"Computed tomography evidence of psoas muscle atrophy without concomitant tendon wasting in early sepsis"

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Abstract

Background: Morphomic studies have demonstrated a correlation between sarcopenia and clinical outcomes in septic patients. However, tendon morphomics has not yet been studied in this context. The purpose of the present study was to evaluate tendon morphology in septic patients through analytic morphomics. We hypothesized that morphomic analyses would reveal concomitant muscle and tendon wasting in sepsis patients. The results of this study may help to implement different rehabilitation modalities for critically ill patients.

Materials and Methods: The volume and fat content of bilateral psoas muscles and tendons were measured on abdominal CT scans of 25 ICU septic and 25 control trauma patients admitted to the University of Michigan between 2011 and 2012. Univariate and multivariate analyses were performed to determine the relationship between psoas muscle and tendon morphometric data, and the association with clinical variables such as smoking and comorbidities.

Results: Average psoas muscle volume was 12.21 ±5.6 cm^3 for control patients and 9.318 ±3.3 cm^3 in septic patients (p=0.0023). The average psoas muscle/fat ratio for septic patients was 0.0288 ±0.071 cm^3, compared to 0.0107 ± 0.008 cm^3 in the control group (p= 0.075). Average tendon volume in the septic population (0.508 ±0.191 cm^3) was not different than the control cohort (0.493 ± 0.182 cm^3) (p=0.692).

Conclusions: Our results demonstrate significantly smaller psoas muscle volume in septic patients than in age, gender and BMI-matched trauma patients but no demonstrable change in

tendon morphology between patient groups. These findings begin to define the boundaries of clinical application within the field of morphomics.

Keywords

Morphomics; Tendon; Sarcopenia; Sepsis; ICU-acquired weakness

Introduction

Muscle wasting in the acutely ill has become a well-established and extensively-studied phenomenon[1-4] that is estimated to occur in 50-100% of septic ICU patients[5-9]. The severity of sarcopenia has been shown to be both a marker for overall patient health status as well as a predictor of patient outcomes[6,10-13]. The biochemical mechanisms behind the physiology of muscle wasting in acute illness are complex and multifactorial [1-4,14,15]. Acute systemic illness leads to inflammation and metabolic derangements resulting in dysregulation of protein metabolism with increased protein degradation and decreased protein synthesis[3]. Moreover, the loss of muscle mass has also been repeatedly associated with increased intramuscular fatty accumulation[16-18].

While the clinical implications of muscle wasting and ICU-acquired weakness are well established, tendon morphology in these acutely ill patients has thus far been unexplored. The tendon attached to the terminal aspect of a sarcopenic muscle (i.e., the psoas major muscle) are subject to the same inflammatory cytokines and metabolic derangements of acute illness and it is therefore reasonable to surmise that tendon tissues would also be adversely affected. In addition, cell sclerasix lineage found in high densities in tendon tissues, have been implicated in both muscle fibrosis and atrophy[19]. Findings of tendon degradation or atrophy in septic patients could have significant implications with development of ICU mobility protocols or rehabilitative efforts. For example, muscle health is often optimized with movement, weight bearing and exercise, while tendon injury is typically treated with weight bearing relief, immobilization and rest. If both muscle and tendon are found to be adversely affected in an acutely ill patient, one might consider reformatting therapeutic or rehabilitative efforts.

Morphomics has recently emerged as a technique for measuring morphological characteristics of biological systems in 3 dimensional space [20-23]. This measurement tool was first utilized as a predictor of patient outcomes based on the quantification of trunk muscle area using computed tomography (CT) scans. Specifically, the psoas major muscle volume has since been shown to be a predictor of patient functional status, postoperative morbidity, length of stay, cost of care, and overall mortality for surgical patients[10,24-26]. Morphomics has subsequently been used in a variety of clinical contexts with applications across the pediatric[27], geriatric[28], oncologic[29-32], endocrinologic[33], and nutrition[26] literature. Muscle volume, muscle density, visceral fat, subcutaneous fat, body fat content, vessel calcification, trabecular and cortical bone density have all been studied with this method. However, morphomic analysis of tendons have not yet been examined.

