Skeletal muscle adiposity and outcomes in candidates for lung transplantation: a lung transplant body composition cohort study

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ABSTRACT

CT measurement of body composition may improve lung transplant candidate selection. We assessed whether skeletal muscle adipose deposition on abdominal and thigh CT scans was associated with 6 min walk distance (6MWD) and wait-list survival in lung transplant candidates. Each ½-SD decrease in abdominal muscle attenuation (indicating greater lipid content) was associated with 14 m decrease in 6MWD (95% CI −20 to −8) and 20% increased risk of death or delisting (95% CI 10% to 40%). Each ½-standard deviation decrease in thigh muscle attenuation was associated with 15 m decrease in 6MWD (95% CI −21 to −10). CT imaging may improve candidate risk stratification.

INTRODUCTION

In the USA, despite increased lung transplant surgeries performed, wait-list mortality has risen since 2005.[1] Refining metrics for candidate evaluation may help reverse rising wait-list mortality.

Obesity, as measured by body mass index (BMI), is associated with increased risk of death after lung transplantation.[2] BMI cannot discriminate adipose from muscle whereas CT imaging can.[3] CT quantification of body composition may improve lung transplant candidate selection and risk stratification.

We hypothesised that greater skeletal muscle adiposity, as measured by mean muscle attenuation and intramuscular adipose tissue (IMAT) area on thigh and abdominal CT scans, would be associated with decreased 6 min walk distance (6MWD) and wait-list survival among lung transplant candidates.

METHODS

We enrolled subjects ≥18 years old, undergoing transplant evaluation at Columbia University, Duke University or University of Pennsylvania between 2011 and 2014.

Subjects underwent single slice (10 mm) CT of the mid-thigh and/or at the L4/L5 vertebrae.[4] Muscle was outlined by blinded personnel. Tissue within the outlined area with Hounsfield units (HU) of −40 to 124 was quantified as muscle (online supplementary figure S1), and tissue with adipose attenuation (−40 to −170 HU) was quantified as IMAT.

The primary outcome was 6MWD measured in a standardised fashion.[5] Wait-list survival was operationalised as time from evaluation to death or delisting for severe illness. Subjects with unknown vital status were censored on 4 September 2019.

Predictors were mean muscle attenuation (lower attenuation indicating greater lipid content) and IMAT area/height^2 (IMAT index).[6] Change in outcome was reported per ½-SD change in attenuation. IMAT index was $\log_2$-transformed to normalise its distribution with change reported per doubling.

We evaluated predictor convergent and divergent validity with traditional body composition measures by Pearson correlation. We used mixed-effects linear regression to evaluate the association between predictors and 6MWD, adjusted for age, sex, diagnosis, forced vital capacity and muscle index (muscle cross-sectional area/height),[2] with centre as random effect. We controlled for BMI in sensitivity analyses given potential collinearity. Subgroup analysis was performed by diagnosis using likelihood ratios.

Survival analyses used competing risks regression for competing end points of transplantation and death/delisting adjusted for covariates above. Diagnosis violated the proportional hazards assumption and was included as a multiplicative interaction with time.

Analyses were performed using STATA/IC V.15.1 (StataCorp) and R V.3.3.1 (R-Foundation for Statistical Computing).

RESULTS

Three-hundred and six subjects had thigh or abdominal CT and 6MWD (online supplemenary figure S2). Fifty-five per cent were men with median(IQR) age of 60(52–67) and BMI of 25.5 kg/m^2(22.3–29.3); 48% had interstitial lung disease and 28% had chronic obstructive pulmonary disease (COPD) (online supplementary table S1). Subjects in the lowest tertile of muscle attenuation (ie, more adiposity) were older, more likely to have COPD and higher BMI (online supplementary tables S1–S2).

Thigh and abdominal muscle attenuation was

Table 1 Convergent and divergent validity of measures of muscle quality with traditional measures of body composition

