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Original article

Skeletal muscle mass and quality in gout patients versus non-gout controls: A computed tomography imaging study

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ABSTRACT

Objective. – Patients with gout are at elevated risk of multiple vascular and metabolic comorbidities. Whether they are also at risk of sarcopenia, which is known to affect patients with other rheumatic diseases, has not been previously assessed. We examined whether patients with gout have decreased lumbar muscle quality and quantity, indicating an association between gout and sarcopenia.
Methods. – Fifty gout subjects and 25 controls, ages 45–80, underwent computed tomography imaging of the lumbosacral spine. We measured muscle quantity (skeletal muscle area [SMA] and index [SMI]) and quality (skeletal muscle radiation attenuation [SMRA] and intermuscular adipose tissue [IMAT] area and index [IMATI]) of the psoas and erector spinae muscles at the L3 level.
Results. – Seventy subjects (45 gout and 25 controls) were included in the analysis. Gout subjects had higher BMI, more kidney disease and hypertension, lower exercise frequency, and higher mean serum urate and creatinine vs. controls. Lumbar SMRA was significantly lower in gout subjects vs. controls, indicating reduced muscle quality. Lumbar IMAT area was significantly higher in gout subjects vs. controls, as was lumbar IMATI, indicating increased muscle adiposity. These differences persisted after adjusting for potential confounders. In contrast, there was no significant difference between gout and control groups in lumbar SMA or lumbar SMI, suggesting that muscle quantity may not be routinely affected by the diagnosis of gout.
Conclusions. – Gout patients exhibit decreased lumbar muscle quality compared with controls, consistent with an association between gout and sarcopenia.

1. Introduction

Gout, the most prevalent inflammatory arthritis, affects over 40 million adults worldwide with increasing prevalence [1]. Gout occurs due to deposition of monosodium urate (MSU) crystals in joints and periarticular soft tissues of patients with elevated serum urate (SU) levels [2]. In addition to flares, patients with gout may experience chronic inflammation, chronic joint disease, and systemic MSU deposition [3]. Gout patients also experience high rates of

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specific comorbidities, including cardiovascular disease, hypertension, hyperlipidemia, type 2 diabetes, obesity, and chronic kidney disease, as well as premature mortality [2,4,5].

Likely as a consequence of joint disease and comorbidities, patients with gout experience greater functional disability than the general population [6]. In addition to activity impediment during flares, studies suggest that gout patients experience decreased lower extremity strength and worsened performance on tests of standing, balance, and gait speed [7,8]. Although prior reports have been inconsistent, some studies have also shown a correlation between elevated SU levels, the necessary precursor of gout, and sarcopenia [9–11], a disease of muscle failure defined as low muscle strength or function plus low muscle quantity and/or quality [12]. In this definition, muscle quantity refers to muscle mass, and muscle quality refers to other important aspects of muscle composition and architecture. Earlier definitions of sarcopenia focused on muscle quantity and quality only, without requiring a correlate with strength or function.

While common among older adults, sarcopenia is not exclusively a phenomenon of aging. Sarcopenia prevalence is increased in a number of autoimmune and autoinflammatory conditions, including rheumatoid arthritis (RA), psoriatic arthritis, systemic lupus erythematosus, systemic sclerosis, and ankylosing spondylitis [13,14]. Chronic elevations of cytokines in autoimmune and autoinflammatory conditions, including interleukin-1β, interleukin-6 and tumor necrosis factor, can drive muscle catabolism that leads to decreased muscle mass [15–17]. Animal models suggest that dysregulation of the ubiquitin proteasome system contributes to increased muscle breakdown in conditions of inflammatory arthritis [18]. Based on similar cytokine-mediated mechanisms of inflammation between gout and other inflammatory arthritides, and the previously reported connection between hyperuricemia and sarcopenia, it is possible that gout patients also experience an increased incidence of sarcopenia. On the other hand, any connection between gout, hyperuricemia, and sarcopenia is complicated by the notion that the antioxidant properties of urate may protect against muscle damage, with some studies showing muscle mass and function are actually better, not worse, in older adults with higher SU [19–22]. To date, however, no studies have directly assessed the relationship between gout and muscle mass and quality.