The purpose of the present study was to evaluate tendon morphology septic patients through analytic morphomics. Through evaluation of psoas major muscle and psoas major tendon in

both septic and healthy patients, we set to examine for concomitant muscle and tendon wasting in acute illness. We hypothesized that morphomic analyses would reveal concomitant muscle and tendon wasting in sepsis patients. The results of this study may help to implement earlier or different rehabilitation modalities for critically ill patients.

Methods

This study was approved by the University of Michigan Institutional Review Board, allowing access to any CT scan performed retrospectively on patients for trauma and nontrauma indications within the University of Michigan Health System. Informed consent was waived by the IRB.

Patient Enrollment:

A sepsis patient cohort was selected from a group of adult patients admitted to the University of Michigan Surgical Intensive Care Unit with sepsis between July 2011 and June 2012. Patients with CT scan of the abdomen and pelvis obtained 0-25 days following ICU admission were included in the study. Patients were excluded if there was incomplete or temporally inappropriate imaging. Control patients were selected from a group of blunt trauma patients admitted from January 2011 to September 2012. Blunt trauma patients were included in the control cohort as these individuals are likely to represent a healthy member of the general population as well as have an abdominal CT scan upon admission.

On first examination of our database, a total of 35 septic patients met inclusion criteria. Thirty-five blunt trauma patients admitted to UMHS with comprehensive CT imaging within 24 hours of admission were included as control patients. Patients were excluded from the control cohort if they had a personal history of sepsis or if they were victim of penetrating or musculoskeletal trauma that would preclude accurate morphometric measurements.

The characteristics of the initial patient cohorts (n=35) are presented in Table 1. Morphomic analysis in revealed dramatic differences in both psoas muscle volume and psoas muscle fat content as displayed in Table 2. However, the patient groups were very different with regards to both age and gender, two variables established as predictors in morphomic analysis[24,34]. For example, men and younger individuals are known to have larger psoas muscles. Some studies have also shown a positive correlation between BMI and muscle attenuation caused by fat accumulation, but other analyses have shown the exact opposite[17,35]. Because of this conflicting information, it was deemed most prudent to also BMI-match our patient groups as well in effort to avoid this potential confounder. This change in protocol was established in order to make accurate morphomic comparisons between cohorts by eliminating possible confounding factors including age, gender and BMI. Our final patient cohort then included 25 ICU patients and 25 age, gender and BMI-matched adult blunt trauma patients.

Age, gender, BMI, comorbidity, and laboratory data were collected via chart review of the electronic medical record for all 50 patients. Malignancy, diabetes, COPD, kidney disease, heart disease, liver disease, hypertension, and hyperlipidemia were included as comorbidities in this analysis.

Analysis:

Using the McKesson imaging software system, CT scans with IV contrast of both sepsis and trauma patients were studied. Specifically, the bilateral psoas muscles and psoas major tendons were analyzed. The right psoas major muscle was first identified at the level of vertebral body of L4. Depending on CT slice thickness, the cross-sectional area of the psoas muscle was traced on 2-4 cuts to calculate psoas muscle volume spanning 1cm thick slices (cm^3). While maintaining this muscle volume selection, fat volume was measured. Fat volume was defined as the summated volume of pixels that have attenuation coefficients between −50 and −250 Hounsfield units, the known attenuation range for fat[36-38]. This allowed for software analysis of total volume of fat within the measured psoas volume, or, muscle fat content (cm^3). Fat volume:total volume ratio was next calculated to provide overall percentage of fat as a surrogate for muscle atrophy. This process was repeated for the left psoas muscle. Differences in psoas muscle size and muscle fat content between left and right sides in individual patients were observed. For this reason, unilateral volume values were averaged to determine final patient values.