	Thigh MMA r (95% CI)	P value	TMI r (95% CI)	P value	Thigh IMAT Index r (95% CI)	P value	Abdominal MMA r (95% CI)	P value	AMI r (95% CI)	P value
Thigh MMA	1									
TMI	0.05 (−0.07 to 0.16)	0.44	1							
Thigh IMAT Index	−0.52 (−0.62 to −0.41)	<0.001	0.07 (−0.07 to 0.21)	0.31	1					
Abdominal MMA	0.78 (0.72 to 0.82)	<0.001	0.11 (−0.01 to 0.22)	0.08	−0.47 (−0.57 to −0.35)	<0.001	1			
AMI	0.19 (0.07 to 0.30)	0.002	0.61 (0.54 to 0.68)	<0.001	−0.003 (−0.15 to 0.14)	0.97	0.27 (0.16 to 0.37)	<0.01	1	1
Body mass index	−0.35 (−0.45 to −0.24)	<0.001	0.59 (0.50 to 0.66)	<0.001	0.52 (0.41 to 0.62)	<0.001	−0.38 (−0.48 to −0.28)	<0.001	0.28 (0.18 to 0.38)	<0.01
Height	−0.05 (−0.17 to 0.06)	0.37	0.18 (0.06 to 0.29)	0.003	0.11 (−0.03 to 0.25)	0.12	0.1 (−0.01 to 0.21)	0.09	0.06 (−0.05 to 0.17)	0.28
Weight	−0.31 (−0.42 to −0.20)	<0.001	0.57 (0.49 to 0.65)	<0.001	0.47 (0.36 to 0.58)	<0.001	−0.25 (−0.36 to −0.15)	<0.001	0.27 (0.16 to 0.37)	<0.001
Abdominal VAT area (mm^2)	−0.33 (−0.43 to −0.22)	<0.001	0.20 (0.08 to 0.31)	0.001	0.40 (0.28 to 0.52)	<0.001	−0.44 (−0.53 to −0.34)	<0.001	0.06 (−0.06 to 0.17)	0.32
Triceps skinfold thickness	−0.19 (−0.35 to −0.03)	0.03	−0.11 (−0.27 to 0.06)	0.2	0.2 (−0.006 to 0.39)	0.06	−0.24 (−0.38 to −0.08)	0.003	−0.26 (−0.40 to −0.10)	0.001

Results displayed as Pearson correlation coefficient (95% CI).
AMI, abdominal muscle index (abdominal skeletal muscle area/height^2); Thigh IMAT Index, thigh intramuscular adipose tissue (intramuscular adipose tissue area/height^2); MMA, mean muscle attenuation (Hounsfield unit); TMI, thigh muscle index (thigh muscle area/height^2); VAT, visceral adipose tissue.

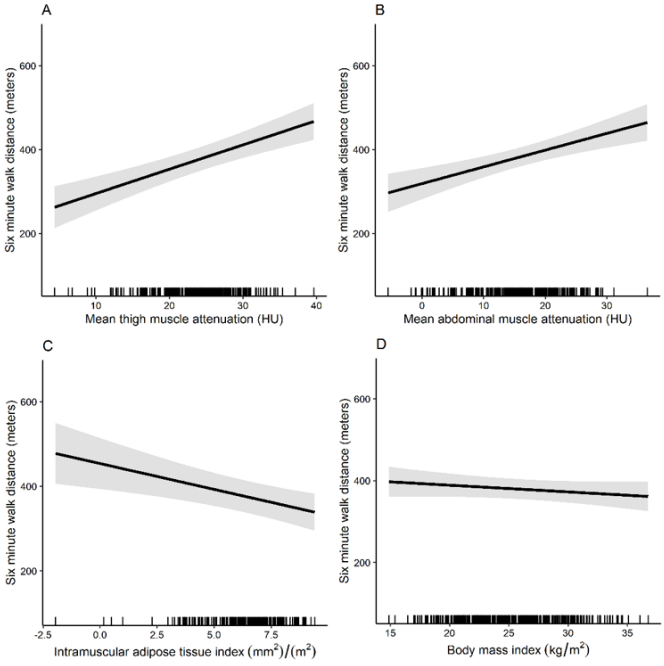

Figure 1 Association between 6 min walk distance and (A) mean thigh muscle attenuation, (B) mean abdominal muscle attenuation, (C) thigh intramuscular adipose tissue index and (D) body mass index. Black line represents the mixed-effects linear model with median values for covariates (sex, forced vital capacity, diagnosis and age) and centre as random effect. Models A–C are additionally adjusted for muscle index (area/height^2). Surrounding grey areas represent 95% confidence bands. Vertical lines along the x-axis each represent a single study subjects.

weakly correlated with BMI while thigh IMAT index was moderately correlated with BMI (table 1). There was no correlation between thigh muscle attenuation or IMAT and thigh muscle index. Abdominal muscle attenuation was weakly correlated with abdominal muscle index.

In adjusted models, each ½-SD decrease in thigh muscle attenuation (indicating greater lipid content) was associated with a 15 m decrease in 6MWD (95% CI −21 to −10, p<0.001, figure 1A, table 2). Each ½-SD decrease in abdominal muscle attenuation was associated with a 14 m decrease in 6MWD (95% CI −20 to −8, p<0.001, figure 1B). Associations remained after controlling for BMI.

Each doubling in IMAT index was associated with a 13 m decline in 6MWD (95% CI −20 to −6, p=0.001, figure C). BMI was not associated with 6MWD (figure D).

Among subjects with suppurative lung disease, decreased muscle attenuation may be associated with increased walk distance, though this was not statistically significant (online supplementary table S3).