To investigate the relationship between gout and sarcopenia, we employed computed tomography [CT], the reference non-invasive tool for assessing skeletal muscle, to evaluate muscle quantity and quality [12,23]. We used imaging of psoas muscles, a previously validated muscle for assessing sarcopenia [12,24,25], and erector spinae muscles in our analyses. We performed cross-sectional and logistic regression analyses to compare the muscle quantity and quality of gout vs. control subjects. We hypothesized that patients with gout would exhibit significantly lower lumbar muscle quantity and quality vs. controls, consistent with an association between gout and sarcopenia.

2. Methods

2.1. Study population

We utilized previously collected data from a cross-sectional study that enrolled 50 gout subjects (25 tophaceous, 25 non-tophaceous) and 25 controls ages 45–80 years to compare spinal MSU deposition using dual-energy CT (DECT) [3] (Doc S1). The study was approved by the NYU Grossman School of Medicine Institutional Review Board.

Demographic data, medical history, serologic data, and the Multidimensional Health Assessment Questionnaire (including physical activity assessment) [26] were collected for all subjects. All subjects underwent axial scanning of the lumbosacral spine from the thoraco-lumbar junction through the sacrum, including the psoas and erector spinae muscles, using a Somatom Force DECT system (Siemens Healthineers) [3]. Relevant data acquisition parameters were: tube potentials, 100 and 150 with tin filter (Sn150) kV; tube currents at 100 and Sn150 kV, 174–224 and 348–446 mA, respectively; pitch, 0.4; volume CT dose index, ~30 mGy. Image series were reconstructed at a section thickness/interval of 0.75/0.5 mm with a smooth kernel (Qr32d), resulting in an in-plane pixel size of ~0.3 × 0.3 to ~0.4 × 0.4 mm^2.

2.2. Image analysis and muscle metrics

To quantify subjects' muscle quantity, we measured the skeletal muscle area (SMA) of the psoas and erector spinae muscles at the third lumbar (L3) vertebral level. To quantify subjects' muscle quality, we measured skeletal muscle radiation attenuation (SMRA) and intermuscular adipose tissue (IMAT) area of the psoas and erector spinae muscles at the L3 level. Muscle segmentations to determine SMA were performed by a musculoskeletal radiologist using a custom graphical user interface. Muscle quality metrics (SMRA and IMAT area) were obtained by distinguishing within SMA pixels that attenuated as muscle from those that attenuated as adipose tissue using standard Hounsfield unit [HU] thresholds: −29 to +150 HU for skeletal muscle, and −190 to −30 HU for adipose tissue. SMRA was calculated by averaging the density of psoas and erector spinae muscle pixels representing only skeletal muscle, i.e. those with a HU value between −29 and +150 HU. IMAT area was calculated by measuring the total area of all pixels of −30 HU or lower. These measurements were made using custom-designed software validated on large CT data sets and utilized in prior studies [27].

SMRA and IMAT area are both recognized as important indicators of muscle quality that provide a more granular look at the health of muscle fibers than muscle mass alone. Prior research indicates that changes in muscle quality may explain observed declines in muscle strength that do not correlate with declines in muscle mass [28]. These two quality metrics differ in that SMRA reflects intramyocellular adipose tissue, as fat inside muscle decreases muscle density, while IMAT area measures extramyocellular adipose tissue. Fig. 1 illustrates the SMA, SMRA, and IMAT area for a representative gout and control patient.

Lumbar SMA (in cm^2) was defined as the sum of the psoas and erector spinae muscle cross-sectional areas, and the skeletal muscle index (SMI, in cm^2/m^2) was derived by dividing the SMA by the square of patient height. Similarly, lumbar IMAT area (in cm^2) was defined as the sum of the psoas and erector spinae IMAT areas, and IMAT index (IMATI, in cm^2/m^2) was derived by dividing the IMAT by the square of patient height. Lumbar SMRA, or density (in HU), was defined as the average density (not area) of all pixels within the psoas and erector spinae muscle tissues.

2.3. Statistical analysis

Demographic characteristics of gout and control subjects were compared using Pearson's Chi-^{2} test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test or Student's *t*-test for continuous variables. SMA, SMI, SMRA, IMAT, and IMATI were compared across gout and control subjects using the Wilcoxon rank-sum test. Logistic regression was used to adjust for potential confounders, including BMI, creatinine, hypertension, and exercise frequency. Significance was defined as a *P*-value < 0.05 for cross-sectional comparisons and a confidence interval not crossing 1 for logistic regression.

