative computed tomography (pQCT) scans are often used as a surrogate for muscle force¹⁴. In subjects with complete SCI muscle CSA, does not depend on motor function of the lower limbs¹⁵.

There are no guidelines or even recommendations about sarcopenia in spinal cord injury (SCI). The study is investigating the suitability to apply in spinal cord injured subjects the current definition of EWGSOP for sarcopenia.

Material and methods

Study population

Thirty-one men with complete paraplegia, (American Spinal Injury Association Impairment Scale, AIS A, Thoracic (T)4-T12 neurological level of injury, mean age 39.23 ± 15 years (yrs.), duration of paralysis: 5.7 ± 5 years, were compared with 33 age matched able bodied men (controls). Anthropometric data of our study population are presented in Table 1.

Study protocol

Whole body dual X-ray absorptiometry (NORLAND X-36, Wis., USA) was used for estimation of regional-appendicular (upper and lower limbs) lean mass (aLM, kg) and total

fat mass (FM, kg). All subjects of both groups were also examined by peripheral quantitative computed tomography system (pQCT XCT-3000, Stratec Medizintechnik, Germany) in midshaft of the tibia. Measurements were performed at the left tibia (one leg study). The distal end of the tibia was used as an anatomical point. From the shaft scans muscle cross sectional area (muscle CSA, mm²) was determined with a single slice taken at 66% of the tibia length proximal to the ankle joint where muscle CSA is maximal. Technical details are described elsewhere¹6.

This study was carried out in the 2nd Rehabilitation department of the National Rehabilitation Center "EIAA" (now called EKA-KAT) in Athens, in cooperation with the Laboratory for Research of the Musculoskeletal system in the University of Athens, in KAT Hospital and the Radiology department of the National Rehabilitation Center "EIAA" in Athens. The protocol was designed according to the Declaration of Helsinki and approved by the Ethics Committee of Athens University. All subjects gave written informed consent to be included in this study. A more detailed description of the protocol and inclusion/exclusion criteria are presented here².

Definitions of sarcopenia

The component of low muscle mass in sarcopenia definition was initially defined by skeletal muscle index (SMI). SMI was calculated using the index (aLM/ht² in Kg/m²) proposed by Baumgartner, and sarcopenia was defined as values that were two standard deviations (SDs) below the mean from our able-bodied population (controls)9. The cut point of $5.8 \, \text{kg/m²}$ for definition of sarcopenia (2SD below 8.4 ± 1.3 , which was the mean SMI value from our control, SMI para) was lower than Baumgartner's values previously reported of $7.26 \, \text{kg/m²}$ as cut off point in men (Table 2).

To investigate our sample further, instead of comparing index values with a cutoff from our control population, participants were classified as sarcopenic if their value fell into the specific lowest 20% of the distribution of the index SMI as relative appendicular skeletal mass (RASM). The cut off in this case was 5.28. Further to this approach of relative aLM measurement we performed an adjustment for fat mass in addition to height, a method first published by Newman et al.¹⁷. Linear regression was used to model the relationship between aLM on height (meters) and fat mass (Kg). The residuals (RASM 2) of the regression were used to identify those who's LM was much lower or higher than the predicted value. A positive residual would indicate a relatively muscular individual, whereas a negative a sarcopenic one. The 20th percentile of the distribution of residuals was used as the cut point for sarcopenia (-5.20). Separate model was fit for men in our study (aLM (kg): -17.83 + 24.29 x height (m) -0.31 x total fat mass (kg)).

The component of muscle strength and/or physical performance of the definition was measured with muscle cross sectional area (CSA) in mm². This method has been proposed as a surrogate for muscle effectiveness or loading (force), which is already proven in children and healthy

population and using peripheral quantitative computed tomography (pQCT) is obtained with a single slice at 66% of bone length (i.e. tibia), where it is maximal. In subjects with complete SCI muscle CSA, does not depend on motor function of the lower limbs, or other factors such as mood and fatigue¹⁵.

Statistical analysis

Descriptive statistics (means, SDs, proportions) were used to describe demographic and key clinical characteristics of the study population. Linear regression was used to model the relationship between RASM on height (meters) and fat mass (kg). The 20th percentile of the distribution of residuals was used as the cut point for sarcopenia. All assumptions of linear regression analysis (homoscedasticity, linearity, normality and independence of error terms, as well as multicollinearity of independent variables) were examined. Prevalence of sarcopenia was determined, and scatter plots of the two indices of sarcopenia were used to show the correlation and the degree of overlap between them. All tests were two-sided, a p-value of <0.05 was used to denote statistical significance. All analyses were carried out using the statistical package SPSS version 17.00 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, III., USA).