In the full cohort, 41 subjects died or were delisted; 144 underwent transplantation over median 2.3 years (IQR 0.5–4.4). Every ½-SD decrease in abdominal muscle attenuation was associated with 20% increased risk of death/delisting (subdistribution HR 1.2, 95% CI 1.1 to 1.4, p=0.006, table 2). Thigh muscle attenuation was not associated with death/delisting. Among subjects with IMAT, 24 died or were delisted, 97 were transplanted over median 2.3 years (IQR 0.5–4.5). There was no association between IMAT index and death/delisting. Survival was not assessed by subgroups due to small number of events for each diagnosis.

Table 2 Association between muscle attenuation, thigh IMAT index, muscle attenuation and 6 min walk distance, gait speed and survival

6MWD	N	Change in 6MWD (m) per ½-SD decrease in thigh mean muscle attenuation	95% CI	P value	N	Change in 6MWD (m) per doubling in thigh IMAT index	95% CI	P value	N	Change in 6MWD (m) per ½-SD decrease in abdominal mean muscle attenuation	95% CI	P value
Unadjusted	276	−19	−25 to −13	<0.001	206	−10	−19 to −2	0.01	302	−18	−24 to −13	<0.001
Model 1*	275	−15	−21 to −10	<0.001	205	−12	−19 to −4	0.002	301	−14	−20 to −8	<0.001
Model 2†	275	−15	−21 to −10	<0.001	190	−13	−20 to −6	0.001	301	−14	−20 to −8	<0.001
Model 3‡	275	−13	−19 to −7	<0.001	190	−6	−16 to 3	0.18	301	−14	−20 to −7	<0.001

Survival	N	Sub-hazard distribution for death or delisting per ½-SD decrease in thigh mean muscle attenuation	95% CI	P value	N	Subhazard distribution for death or delisting per doubling in thigh IMAT index	95% CI	P value	N	Subhazard distribution for death or delisting per ½-SD decrease in abdominal mean muscle attenuation	95% CI	P value
Unadjusted	276	1.1	0.9 to 1.3	0.40	206	1.0	0.9 to 1.1	0.86	302	1.2	1.01 to 1.5	0.04
Model 1*	275	1.1	0.9 to 1.3	0.31	205	1.0	0.9 to 1.1	0.83	301	1.2	0.99 to 1.5	0.06
Model 2†	275	1.1	0.9 to 1.2	0.25	190	1.0	0.98 to 1.04	0.47	301	1.2	1.1 to 1.4	0.006
Model 3‡	275	1.1	0.96 to 1.2	0.21	190	1.0	0.8 to 1.4	0.89	301	1.3	1.2 to 1.4	<0.001

*Adjusted for sex, age, forced vital capacity and diagnosis; centre as random effect in 6MWD models; standard errors clustered by centre in survival models.
†Model 1+skeletal muscle index.
‡Model 2+body mass index.
IMAT, intramuscular adipose tissue; 6MWD, 6 min walk distance.

DISCUSSION

Greater skeletal muscle adiposity was associated with decreased 6MWD and wait-list survival. While BMI remains the primary metric for evaluating body composition in lung transplant candidates, it was not associated with walk distance. This contrasts with work demonstrating an inverse association between BMI and walk distance in COPD and may reflect transplant candidate selection criteria. Ours adds to work demonstrating the utility of cross-sectional imaging to improve assessments of frailty,[7] post-transplant mechanical ventilation and tracheostomy.[8]

Concordantly, prior work demonstrated an association between greater muscle adiposity and decreased 6MWD in COPD[9] and decreased liver transplant survival.[3] Numerous mechanisms link muscle adiposity and 6MWD. Increased fatty acid accumulation in and around muscle drives preferential utilisation of fatty acids resulting in decreased protein synthesis and regenerative capacity.[10] Obese and aged adipose contains more senescent cells that impair muscle regeneration[11] and are associated with decreased gait speed.[12]

In contrast, greater muscle adiposity may be associated with increased 6MWD in suppurative lung disease. This may reflect nutritional status given known associations between higher BMI and greater 6MWD in cystic fibrosis.[13]

Adipose tissue is a buffer for free fatty acids, and in states of inflammation insufficient buffering may lead to ectopic deposition.[14] Frailty is associated with decreased survival and greater abdominal visceral adipose tissue (VAT) deposition in lung transplant candidates.[7 15] Whether muscle adiposity, which moderately correlates with VAT, is a similar marker of metabolic derangement or causes frailty, is unknown.

Our study has limitations. We found no association between thigh muscle attenuation and survival despite an association with abdominal muscle attenuation potentially reflecting underpowered analyses or different mechanisms of adipose deposition. Our cross-sectional analysis does not establish causality. Thirty-four subjects were censored at the time of analysis for unknown vital status, though missing deaths are unlikely given close clinical follow-up at transplant centres.

Cross-sectional imaging provides information not captured by BMI. Future work should investigate its role in candidate selection and prioritisation.

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