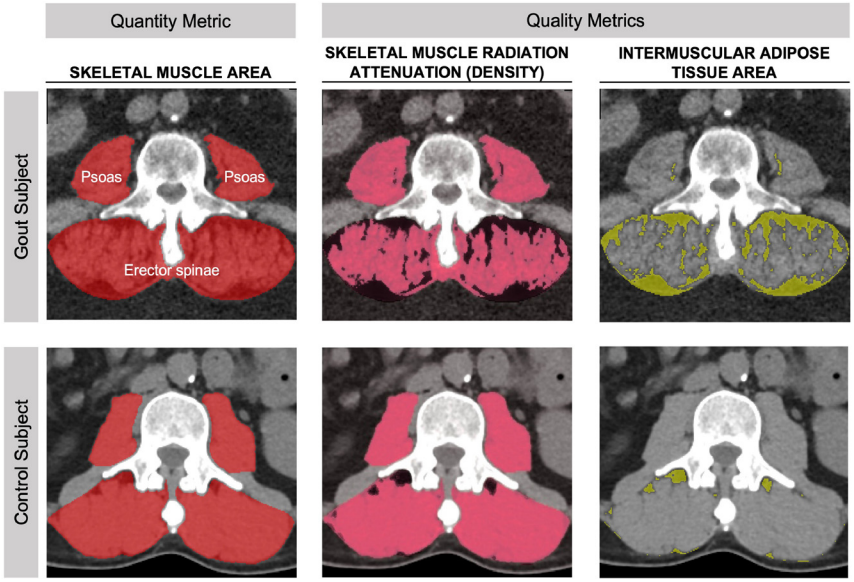

Fig. 1. Lumbar muscle quantity and quality in representative gout vs. control subjects. Skeletal muscle area (SMA), highlighted in red, is the total area of the psoas and erector spinae muscles and reflects lumbar muscle quantity. Skeletal muscle radiation attenuation (SMRA) is the average density (not area) of all pixels within the lumbar muscles that represent skeletal muscle itself and is highlighted in pink. Intermuscular adipose tissue (IMAT) area is the total area of all pixels within the lumbar muscles (extrinsic to the muscle fibers) that represent adipose tissue (not skeletal muscle) and is highlighted in yellow. Both SMRA and IMAT area reflect lumbar muscle quality. All measurements were made at the L3 level.

3. Results

3.1. Subjects

From 75 subjects enrolled in the original study, 70 (45 gout and 25 control subjects) were included in the psoas muscle analysis, and 64 (41 gout and 23 control subjects) were included in the erector spinae and combined lumbar muscle analysis. Five patients with gout were excluded: one was lost to follow-up prior to imaging, 2 were excluded for low SU measurements on repeat SU testing, and 2 others were excluded because of incomplete psoas muscle coverage on reconstructed CT images. Six additional subjects (4 gout, 2 controls) were excluded for incomplete erector spinae muscle coverage on CT, and these subjects were analyzed for psoas muscle alone (Figure S1). Mean age at study entry was 62 years, and 93% were men. Consistent with prior reports, patients with gout had greater incidence of chronic kidney disease and hypertension, and higher BMI, mean SU, creatinine, and inflammatory marker levels vs. control subjects. Gout subjects also exhibited lower exercise frequency compared with controls (Table 1).

3.2. Lumbar muscle quantity and quality in gout vs. control subjects

Lumbar muscle density (SMRA) was significantly lower in gout subjects compared with controls (median: 32.5 HU, IQR: 20.9–39.6 in the gout group vs. median: 39.2 HU, IQR: 31.8–43.2 in the control group, $P<0.01$). Lumbar extramyocellular adiposity (IMAT area) was significantly higher in gout subjects compared with controls (median: 6.84 cm^2, IQR: 4.78–10.2 in the gout group vs. median: 4.88 cm^2, IQR: 3.49–6.44 in the control group, $P<0.01$), as was lumbar IMATI (median: 2.23 cm^2/m^2, IQR: 1.60–3.39 in the gout group vs. median: 1.56 cm^2/m^2, IQR: 1.17–2.17 in the control group, $P<0.01$). In contrast, there was no significant difference between the gout and control groups regarding lumbar muscle quantity (SMA) (median: 73.9 cm^2, IQR: 64.3–85.9 in the gout group vs. median: 73.8 cm^2, IQR: 69.3–82.5 in the control group) or SMI (median: 24.4 cm^2/m^2, IQR: 21.0–27.6 in the gout group vs. median: 24.4 cm^2/m^2, IQR: 22.5–28.4 in the control group) (Figs. 1 and 2).

