Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder associated with multisystemic morbidity, including seizures and benign tumors of the kidney, brain, heart, and skin (1,2). Affected genes, TSC1 and TSC2, regulate the mammalian target of rapamycin (mTOR) cellular signaling pathway responsible for cellular proliferation, including that of skeletal muscle, and, when mutated, lead to mTOR pathway overactivation (3–6). mTOR inhibitors, including sirolimus and everolimus, belong to a class of drugs used in the treatment of TSC that target the affected pathway to reverse TSC pathophysiological processes (7–13). However, given their mechanism of action, these drugs carry a theoretical risk of growth impairment and have been implicated in the sarcopenia pathway, although the topic remains mostly unstudied (14,15).

Depletion of skeletal muscle mass, or sarcopenia, is associated with aging and disuse and can negatively impact quality of life and disease prognosis (6,16–18). Cross-sectional imaging provides validated methods of skeletal muscle mass assessment (18–26); one study measured skeletal muscle area at L3 and showed that chronic mTOR inhibitor use was significantly correlated with loss of muscle mass in adult patients with malignancy (27). Given the confounding relationship of cachexia and sarcopenia, the lack of published data, especially in young adults and in TSC, and the clinical significance of sarcopenia, a study of muscle mass in the setting of mTOR inhibitor therapy for TSC could elicit valuable data.

The purpose of this study was to retrospectively determine the longitudinal effect of mTOR inhibitor therapy on muscle mass, estimated by psoas muscle area at the L3 level on cross-sectional abdominal imaging in children and adults with TSC. A secondary objective of this study was to identify covariates related to longitudinal change in psoas muscle area, including demographic and additional anthropometric data. We hypothesized that the duration of mTOR inhibitor therapy would negatively correlate with psoas muscle area.

Materials and Methods

Study Design

The institutional review board approved this observational, retrospective, longitudinal, Health Insurance Portability and Accountability Act–compliant study. All patients included in this study had previously signed an informed consent for their data, including imaging data, to be used for research purposes as part of a tuberous sclerosis clinical research database.

Patients with a diagnosis of TSC who underwent at least two abdominal cross-sectional imaging examinations with CT or MRI at our institution, while receiving mTOR inhibitor therapy, were included. Sixty-five patients met inclusion criteria and underwent at least two abdominal CT or MRI examinations between 2005 and 2017. Median duration of mTOR inhibition at last examination was 106 months (range, 1310–3717 days). There was no significant association between the duration of mTOR inhibitor therapy and psoas muscle area on multiple linear mixed-effect modeling (P = .055); however, patient height and height squared were significant predictors of psoas area (P = .014 and P < .0001, respectively).

Conclusion: Duration of mTOR inhibition in TSC was not significantly associated with a decrease in psoas muscle area, suggesting that chronic mTOR inhibition is not associated with sarcopenia.

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inhibitor therapy (everolimus) for the treatment of TSC-related pathologies, between January 2005 and October 2017 were included in the study. Participants were identified through an institutional TSC research database. Given the low prevalence of TSC, no exclusion criteria were applied.

Patient demographic and medical history data were derived from a query of the institutional medical record (Epic; Epic Systems, Verona, Wis). Patient height and weight obtained closest to and within 90 days of each imaging examination were recorded. Height squared and body mass index were calculated. Body surface area was calculated using the formula: 0.007184 · height$^{0.725}$ · weight$^{0.425}$ (28). For adult patients without height and/or weight recordings within 90 days of an imaging examination, the height and/or weight recordings most recently obtained after 18 years of age were used for analysis.

CT and MRI

Given the long course of this study, imaging was performed with several CT and MRI scanners across multiple vendors within our institution, all using similar protocols. For CT, axial images were reconstructed at 5-mm intervals. For MRI, all examinations included axial T1- and T2-weighted sequences. Contrast material was not routinely used in our abdominal CT or MRI protocols for the evaluation of tuberous sclerosis. Of note, the majority of CT and MRI studies were performed for surveillance of neoplasms.