Results

The 64 participants in the present analysis included 48.4% spinal cord injured paraplegics (SCI-paraplegics) and 51.6% controls. Controls had higher values of lean mass than SCI-paraplegics. Total fat mass was higher in SCI-paraplegics than controls (Table 1). Between groups, controls had higher mean values for aLM/ht² (8.4±1.29 kg/m² for controls vs. 5.53±0.84 kg/m² for SCI-paraplegics). Similarly, controls had higher appendicular lean mass (26.26±4.6 kg) than SCI-paraplegics (17.18±3.14 kg) but also had a higher mean BMI (26.12±4.38 kg/m² for controls vs. 23.9±3 kg/m² for SCI-paraplegics). Groups differed significantly according to muscle CSA. The paraplegic group had significantly less muscle CSA compared with controls (5327.31±1640 mm² in paraplegics vs. 8028.7±1136 mm² in controls, p<0.001) (Table 1).

Using 7.26 cut off 97% (n=30) of spinal cord subjects were classified as sarcopenic vs. 41.9% (n=13) using 5.8 as cut off. This result has an effect to the percent of normal according to sarcopenia classified subjects in paraplegics and controls, 3.2% (n=1) and 58.1% (n=18) vs. 84.8% (n=28) and 97% (n=32), respectively. Interestingly using 7.26 cut off 15% of able bodied subjects in our sample were classified as sarcopenic (n=5) vs. 1 (3%) using 5.8 cut off.

Using the specific lowest 20% of the distribution of the index SMI as relative appendicular skeletal mass (RASM), cut off 5.28, more SCI paraplegics 61.3% (n=19) and only one control were sarcopenic, while 38.7% (n=12) of paraplegics categorized as normal.

Table 2. Classification and percent of subjects as sarcopenic and normal based on SMI cut off * using Baumgartner's Rosetta study and our sample's (SMI para), according to -2SD from the mean SMI value of Rosetta study controls and our study's controls, respectively. Participants were also classified with the specific lowest 20% of the distribution of the index SMI as relative appendicular skeletal mass (RASM).

| | | | Paraplegic | Control | p-value |
|-----------------------|------------|---|------------|---------|---------|
| SMI (cut off 7.26) | Sarcopenia | n | 30 | 5 | <0.001 |
| | | % | 96.8% | 15.2% | |
| | Normal | n | 1 | 28 | |
| | | % | 3.2% | 84.8% | |
| SMI para (cut of 5.8) | Sarcopenia | n | 13 | 1 | <0.001 |
| | | % | 41.9% | 3.0% | |
| | Normal | n | 18 | 32 | |
| | | % | 58.1% | 97% | |
| RASM (Cut off 5.28) | Sarcopenia | n | 19 | 1 | |
| | | % | 61,3% | 3.0% | <0.001 |
| | Normal | n | 12 | 32 | |
| | | % | 38.7% | 97.0% | |

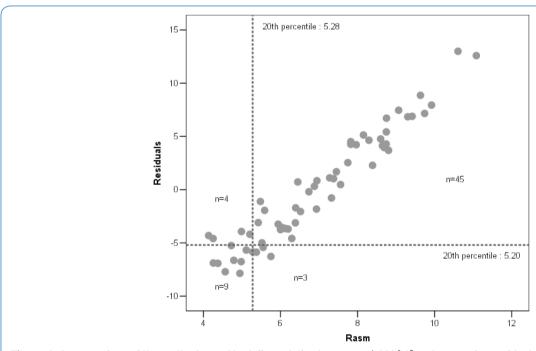


Figure 1. A comparison of the methods used to define relative lean mass (aLM/ht² and regression residuals method including fat mass) in both groups. Residuals (obtained from linear regression of appendicular lean mass (aLM) (kg) on height (meters) and fat mass (kg)) and the ratio (aLM/ht²) of aLM (kg) and height squared (m²). Horizontal and vertical lines indicate the 20th percentile of residuals and aLM/ht² distributions, respectively. Frequencies in each quadrant are indicated by n.