Next, the right psoas major tendon was identified at the level at which it directly opposes the anterior acetabulum. Volume measurements of the tendon were performed and recorded in a fashion identical to that described above. These measurements were performed bilaterally and averaged, as above.

All CT scan measurements were performed by an 18 year-experienced musculoskeletal radiologist who was blinded to patient age and cohort. Average psoas muscle volume at the L4 vertebral body, psoas muscle fat content, and psoas major tendon volume were measured bilaterally for each patient.

Statistical design:

Continuous variables were summarized using means and standard deviations and categorical variables were summarized as percentages. The relationship between patient characteristics, psoas muscle volume, fat content, and tendon volume was compared between patient groups by independent samples t-tests or univariate analysis of variance (ANOVA) as appropriate. Multivariable regression analysis was used to assess the relationship between the outcomes and sepsis while controlling for age, gender, and known confounders such as smoking and comorbidities. Significance was set at $\alpha < 0.05$ and all analyses were conducted using STATA13.

Results

A total of 50 patients were included in this study with volumetric data from 100 psoas muscles and 100 psoas tendons. A summary of patient demographic and clinical data is presented in Table 3. The control (trauma) and sepsis patient groups were age, gender, and BMI-matched. 56% of control patients and 52% of the sepsis cohort were men. The average age in the control group was 49.71 years compared to 53.48 years in the sepsis cohort (p=0.377). The BMI in the control group averaged to 26.97 kg/m^2 versus 28.19 kg/m^2 in the sepsis group (p=0.587). A brief clinical summary of the sepsis patient cohort is presented in

Table 4. The majority of ICU patients were diagnosed with intraabdominal sepsis (n=19, 75%). Average length of stay in the ICU was 22.5 days ± 16.7. The average day at which the CT scan was obtained was 5.68 ± 6.55.

Morphometric analysis results summarized in Table 5. Early sepsis and control patient groups were age, gender and BMI matched. The vast majority of the subjects had IV contrast imaging (n=42, 84%). There was a statistically significant difference in average psoas muscle volume between control patients and septic patients (12.2 vs 9.3, p<0.029). Average psoas muscle fat content in septic patients was 0.0288 ±0.0626 (2.88 ± 6.26%) compared to the control group average of 0.0107 ±0.007 (1.07 ± 0.7%). The muscle fat content in the septic group was more than twice that found in control patients. However, this difference was not found to be statistically significant (p=0.156).

There were no observed differences of psoas major tendon volume between patient groups. The average volume of the psoas major tendon in the septic patient population was 0.508 ± 0.171 cm^3 compared to 0.493 ±0.166 cm^3 in the trauma cohort (p=0.758).

Importantly, the number of comorbidities (coded as 0=0 comorbidities, 1=1 comorbidity, 2= 2 or more) was not associated with any of the outcomes in this sample including psoas muscle volume, psoas muscle fat content, and tendon volume. A multiple regression analysis was conducted for each of the outcomes. Septic/control, age, gender, smoking status and number of comorbidities were included in each model as adjustments. The results indicated psoas muscle volume was significantly reduced by 2.43 cm^3 (p<0.045) for the septic group when compared to the control group while adjusting for age, gender, smoking and comorbidities.

Discussion

Computed tomography has been established as the primary means of conducting morphomic analysis [21,24,34,39,40]. Advantages of CT imaging include its wide availability and reproducibility using standard anatomic landmarks. CT scans are regularly obtained for a number of indications and were readily available in our patient cohort. Although ultrasonography is sometimes utilized to examine tendon morphology[41], it remains quite user dependent. Furthermore, uninjured tendons are not routinely evaluated by ultrasounds and as such, these images were not available for our retrospective analysis.