Image Processing

All psoas muscle area measurements were performed with a vendor-neutral postprocessing platform (Vitrea Advanced Visualization; Vital Images, Minnetonka, Minn). For each imaging examination, one blinded reviewer, a pediatric neurologist (C.R.), selected the axial CT image or T1-weighted MR image closest to the midvertebral body of L3 and drew one freehand region of interest around the periphery of each of the right and left psoas muscles, using previously published and validated methods for estimating total body muscle area (21,29,30). After each individual area was recorded, the mean area of the two measurements was calculated (Fig 1). All drawn regions of interest were validated by a pediatric radiologist (A.J.T.) with 9 years of postgraduate experience.

Statistical Analysis

Continuous data were summarized as means and standard deviations; categorical data were summarized as counts and percentages. Patient characteristics were compared between cohorts using Fisher exact test or Student t tests (unpaired, two tailed), as appropriate. A Student t test (paired, two tailed) was used to compare mean right and left muscle areas. Multiple linear mixed-effect regression and stepwise model selection were performed to evaluate the association between muscle mass and the covariates over time considering the correlation between repeated measurements within each patient. Simple linear mixed-effect regression was performed to determine association of average psoas muscle area and days of mTOR therapy for (a) the entire population and (b) only patients 18 years of age or older, as an internal control to correct for growth before 18 years of age as a possible confounder of muscle mass. Simple linear regression models were created to evaluate the relationships between duration of mTOR inhibition and (a) psoas area, (b) change in psoas area (between first and last examination), and (c) change in psoas area normalized to age, (d) height, and (e) height squared.

A P value less than .05 was considered statistically significant for inference testing; 95% confidence intervals and β levels were calculated as appropriate. All statistical analyses were performed using SAS (SAS Institute, Cary, NC) or GraphPad QuickCals (GraphPad Software, La Jolla, Calif).

Results

Patient Characteristics

A total of 24 patients (14 males) with TSC underwent two or more imaging examinations while receiving mTOR therapy and were included in this study. The study population underwent a total of 129 cross-sectional abdominal imaging examinations during the study period. Median number of imaging examinations per patient was five (range, two–15). Mean patient age at the time of first imaging examination was 14.5 years ± 7.8 (standard deviation) (range, 1.5–35.8 years); mean patient age at the time of last examination was 21.8 years ± 8.7 (range, 11.3–43.7 years). At the time of first examination, eight patients were not receiving mTOR inhibitor therapy, and for the remaining 16 patients, median duration of mTOR inhibitor therapy was 22 months (range, 1–1918 days). At the time of last examination, median duration of mTOR inhibitor therapy was 106 months (range, 1310–3717 days). Across all time points, left psoas muscle area was significantly greater than the right psoas muscle area (right, 643 mm$^2$ ± 259; left, 677 mm$^2$ ± 280; P = .0006). Additional patient demographic
Predictors of Psoas Muscle Area

Figure 2 demonstrates a spaghetti plot of duration of mTOR therapy and average psoas area for all included patients. With multiple linear mixed-effect modeling and stepwise model selection for all time points, the best model for prediction of average psoas muscle area included duration of mTOR inhibitor therapy and height squared. In the final model, duration of mTOR inhibitor therapy approached statistical significance as a positive predictor \((P = .055)\), and height and height squared were significant predictors of average psoas muscle area \((P = .014 \text{ and } P < .0001, \text{ respectively})\). Simple linear mixed-effect modeling for the entire population did show a significant positive association between average psoas muscle area and days of therapy \((\beta = .08, P < .0001)\). However, simple linear mixed-effect modeling for patients 18 years or older showed no significant association between average psoas muscle area and days of therapy \((\beta = .03, P = .087)\).

Predictors of Longitudinal Change in Psoas Muscle Area

Simple linear regression showed no significant association between duration of mTOR inhibitor therapy and change in average psoas muscle area over time (between first and last examination) or change in average psoas muscle area over time adjusted for age or height or height squared (Table 2 and Fig 3).

Discussion

mTOR inhibitors are used as therapy for patients with TSC to reduce the size of subependymal giant cell astrocytomas, angiomyolipomas, and renal cysts and to decrease seizure rate (7–13,31). Importantly, the mTOR pathway is a key regulator of skeletal muscle mass due to its role in cell growth, differentiation, autophagy, survival, and metabolism (6,25). Studies of muscle-specific mTOR knockout mice have shown severe myopathy, altered contractile properties, decreased dystrophin, impaired oxidative capacity, glycogen accumulation, and decreased mitochondrial gene expression in skeletal muscle compared with normal controls (6,32–34). Furthermore, studies of mTOR inhibitors have demonstrated impaired glucose metabolism in muscle cells of mice (35) and failure of mechanical loading to induce muscle hypertrophy in humans (36).