Figure 1 shows a comparison of the methods used to define sarcopenia (aLM/ht² and regression residuals method including fat mass) in both groups. Using either method, subjects falling in the lowest 20th percentile of the distribution were classified as sarcopenic relative to the rest of the analysis sample. The vertical line indicates the 20th percentile RASM and the horizontal line the 20th percentile

for the residuals (RASM 2). Those who would be classified as being sarcopenic (lowest 20th percentile) are those falling to the left of the line for RASM and below the line for the residual score RASM 2.

These definitions of sarcopenia classify a different subset of individuals as sarcopenic, although with some overlap. Nine men (n=9) were classified as sarcopenic (20%) vs. 45

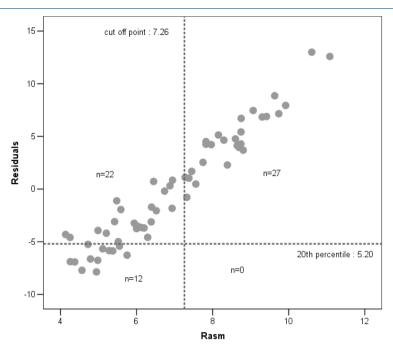


Figure 2. A comparison of the methods used to define relative lean mass (aLM/ht² and regression residuals method including fat mass) in both groups using cut off 7.26 as Baumgartner proposed⁷.Residuals (obtained from linear regression of appendicular lean mass (aLM) (kg) on height (meters) and fat mass (kg)) and the ratio (aLM/ht²) of aLM (kg) and height squared (m²). Horizontal and vertical lines indicate the 20th percentile of residuals and aLM/ht² distributions, respectively. Frequencies in each quadrant are indicated by n.

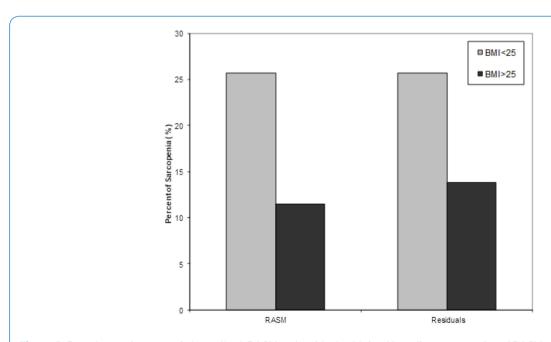


Figure 3. Prevalence of sarcopenia by method, RASM and residuals obtained from linear regression of RASM on height and total fat mass.

as normal (80%) by both methods, with 7 classified by one method and not the other as sarcopenic (Figure 1).

Because the cut off point of 5.8 kg/m² for definition of sarcopenia in our sample group was lower than Baumgartner's

values previously reported of 7.26 kg/m 2 as cut off point in men, we performed an analysis of our sample using the above value of 7.26 kg/m 2 as a cut off for sarcopenia in the whole group. Using this value for sarcopenia we classified a

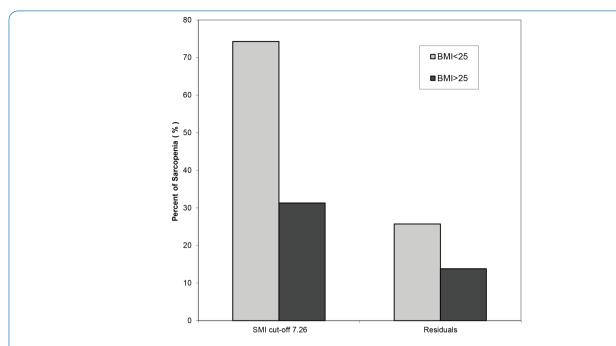


Figure 4. Prevalence of sarcopenia by method, SMI cut-off 7.26 and residuals obtained from linear regression of SMI on height and total fat mass.

Table 3. Analysis of paraplegia with SMI para index adjusted to demographic and clinical indices.

| | Reference category | Beta coefficient | SE | p-value |
|----------------|--------------------|------------------------|-------|---------|
| Constant | | 5,896 | 3,433 | 0.092 |
| Paraplegia | control | -2,741 | ,283 | <0.001 |
| Age | | -,015 | ,009 | 0.084 |
| Height | | -1,313 | 1,867 | 0.485 |
| Total Fat Mass | | -1,02E ⁻⁰⁰⁵ | ,000 | 0.570 |

different subset of individuals as sarcopenic, compared with the former cut off value of 5.28. Thirty-four men (n=34) were classified as sarcopenic (56%) vs. 27 (44.5%) as normal by both methods, with 22 classified by one method and not the other as sarcopenic (Figure 2).