Table 1
Baseline sample size and cohort characteristics.

Variable	Gout $n=45$	Control $n=25$
Age (years)	62.5 ± 8.8	61.8 ± 3.8
Male sex	42 (93.3%)	23 (92.0%)
Race & ethnicity		
White	23 (51.1%)	18 (72.0%)
Black	14 (31.1%)	6 (24.0%)
Hispanic or Latino/a/x	6 (13.3%)	1 (4.0%)
Asian or Pacific Islander	2 (4.4%)	0 (0.0%)
BMI (kg/m^2)**	32.0 ± 6.5	28.3 ± 6.5
Medical conditions		
Hypertension***	32 (71.1%)	6 (24.0%)
Chronic kidney disease**	12 (26.7%)	0 (0.0%)
Diabetes mellitus type 2	9 (20.0%)	3 (12.0%)
Hyperlipidemia	28 (62.2%)	14 (56.0%)
History of myocardial infarction	4 (8.9%)	1 (4.0%)
History of cancer	6 (13.3%)	3 (12.0%)
Serum levels		
Urate***	8.5 ± 1.7	5.3 ± 1.0
Creatinine***	1.24 [1.08, 1.52]	0.92 [0.85, 1.11]
ESR**	24.0 [13.5, 39.5]	9.0 [3.5, 17.0]
CRP**	3.60 [1.60, 8.05]	1.20 [0.55, 2.70]
Exercise frequency*		
0 times per week	27 (60.0%)	7 (28.0%)
1–2 times per week	7 (15.6%)	6 (24.0%)
3+ times per week	11 (24.4%)	12 (48.0%)

BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. Values are mean ± standard deviation, *n* (%), or median (interquartile range). *P*-values were generated using Pearson's Chi^2 test, Fisher's exact test, Wilcoxon rank-sum test or Student's *t*-test. Race and ethnicity are defined based on participant self-report, using participants' primary response.

* $P<0.05$.
** $P<0.01$.
*** $P<0.001$.

SMI for the psoas muscle in gout and control subjects was consistent with data from prior work on healthy US adults [29]. There was no significant difference in any measure of muscle quality or quantity when comparing patients with tophaceous versus non-tophaceous gout (not shown).

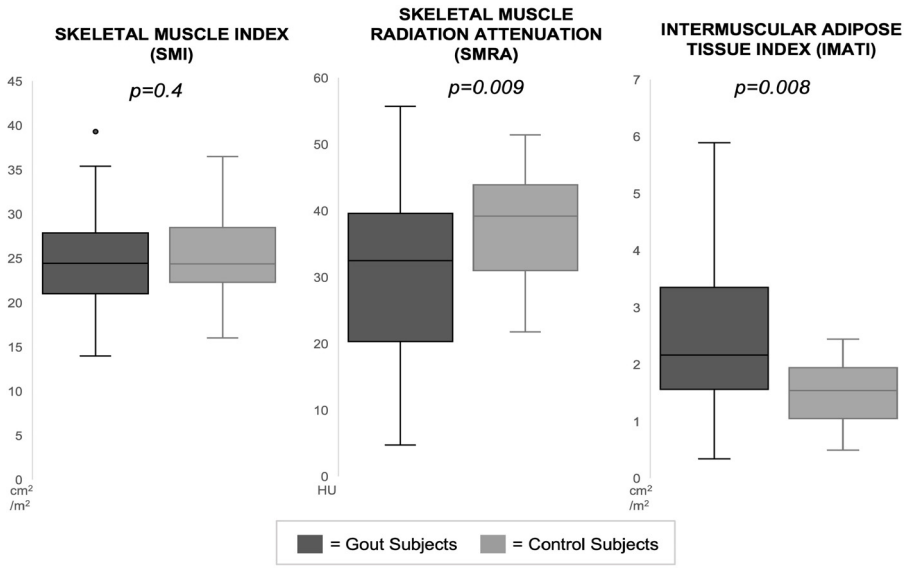

Fig. 2. Comparison of lumbar muscle quantity and quality metrics in gout vs. control subjects. All plots show median, interquartile range, and minimum and maximum values excluding outliers, which are defined as > 1.5 times the interquartile range and shown as individual data points. Lumbar muscles include the erector spinae and psoas muscles, and measurements are taken at the L3 level. Skeletal muscle index (SMI) reflects muscle quantity, while skeletal muscle radiation attenuation (SMRA) and intermuscular adipose tissue index (IMATI) reflect muscle quality. Lumbar SMI and IMATI are measured in cm^2/m^2, and SMRA (density) is measured in Hounsfield units.