In this study, our results demonstrate significantly smaller psoas muscle volume in septic patients than in control trauma patients. While we cannot definitively conclude that these differences are not related to patient baseline characteristics, we have limited baseline confounders by age, gender and BMI-matching our control cohort. As mentioned above, blunt trauma patients were included as controls because they represent healthy members of the general population who also frequently have an abdominal CT scan upon admission. As such, this population was derived from a cohort with the majority of patients without many baseline comorbidities. The average number of comorbidities in sepsis group was 1.98 compared to only 0.8 in the control group. This difference in comorbidities may reflect increased rates of malignancy or COPD, for example. Even with this consideration, multiple

regression analysis demonstrated no significant association between the number of comorbidities and any of the outcomes in this sample. These findings combined with age, sex and BMI-matching suggest that patient baseline comorbidities and characteristics did not contribute to overall psoas muscle size.

Muscle wasting in acute illness reportedly takes between 2-4 weeks to become clinically apparent. In our patient cohort however, morphometric analysis was performed on CT scans obtained an average of only 5.7 days after ICU admission. Earlier muscle atrophy in this patient cohort may be attributed to a number of factors including infectious or inflammatory processes starting days *earlier* than actual ICU admission. A 2006 study by Khan et al. set out to characterize the prevalence and time of onset of neuromuscular dysfunction in patients with severe sepsis[8]. In this study, the majority of patients demonstrated changes in nerve conduction studies (NCS) very early in the course of severe sepsis (i.e., <7 days after admission). These NCS changes were also predictive of the development of acquired neuromuscular dysfunction and mortality in ICU patients. A more recent study by Axer et al. demonstrated septic patients to have electrophysiologic evidence of peripheral nerve axonal damage during the first week after onset of sepsis[42]. These findings suggest that neuromuscular pathology may start earlier in the time course than previously described.

Radiographic fat content of the psoas major muscles in the septic patients was found to be twice that of the control population in our study. Increased intramuscular fatty infiltration is consistent with the natural disease course in muscle atrophy[16-18] and further lends support to the presence of muscle atrophy in the early sepsis population. Most of the quantitative CT literature on intramuscular fat has been completed in rotator cuff analyses. However, quantitative CT has also been used to investigate site-specific adipose deposition in different body compartments and to assess differential fat deposition and lean muscle mass[36-38]. Computed tomography was the original gold standard for intramuscular fat content measurement, though MRI is now used as another method of measuring intramuscular adiposity[43].

Our laboratory has recently defined the role of fascial tissues in aberrant wound healing after trauma[44]. In adulthood, muscle and tendon repair is guided by progenitor cells of the scleraxis cell lineage, found in high densities in both fascia and tendon tissues. These scleraxis cell types have been implicated in promoting muscle atrophy and fibrosis[19]. Given the small diameter of fasica compared to myofibers in a muscle, we chose to quantify regions with high percentage of scleraxis (i.e., the psoas tendon) in the setting of acute illness to evaluate for concomitant tissue wasting. Our results demonstrate that psoas tendon size was not significantly different between sepsis patients when compared with controls. This critical conclusion is perhaps the most important finding in this study and specifically, its implications for future studies in the field of morphomics. Also subject to the same inflammatory cytokines, gross tendon morphology appears to remain unaffected in our patient population. Thus, tendon morphology is unlikely to be a useful metric in CT morphomic studies of the future.

There are several limitations of this study that must be discussed. The primary limitation of this study is that the results reflect the state of the muscle tendon unit at only a single point

in time. Because of the constraints in retrospective design, sequential morphomic measurements were unable to be obtained in our cohort. Only three septic patients had more than one abdominal CT during their ICU hospitalization. Furthermore, our limited cohort did not allow for subgroup analysis with consideration of ICU day at CT scan. Muscle wasting in sepsis would be ideally studied in many individual patients through analysis of serial CT scans throughout course of sepsis in order to establish a time course of atrophy. In this way, a muscle wasting pattern could be clearly delineated and described. However, unfortunately this optimal patient population was not available for study in our retrospective analysis.