The prevalence of sarcopenia in those who had normal BMI values (BMI<25) vs. overweight or obese (25<BMI>30) also varied according to the definition (Figure 3). Using SMI para index (cut off 5.8) the prevalence of sarcopenia in the overweight and obese subgroups was 14% (n=4), while in normal BMI values was 26% (n=10). Using the lowest 20th percentile of the residuals for LM adjusted for height and total fat mass, the prevalence of sarcopenia in the overweight and obese subgroups was lower (11%, n=3), while in normal BMI values was 25% (n=9). Therefore, when adjusting for height, more thin people would be considered sarcopenic than when accounting for total fat mass and height, and more overweight individuals would be considered sarcopenic.

Same as before, we used also SMI cut off 7.26 to

investigate prevalence of sarcopenia in those who had normal BMI values (BMI<25) vs. overweight or obese (25<BMI>30) (Figure 4). Using this index, the prevalence of sarcopenia in the overweight and obese subgroups was even higher 31% (n=9), while in normal BMI values was 74.3% (n=26).

Muscle CSA with duration of paralysis (DoP) correlation of paraplegic group was weak (r=-0.12, p=0.6). In the adjusted analysis according to age, height and relative fat mass, only paraplegia was associated with lower values of SMI para (beta±se; -2.74±0.28, p<0.001) (Table 3).

Discussion

The purpose of this study was to investigate the suitability of application current definition of EWGSOP for sarcopenia in subjects with spinal cord injury. We presented data using 2 different definitions for assessing low muscle mass and an alternative for muscle strength (force). Using these approaches of defining sarcopenia in

SCI paraplegics with similar functional status, different individuals were classified as sarcopenic. The same is sound in the group of able-bodied subjects.

The cut off point to classify a person as sarcopenic was 5.8 kg/m² using SMI approach or 5.28 using the specific lowest 20% of the distribution of the index. Both values are lower than Baumgartner's values previously reported: 7.26 kg/m² as cut off point in men for sarcopenia9. To this end, except of one case, all SCI paraplegic subjects were classified as sarcopenic. Moreover, 5 controls were found sarcopenic. This result seems reasonable for SCI subjects but it's a paradox for the able -bodied subjects. A possible answer may be found on the characteristics of our control group. With a mean age of almost 37 years and SD of 19 years, it seems that able-bodied subjects were not a typical young group of persons. The one paraplegic found normal because of a short duration of paralysis (=1.5 years) or because of his previous athletic background.

On the other side, when we used SMI para index (cut off 5.8) all controls were classified as normal (except one) and the same did 58% of paraplegics. These were paraplegic subjects with aLM/ht² values above 5.8 Kg/m² but below 7.26 Kg/m². This category is of interest. We are lacking data according to paraplegic population, but it seems that this group is different. Maybe in the future when validated performance measurements will be available we will have a clearer picture.

Moreover, using residual method of the specific lowest 20% of the distribution of the index aLM/ht² (cut off 5.28) we identified 1 more SCI subject as sarcopenic (61.3%) and the percentage of sarcopenic SCI increased by one compared to 5.8 cut-off. This result suggests that both cut-off points can screen sarcopenia in paraplegics with only slight differences.

The hypothesized relationship between sarcopenia and disability was clear established here connecting low SMI with disability (paraplegia). Not age, height and total fat mass, but only paraplegia was associated with significant lower values of SMI para index in this study. However, the research has already proved the contrary. Others have shown that higher fat mass is a more important factor than low lean mass^{18,19} whereas an independent effect of low lean mass on impaired functional status was also found^{9,20}. This is not the case here because in this population both opinions were verified. Using the index of aLM/ht² in the study's population it was possible to classify few of the overweight and obese as sarcopenic (mainly by able-bodied).

For this reason, the second measure (RASM 2) of relative LM was important derived by adjusting for fat mass in addition to height. With this approach, the overestimation of sarcopenia in the thin is reduced and underestimation in the obese, which is important in SCI, is improved. Identification of obese SCI paraplegics is important as evidence identifies body fat as a significant predictor of mortality and many diseases which occur prematurely and at a higher prevalence in this population².