Together these data support the hypothesis that mTOR inhibitor therapy could be associated with myopathy and/or sarcopenia.

Nonetheless, growth impairment with mTOR inhibitor therapy in children has yet to be confirmed in the literature; however, most published studies have assessed weight, height, height velocity, sexual maturation, or sex hormone levels rather than muscle bulk (9,14,37–40). One study of adults with malignancy did demonstrate loss of muscle mass in patients receiving chronic mTOR inhibitor therapy (27).

Our results demonstrated that, in a population of children and adults with TSC treated with mTOR inhibitors for an average of 53 months, duration of mTOR inhibitor drug therapy was not significantly associated with average (of right and left) psoas muscle area measured by

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Table 1: Demographic Characteristics of Study Population by Imaging Examination

| Parameter                  | First Examination (n = 24) | Last Examination (n = 24) | All Time Points (n = 129) |
|----------------------------|---------------------------|---------------------------|---------------------------|
| Age (y)                    | 14.5 ± 7.8                | 21.8 ± 8.7                | 19.5 ± 8.2                |
| Height (cm)                | 154 ± 28*                 | 171 ± 12†                 | 158 ± 21                  |
| Height squared (m²)        | 2.5 ± 0.8*                | 3.0 ± 0.4†                | 2.5 ± 0.6                 |
| Weight (kg)                | 51.8 ± 24.2‡              | 73.7 ± 25.5§              | 68.0 ± 26.9               |
| BMI (m/kg²)                | 22.3 ± 5.8‡               | 26.2 ± 4.6³               | 21.8 ± 5.4                |
| BSA (m²)                   | 1.4 ± 0.5†                | 1.8 ± 0.3²                | 1.5 ± 0.4                 |
| Duration of mTOR inhibitor therapy (mo) | 27.1 ± 17.1*          | 106.1 ± 21.2             | 52.7 ± 39.4               |

Note.—Data are means ± standard deviations. A total of 24 patients (14 [58.3%] male) with 129 imaging examinations were included in this study. BMI = body mass index, BSA = body surface area, mTOR = mammalian target of rapamycin.

* n = 21.
† n = 19.
‡ n = 12.
³ n = 23.
§ n = 8.
¶ n = 16.
cross-sectional abdominal imaging. Further, we found a positive correlation between muscle mass and time receiving mTOR inhibitor therapy that approached statistical significance on univariable regression; however, after correcting for age, height, or height squared, there was no longer a near-significant positive correlation of muscle mass and time. Additionally, using a random effects model, there was a significant positive association between psoas muscle area and duration of mTOR therapy for the entire group, but not for the internal control group of only adult patients. Together, these data suggest that the increase in muscle mass observed over time in patients younger than 18 years was likely related to physiologic growth and that mTOR inhibitors may not induce sarcopenia in a TSC population.

Our results conflict with the work of Gyawali et al who showed decreased muscle mass measured using similar methods in adults with malignancy being treated with mTOR inhibitors (27). This could perhaps be explained by the differences in study populations, as theirs was a study of patients with malignancies (renal cell carcinoma and pancreatic neuroendocrine tumor) and ours was of patients with TSC, or by differences in methods for muscle mass estimation. It could be the case that the psoas muscle is not affected by mTOR-induced muscle loss, as demonstrated in a prior study of mTOR gene knockout mice that exhibited decreased weight and area of fast-twitch skeletal muscles, but not of slow oxidative leg muscles, including the psoas (34). One other possible explanation would be a paradoxical increase in muscle mass due to mTOR inhibition in the context of TSC. Such an effect is theoretically possible based on the finding of decreased muscle mass in TSC1 knockout mice due to the inability to induce the usual process of autophagy (41). Reversal of the inhibition of autophagy through chronic mTOR inactivation (by administration of mTOR inhibitors) could theoretically lead to increased muscle mass.

While mTOR inhibitor therapy was not significantly associated with psoas muscle area on univariable regression, other patient-specific variables were. Specifically, height and height squared were significant predictors of muscle mass in our population, while age, weight, body mass index, and body surface area were not. This is consistent with prior literature demonstrating minimal or insignificant effect of age, body mass index, and body surface area on muscle mass measured in lumbar skeletal muscles with cross-sectional imaging (26,42). This also supports the use of skeletal muscle mass index (vs raw muscle area), in which lumbar skeletal muscle is corrected by dividing by height squared (25).