Table 2
Comparison of psoas, erector spinae, and combined lumbar muscle quantity and quality.

Variable	Gout	Control
	n = 45	*n* = 25
Psoas SMA (cm^2)	24.5 [19.0, 28.6]	22.2 [20.0, 26.4]
Psoas SMI (cm^2/m^2)	7.87 [5.98, 9.54]	7.70 [6.35, 9.32]
Psoas SMRA (HU)*	43.5 [41.1, 46.9]	47.8 [45.7, 49.4]
Psoas IMAT area (cm^2)	0 [0, 0.04]	0 [0, 0.02]
Psoas IMATI (cm^2/m^2)	0 [0, 0.006]	0 [0, 0.012]
	n = 41	*n* = 23
Erector spinae SMA (cm^2)	50.0 [44.5, 59.7]	51.6 [49.7, 54.9]
Erector spinae SMI (cm^2/m^2)	16.5 [14.7, 19.2]	16.7 [16.2, 18.6]
Erector spinae SMRA (HU)*	26.9 [12.3, 37.4]	35.7 [26.4, 41.3]
Erector spinae IMAT area (cm^2)**	6.84 [4.78, 10.2]	4.66 [3.48, 6.37]
Erector spinae IMATI (cm^2/m^2)**	2.20 [1.60, 3.39]	1.56 [1.17, 2.17]
	n = 41	*n* = 23
Lumbar SMA (cm^2)	73.9 [64.3, 85.9]	73.8 [69.3, 82.5]
Lumbar SMI (cm^2/m^2)	24.4 [21.0, 27.6]	24.4 [22.5, 28.4]
Lumbar SMRA (HU)**	32.5 [20.9, 39.6]	39.2 [31.8, 43.2]
Lumbar IMAT area (cm^2)**	6.84 [4.78, 10.2]	4.88 [3.49, 6.44]
Lumbar IMATI (cm^2/m^2)**	2.23 [1.60, 3.39]	1.56 [1.17, 2.17]

SMA: skeletal muscle area; SMI: skeletal muscle index; SMRA: skeletal muscle radiation attenuation; HU: Hounsfield units; IMAT: intermuscular adipose tissue; IMATI: intermuscular adipose tissue index. Values are median (interquartile range). *P*-values were generated by Wilcoxon rank-sum test.

* $P < 0.05$.

** $P < 0.01$.

Table 3
Adjusted comparison of psoas, erector spinae, and combined lumbar muscle quantity and quality in gout subjects vs. controls.

Variable	Adjusted odds ratio	95% confidence interval
Psoas SMA (cm^2)	0.98	0.87–1.11
Psoas SMI (cm^2/m^2)	0.79	0.51–1.16
Psoas SMRA (HU)	0.95	0.82–1.11
Erector spinae SMA (cm^2)	0.96	0.87–1.06
Erector spinae SMI (cm^2/m^2)	0.8	0.57–1.06
Erector spinae SMRA (HU)*	0.93	0.87–0.99
Erector spinae IMAT area (cm^2)*	1.26	1.03–1.62
Erector spinae IMATI (cm^2/m^2)*	2.07	1.06–4.75
Lumbar SMA (cm^2)	0.96	0.88–1.03
Lumbar SMI (cm^2/m^2)	0.79	0.59–0.98
Lumbar SMRA (HU)*	0.91	0.82–0.99
Lumbar IMAT area (cm^2)*	1.26	1.03–1.61
Lumbar IMATI (cm^2/m^2)*	2.06	1.06–4.71

SMA: skeletal muscle area; SMI: skeletal muscle index; SMRA: skeletal muscle radiation attenuation; HU: Hounsfield units; IMAT: intermuscular adipose tissue; IMATI: intermuscular adipose tissue index. Logistic regression was used to generate adjusted odds ratios, 95% confidence intervals, and *P*-values adjusting for BMI, creatinine, prevalence of hypertension, chronic kidney disease, and exercise frequency. Psoas muscle IMAT and IMATI were not included due to median value of 0 for gout and control subjects.