It should further be emphasized that this study is limited in its focus on tendon *morphology* rather than tendon *pathology*. Our study does not examine tendon strength, stiffness and function. These parameters might be best assessed in real-time with different imaging methodologies and are beyond the scope of morphomic analyses. While psoas tendon volume is an important measure of morphology, entire tendon dimensions, stretch, and position might also be considered. Tendon length was unable to be measured in our patients as the gradual coalescence of fibers at the musculotendinous junction rendered exact tendon dimensions unclear. Similarly, retrospective constraints did not allow confirmation of neutral leg position at the time of imaging, and thus variable tension on the tendons in the study patients cannot be excluded.

Conclusion

In this study, morphometric analysis reveals psoas muscle wasting in sepsis patients though there was no evidence to suggest the presence of concomitant tendon atrophy. With these findings, we begin to define the boundaries of clinical application within the field of morphomics. Specifically, computed tomography is unable to elucidate any changes in tendon health in the context of sepsis.

Acknowledgements

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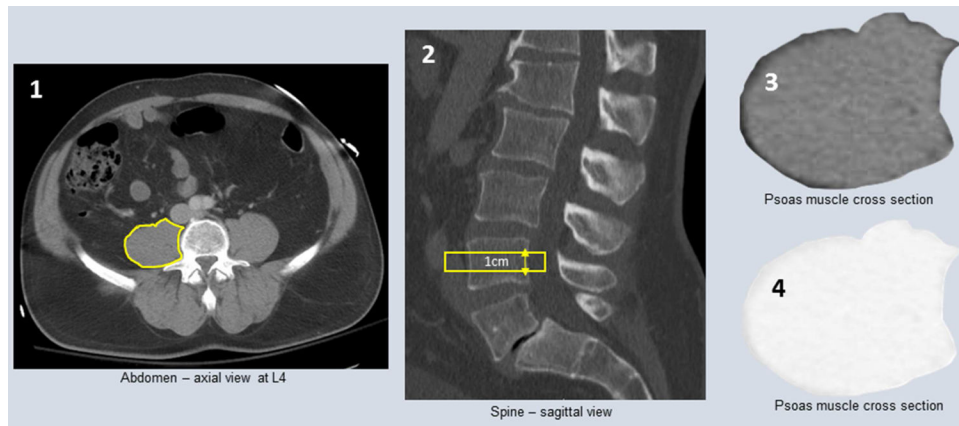
Figure 1: Right psoas muscle measurements.

1) Psoas muscle identified at the L4 vertebrae 2) Cross sectional area of muscle is traced on 2-4 slices to measure 1cm thick section of muscle 3) McKesson software calculates volume of muscle 4) Threshold changed to calculate volume of fat within defined muscle
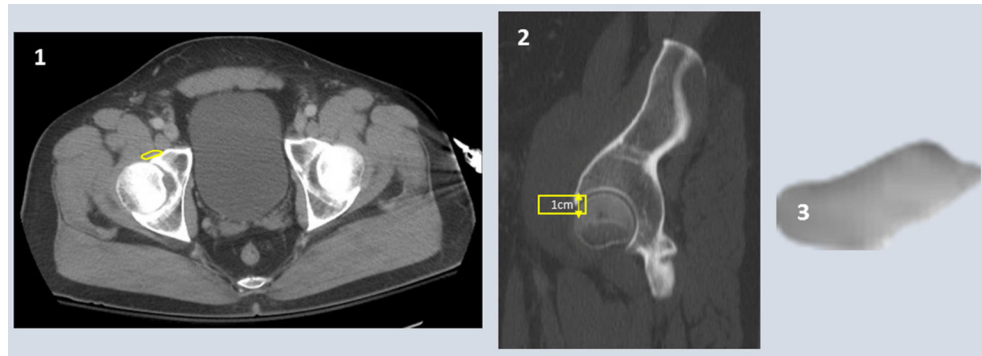
Figure 2: Right psoas major tendon measurements.
1) Psoas major tendon identified at the anterior acetabulum 2) Cross sectional area of tendon is traced on 2-4 slices to measure 1cm length of tendon 3) McKesson software calculates volume of defined tendon

Table 1

Summary of patient demographic and clinical data with $n = 35$ in each group.