We found that the left psoas area was significantly larger than the right and are uncertain about the reason for this finding. There are some data demonstrating a significantly larger left psoas in right-handed golfers (43). It is possible that unstudied confounders, such as handedness, physical activity, and musculoskeletal pathologic conditions like scoliosis could have resulted in asymmetry of psoas muscle area, although research would be needed to confirm this. We believe that by using the average psoas muscle area, this limitation was addressed.

There were multiple additional limitations of this study. First, the sample size was small, and no exclusion criteria were applied, due to the low prevalence of TSC. Second, the specific imaging modality used in each patient, the number of serial examinations performed, and the timing of those examinations with respect to the mTOR start date were not standardized, related to the retrospective nature of the study. Third, there were insufficient cases to have a control group of patients with TSC that were not receiving mTOR inhibitors, and we instead used a control group of adults with TSC receiving mTOR inhibitors to correct for growth changes, which is not the ideal control group. Fourth, other covariates of skeletal muscle mass, such as activity and/or muscle use and nutrition, were not reviewed. Fifth, while we saw no overall decline in psoas muscle area in our population, without published data regarding normal ranges of skeletal muscle mass in children for comparison, it is not possible to identify patients with less than average normal muscle growth; we used an internal control group of adult-only patients as a proxy. Sixth, we assessed muscle quantity but did not assess skeletal muscle quality, and we estimated muscle mass with only the psoas for purposes of convenience and simplicity, whereas some studies have used all lumbar skeletal muscles; additional studies observing
other estimates of muscle mass would be helpful to confirm our results (19,24,25,44). Seventh, as this was a retrospective study, clinical data were nonuniform, such as timing of the weight and height measurements. Finally, only one reviewer drew regions of interest for determination of psoas muscle bulk which might have introduced systemic bias.

We have demonstrated that the duration of mTOR inhibitor use in patients with TSC is not significantly associated with a decrease in muscle mass estimated by average psoas area measured by cross-sectional imaging. Our results suggest no link between mTOR inhibitor use and sarcopenia and should be reassuring for patients with TSC requiring long-term mTOR inhibitor therapy.

**Disclosures of Conflicts of Interest:** C.R. disclosed no relevant relationships. L.A.G. disclosed no relevant relationships. A.T.T. disclosed no relevant relationships. D.A.K. Activities related to the present article: disclosed grants received by author’s institution from Novartis Pharmaceuticals to conduct clinical trials using mTOR inhibitor everolimus; disclosed honorarium received by author for advisory boards, consulting, and speaking on behalf of Novartis Pharmaceuticals; and disclosed support for travel and registration to scientific meetings to present results from clinical trials involving everolimus in treatment of TSC, from Novartis Pharmaceuticals and Italpharmaco. Activities not related to the present article: author serves on board of directors for Tuberous Sclerosis Alliance, a non-profit patient advocacy organization, but does not receive compensation for time and/or service; disclosed grants and/or grants pending to author’s institution from Greenwich Bioscience for Phase 4 clinical trial for cannabidiol; disclosed payment for service on speakers bureau from Novartis Pharmaceuticals and Greenwich Bioscience; disclosed payment from AXIS Media for CME lecture on TSC treatment of SEGA and epilepsy. Other relationships: disclosed no relevant relationships. D.N.F. Activities related to the present article: disclosed money paid to author for consulting fee or honorarium from Novartis; disclosed support for travel to meetings for the study or other purposes from Novartis; disclosed money paid to author’s institution from

**Author contributions:** Guarantors of integrity of entire study, L.A.G., D.N.F., A.J.T.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, L.A.G., A.T.T., D.N.F.; clinical studies, C.R., A.T.T., D.A.K., D.N.F., A.J.T.; statistical analysis, L.A.G., B.Z.; and manuscript editing, all authors.

**Figure 3:** (a) Scatterplot of duration of mammalian target of rapamycin (mTOR) inhibitor therapy versus change in average psoas muscle area between first and last examinations and change in average psoas muscle area over time adjusted for (b) age, (c) height, or (d) height squared with linear trendline.
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