* $P \leq 0.05$ and confidence interval not crossing 1. For lumbar SMI, confidence interval does not cross 1 and $P = 0.059$.

Decreases in lumbar muscle density among gout subjects were observed independently for the psoas and erector spinae muscles, respectively (Table 2). In contrast, the psoas muscle did not have significant intermuscular adipose tissue deposition, with a median IMAT area and IMATI of 0 for both gout and control subjects, so the difference in overall lumbar IMAT area and IMATI was driven by differences in the erector spinae muscle IMAT area and IMATI.

After accounting for potential confounders (BMI, creatinine level, presence of hypertension, and exercise frequency) using logistic regression, lumbar IMAT area remained significantly higher in gout vs. control subjects (adjusted odds ratio [aOR] = 1.26, 95% confidence interval (95% CI): 1.03–1.61, $P < 0.05$), as did lumbar IMATI (aOR = 2.06, 95% CI: 1.06–4.71, $P = 0.05$) (Table 3). Similarly, lumbar muscle density remained significantly lower in patients with gout (OR = 0.79, 95% CI: 0.59–0.98, $P = 0.05$), driven by lower SMRA in the erector spinae specifically (aOR = 0.93, 95% CI: 0.87–0.99, $P < 0.05$). There remained no difference in lumbar SMA (e.g., quantity) across the two groups (aOR = 0.96, 95% CI: 0.88–1.03, $P = 0.24$). However, adjustment for confounders revealed a significant difference in lumbar SMI between the two groups, with gout patients having a lower SMI that was not apparent prior to adjustment (aOR = 0.79, 95% CI: 0.59–0.98, $P = 0.059$).

3.3. Secondary analysis: hyperuricemic vs. normouricemic subjects

Hyperuricemic subjects differed from normouricemic subjects in age, BMI, creatinine level, presence of hypertension, and age (Table S1). To assess the impact of hyperuricemia on lumbar muscle quantity and quality, we conducted a secondary analysis to compare SMA, SMI, SMRA, IMAT area, and IMATI between hyperuricemic (SU > 6.8) and normouricemic subjects. Thirty-five patients were hyperuricemic (34 with gout and 1 control), and 35 patients were normouricemic (11 with gout who were on ULT with SU 6–6.8, and 24 controls). Lumbar muscle density (i.e., SMRA) was significantly lower in hyperuricemic subjects compared with normouricemic subjects (median: 30.1 HU, IQR: 19.8–38.2 for the hyperuricemic group vs. median: 38.3 HU, IQR: 31.8–42.3 in the control group, $P < 0.01$). The difference in lumbar muscle density was observed for both the psoas and erector spinae muscles (Table S2). Similarly, lumbar IMAT area was significantly higher in hyperuricemic subjects (median: 7.36 cm^2, IQR: 5.53–10.36 for the hyperuricemic group vs. median: 4.88 cm^2, IQR: 3.49–6.91 in the control group, $P < 0.01$), as was lumbar IMATI (median: 2.41 cm^2/m^2, IQR: 1.80–3.48 for the hyperuricemic group vs. median: 1.57 cm^2/m^2, IQR: 1.17–2.35 in the control group, $P < 0.01$). There was no significant difference between the two groups in lumbar SMA (median: 76.6 HU, IQR: 64.2–89.0 for the hyperuricemic group vs. median: 73.7 HU, IQR: 69.1–79.0 in the control group, $P = 0.66$) or lumbar SMI (median: 24.9 cm^2/m^2, IQR: 20.8–28.2 for the hyperuricemic group vs. median: 24.3 cm^2, IQR: 22.3–28.0 in the control group).

After adjusting for potential confounders, lumbar IMAT area remained significantly higher in hyperuricemic vs. normouricemic subjects (aOR = 1.25, 95% CI: 1.02–1.60, $P = 0.05$). However, lumbar IMATI did not differ between hyperuricemic vs. normouricemic subjects (aOR = 1.77, 95% CI: 0.95–3.83). SMRA also did not differ between the two groups (aOR = 0.94, 95% CI: 0.85–1.02). There remained no difference in lumbar SMA (aOR = 1.01, 95% CI: 0.94–1.09) or lumbar SMI (aOR = 0.80, 95% CI: 0.61–1.00) across the two groups (Table S3).