In this study mean BMI in paraplegics was below values considered to signify overweight or obese (BMI>25 kg/

m²). Lower values of BMI were found in paraplegics in comparison with controls. However, some controls (able-bodied subjects) were overweight or obese. On the other site the values of total fat mass in paraplegics' body composition compared with controls using whole body DXA were significantly increased. We have already shown in a previous publication that paraplegics had more total fat mass at any given BMI value than the ablebodied subjects². A normal BMI does not mean that a SCI paraplegic subject is not sarcopenic and this is also the case for an overweight or obese able-bodied subject. Additionally, this method resulted in a higher prevalence of sarcopenia in those who were more overweight, mainly controls, which may be wrong because controls fulfil the criterion of physical performance while paraplegic do not. Moreover, it is under question if the cut-points for underweight, normal, overweight, and obese used in ablebodied populations can be applied to SCI subjects; more studies are needed to define cut-off points of obesity in SCI subjects and analysing the impact injury types and duration of injury on the extent of obesity. One study showed that the current BMI cut-off fails to identify most obese individuals in the SCI population and used lower BMI cut-offs (that is, above 22 kg/m²) to better identify persons with chronic SCI who are obese²¹.

On the contrary the specific 20th percentile was chosen because there are data in the literature supporting this definition and seemed reasonable to us to apply it in our sample based in the issues raised above. The adjusted definition (RASM 2) includes total fat mass of subjects in the equation. Total fat mass is an important parameter in SCI-paraplegics as explained above. It gives a reliable result of obesity or not, compared to BMI. In SCI-paraplegics fat mass is increased significantly regionally, mostly in the trunk, an area not included in the measurement for sarcopenia according to aLM/ht² definition.

More work is needed to validate the optimal criteria for determining a healthy range of LM for a given individual. Potentially sophisticated models will be developed to derive LM from body composition measurements in different parameters. Further, SCI has a complex pathophysiology and the process of estimating is fraught with difficulties that impede the validity of the results. For example, a variety of factors contribute to aLM/ht² for example gender and body composition, phase of injury and level of injury-physical activity. All these stress factors may alter the results.

According to our results muscle CSA in 66% of the tibia's length was significantly lower in paraplegics with a mean duration of paralysis after injury more than 5.5 years vs. able-bodied controls. According to other paraplegic studies total muscle mass decreases by about 9.5% within 6 months, while the muscle mass of the lower limbs is reduced by 15.1% a 1 year after the injury^{22,23}. However, most studies mentioned above used DXA technology, mixed acute and sub-acute populations of paraplegics and tetraplegics or mixed paraplegic populations with spastic

and flaccid paralysis in contrast with our study which included only chronic paraplegic men.

The weak correlation of muscle CSA with DoP in this study lies in the characteristics of the paraplegic group. Paraplegic's muscles with duration of paralysis (DoP) more than 5.5 yrs (see study's sample) were already in steady state according to the literature. In fact, after the first few months, muscle atrophy reaches a steady state, which is likely maintained by the reflex activity of the lower motor neuron (spasms)²⁴.

The prevalence of sarcopenia may varies compared to other studies depending on the criteria, reference populations, and definitions used. Criteria that may help a clinician to identify persons with impaired muscle function are still lacking. First, we need to take in mind that we have at the time being no proper measurement of performance in SCI like old aged subjects, and strength cannot be measured in the hands with dynamometers because would be biased. In people with paraplegia, a handgrip test may be possible, where it would not be in people with tetraplegia. Moreover, wheelchair users' paraplegics develop stronger upper limbs through the training effect of their daily wheelchair activities²⁵.

Different factors may underlie and contribute in varying degree to the loss of muscle strength and loss of muscle mass. Moreover, loss of muscle quality, an important component of the definition of sarcopenia, supposed an assessment of both muscle strength and muscle mass. There is no clear evidence if muscle impairment in SCI can be assessed with the current EWGSOP definition of sarcopenia. Given the fact that probably the criteria of participation and elimination were different in each study, brings into question the credibility of the results and limits the possibility of generalization. This study suggests that we may categorize paraplegics with the current functional definition of EWGSOP for sarcopenia for research purposes. However, the sensitivity and specificity of these measurements remain unclear.

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