	Control patients ($n = 35$)	Sepsis patients ($n = 35$)	*P* value
Men	23 (65.7%)	18 (51.4%)	0.3319
Age	42.6 ± 17.94	59.25 ± 18.57	0.0003 [*]
BMI (kg/m^2)	26.31 ± 7.17	27.60 ± 6.34	0.4280
Smoking history	7 (20.0%)	20 (57.1%)	0.0029 [*]
No. of comorbidities			
0	16 (45.7%)	6 (17.1%)	
1	13 (37.1%)	16 (45.7%)	
2 +	6 (17.1%)	13 (37.1%)	

Patient cohorts were not age or gender matched. Malignancy, diabetes, COPD, kidney disease, heart disease, liver disease, hypertension, and hyperlipidemia were included as comorbidities in this analysis.

[*] Denotes statistical significance.

Table 2

Summary of psoas muscle and tendon morphometric data from both control and sepsis patient groups ($n = 35$).

	Control patients	Sepsis patients	*P* value
Average psoas muscle volume (cm^3)	13.10 ± 4.98	8.70 ± 3.2	<0.0001 [*]
Average psoas fat content (%)	0.87 ± 0.70	2.84 ± 5.43	<0.0364 [*]
Average psoas major tendon volume (cm^3)	0.487 ± 0.149	0.518 ± 0.149	0.387

Patient cohorts were not age or gender matched.

[*] Denotes statistical significance. Psoas muscle volume was significantly larger in the control patient cohort. There was no difference in psoas major tendon volume between these groups.

Table 3

Summary of patient demographic and clinical data.

	Control patients ($n = 25$)	Sepsis patients ($n = 25$)	P value
Men	14 (56%)	13 (52%)	0.77
Age	49.71 ± 15.62	53.48 ± 14.29	0.3816
BMI (kg/m^2)	26.97 ± 7.78	28.19 ± 6.99	0.587
Smoking history	6 (24%)	12 (48%)	0.07
No. of comorbidities			
0	11 (44%)	5 (20%)	0.032
1	9 (36%)	6 (24%)	
2 +	5 (20%)	14 (56%)	

The control and sepsis groups were matched by age, gender, and BMI. Malignancy, diabetes, COPD, kidney disease, heart disease, liver disease, hypertension, and hyperlipidemia were included as comorbidities in this analysis.

Table 4

ICU hospitalization summary of sepsis patient cohort.

Etiology of sepsis	
Intra-abdominal	19 (76%)
Pulmonary	3 (12%)
Soft tissue	3 (12%)
ICU d at CT scan (HD#)	5.68 ± 6.55
Total length of stay (d)	22.5 ± 16.7
ICU length of stay (d)	5.96 ± 4.61
Days on ventilator	2.64 ± 4.09
Death during admission	3 (12%)
Death within 30 d of ICU admission	1 (4%)

Data presented as mean ± SD for continuous variables and n (%) for categorical variables.

Table 5

Summary of psoas muscle and tendon morphometric data from both control and sepsis patient groups.

	Control patients	Sepsis patients	P value
Average psoas muscle volume (cm^3)	12.2 ± 5.5	9.3 ± 3.3	0.029 [*]
Average psoas fat content (%)	1.07 ± 0.7	2.88 ± 6.26	0.156
Average psoas major tendon volume (cm^3)	0.493 ± 0.166	0.508 ± 0.171	0.824

The control and sepsis groups were matched by age, gender, and BMI.

[*] Denotes statistical significance. Psoas muscle volume was significantly larger in the control patient cohort. There was no difference in psoas major tendon volume between these groups.