4. Discussion

In this study, gout subjects exhibited decreased lumbar muscle quality, including decreased intrinsic lumbar muscle density (SMRA) and increased extramyocellular adiposity (IMAT area and index) compared with control subjects, and these differences persisted after adjusting for relevant confounders, including BMI and activity level. These results suggest that patients with gout may be at increased risk of sarcopenia due to a decrease in muscle quality. The quality metrics we utilized in our analysis – lumbar muscle density (SMRA) and extramyocellular adiposity (IMAT area and index) – provide an important lens into muscle health that reflects the quality of muscle fibers, not just their size. Prior research has demonstrated that significant changes in muscle density (SMRA) and extramyocellular adiposity (IMAT area and index) can contribute to declines in muscle strength even without significant changes in muscle mass, and that this may be due to a greater percentage of fat and other non-contractile components within the muscle [28]. The persisting difference in these lumbar muscle quality metrics after confounder adjustment suggests that the observed difference is in part due to gout itself, though comorbidities likely contribute as well. While our analysis cannot comment on the causality of the observed relationship between gout and impaired muscle quality, knowledge of this relationship is nonetheless important for physicians looking to provide holistic care for patients with gout.

While we did not find a significant difference in lumbar muscle quantity (SMA and SMI) between gout and control subjects before adjusting for confounders, after adjustment there was a significant difference in SMI between the two groups, with an aOR of 0.79 (95% CI of 0.59–0.98). Given that lumbar skeletal muscles may be larger in people with higher BMI, whether because of weight bearing [30] or increased fat content, adjusting for BMI (which was expectedly higher in the gout group) may have revealed a difference in SMI between the two groups that was inapparent before adjustment. However, given our relatively small sample size, non-normal distribution of data, and high degree of variance (which led to a wider confidence interval and *P*-value of borderline significance), the discrepancy between adjusted and unadjusted SMI results should be interpreted with caution. Research with larger sample sizes may help clarify the relationship between skeletal muscle mass and gout when accounting for BMI or differences in body fat mass.

The factors impacting functioning in patients with gout are complex and include acute flares, chronic pain, development of joint deformity, corticosteroid use, and overlap with conditions such as osteoarthritis [7,8,31]. Based on our results, it is possible that impaired muscle quality and reduced exercise frequency are additional factors contributing to the high prevalence of disability in patients with gout. Our study did not directly assess physical function, so we cannot definitively say that subjects meet the current definition of sarcopenia, which includes both impaired muscle quantity or quality and impaired physical functioning [12]. However, impaired muscle quality and impaired physical function are often concordant in the general population and in patients with rheumatic disorders, suggesting that if patients with gout have impaired muscle quality, they likely also have impaired physical function. For example, a recent study by Baker et al. using whole-body dual-energy X-ray absorptiometry and peripheral quantitative CT demonstrated that patients with RA experience lower muscle density resulting from intramuscular fat accumulation, and that these differences were predictive of worsening performance on a test of balance and gait speed [32]. Other studies in subjects with RA have also shown that greater disease activity is associated with greater decline in muscle density, which in turn negatively impacts physical function [33,34]. The relationship between decreased skeletal muscle density and functional decline has also been shown in older adults more broadly [35]. Additionally, we know from prior studies that gout patients have impaired performance on physical function tests such as balance and gait speed [7,8]. Overall, these findings coupled with our own suggest that gout patients may be at increased risk of sarcopenia due to impaired muscle quality, as well as impaired physical functioning.

We also observed that patients with hyperuricemia have decreased muscle quality vs. normouricemic patients, but that the difference in muscle quality did not persist after adjusting for relevant confounders. The more robust difference in muscle quality between gout vs. control subjects, as compared with hyperuricemic vs. normouricemic subjects, suggests that increased SU may not be the sole driver of impaired muscle quality in patients with gout. These data must be interpreted with caution, given the large overlap between our gout and hyperuricemic groups, our study's inclusion of normouricemic gout patients with SU 6–6.8 who had been treated for < 6 months, and our small number of control patients with hyperuricemia. The small number of normouricemic patients with gout also limited our ability to make comparisons between gout patients with and without hyperuricemia. Nonetheless, these observations may be consistent with prior research showing lower rates of sarcopenia and no difference in rates of sarcopenic obesity in US adults with elevated SU compared with normal SU [36], and with previous work proposing that SU may be protective against muscle damage due to its antioxidant properties [10]. These findings in conjunction with our own suggest

that other inflammatory disease mechanisms, rather than elevated SU directly, may be at play in the connection between gout and decreased muscle quality. It is also possible that confounders not measured in our current study may independently contribute to the development of sarcopenia in gout patients. One possibility is the presence of osteoarthritis, given the co-occurrence of gout and osteoarthritis [31] and the previously shown connection between osteoarthritis and sarcopenia [37]. Other possible confounders we did not have data on included steroid use and markers of metabolic syndrome beyond BMI and diabetes history, such as waist circumference. Lastly, prior work has shown that elevated metabolically active fat, rather than elevated total body fat, is associated with elevated IMAT in patients with rheumatic diseases [38]. While we were able to control for BMI in our analysis, it is possible that patients with gout have disproportionately elevated levels of metabolically active fat, which we did not specifically account for, that in turn influences their IMAT and muscle density.

Our study has several strengths. To our knowledge, this is the first study to directly explore the relationship between gout and sarcopenia. By using cross-sectional CT imaging, we were able to directly examine multiple aspects of lumbar muscle quality – SMRA and IMAT area and index – rather than only measuring lean muscle quantity by whole-body dual-energy X-ray absorptiometry. This allowed us to obtain a more nuanced view of the changes in lumbar musculature in patients with gout. Moreover, the study included information on exercise frequency in addition to commonly collected demographic data and comorbidities, allowing us to account for an important difference in exercise frequency between gout and control subjects.

Our study also has several important limitations. Firstly, we did not have data about participants' muscle strength or function. Given that formal definitions of sarcopenia include low muscle strength or function as well as low muscle quantity and/or quality [12], we could not fully assess for sarcopenia as a clinical entity in our study population, and instead assessed muscle quantity and quality as suggestive of sarcopenia. Despite the established connection between decreased muscle quality and impaired physical function, it is possible that the degree of lumbar muscle quality decrease we observed in gout patients might not translate into clinically apparent impairment in muscle function. An additional limitation of our study is that we imaged only muscles in the lumbar spine. While the psoas muscle has been validated in prior studies on sarcopenia [12,24,25], we were not able to assess muscle in other body parts, which could theoretically differ from the lumbar spinal muscles, and the relatively small area of the psoas muscle may make it more difficult to demonstrate a difference between gout and control participants within our sample size. Additionally, our field of view did not include data on the abdominal wall muscles that have been included in other CT assessments of lumbar musculature at the L3 level [39]. Our study enrolled mainly White and Black men over the age of 60, potentially limiting its generalizability to other genders, ages, and ethnic groups. Our study population of 75 participants may have been under-powered to detect differences in muscle quantity metrics. Lastly, as this study was an ancillary analysis to a prior study from our group [3], the enrollment and data collection were not designed specifically to assess for sarcopenia in patients with gout. Future research can expand upon this study by incorporating metrics of muscle function, including muscles outside of the lumbar spine, and enrolling an additional cohort of subjects with asymptomatic (non-gout) hyperuricemia to better untangle the impacts of hyperuricemia vs. gout on muscle quality and quantity.

In summary, this study demonstrated decreased muscle quality and increased muscle adiposity among patients with gout vs. controls, suggesting an association between gout and sarcopenia. Elucidating the relationship and pathophysiological mechanism between sarcopenia and gout may provide opportunities to better manage the impact of gout on patients' physical function.

Disclosure of interest

A. Covello, None; M. Toprover, Horizon Therapeutics (now part of Amgen Inc), ANI Pharmaceuticals; C. Oh, None; G. Leroy, None; A. Kumar, Amgen Inc; B. LaMoreaux, Amgen Inc; M. Mechlin, Siemens; T. Fields, Amgen Inc; F. Becce, Amgen Inc, Siemens Healthineers; M. Pillinger, Amgen Inc, Hikma Pharmaceuticals, Federation Bio, Fortress Biotech, Scilex.

Availability of data and materials

The datasets used in the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jbspin.2024.105743.

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