Title

Adipose tissue quantification and primary graft dysfunction after lung transplantation: The Lung Transplant Body Composition study.

Journal

The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation, 38(12)

ISSN

1053-2498

Authors

Anderson, Michaela R
Udupa, Jayaram K
Edwin, Ethan
et al.

Publication Date

2019-12-01

DOI

10.1016/j.healun.2019.08.013

Peer reviewed

Published in final edited form as:

J Heart Lung Transplant. 2019 December ; 38(12): 1246–1256. doi:10.1016/j.healun.2019.08.013.

Adipose tissue quantification and primary graft dysfunction after lung transplantation: The Lung Transplant Body Composition study

Michaela R. Anderson, MD MS[1], **Jayaram K. Udupa, PhD**[2], **Ethan Edwin, PhD**[3], **Joshua M. Diamond, MD MS**[4], **Jonathan P. Singer, MD**[5], **Jasleen Kukreja, MD MPH**[6], **Steven R Hays, MD**[5], **John R Greenland, MD PhD**[5], **Anthony Ferrante Jr, MD PhD**[3], **Matthew Lippel**[1], **Tatiana Blue**[1], **Amika McBurnie**[1], **Michelle Oyster, MS**[4], **Laurel Kalman**[4], **Melanie Rushefski**[4], **Caiyun Wu**[2], **Gargi Pednekar, MS**[2], **Wen Liu, PhD**[1], **Selim Arcasoy, MD**[1], **Joshua Sonett, MD**[7], **Frank D'Ovidio, MD**[7], **Matthew Bacchetta, MD**[8], **John D Newell Jr, MD**[9], **Drew Torigian, MD MA**[2], **Edward Cantu, MD MS**[10], **Donna L. Farber, PhD**[6,11,12], **Jon T. Giles, MD MPH**[1], **Yubing Tong, PhD**[2], **Scott Palmer, MD**[13], **Lorraine B. Ware, MD**[14], **Wayne W. Hancock, MBBS PhD**[15], **Jason D. Christie, MD MS**[4,*], **David J. Lederer, MD MS**[1,16,*]

[1]Department of Medicine, Columbia University Medical Center, New York, NY

[2]Department of Radiology, University of Pennsylvania, Philadelphia, PA

[3]Columbia Institute of Human Nutrition, Columbia University Medical Center, New York, NY

[4]Department of Medicine, University of Pennsylvania, Philadelphia, PA

[5]Department of Medicine University of California at San Francisco, San Francisco, CA

[6]Department of Surgery, University of California at San Francisco, San Francisco, CA

[7]Department of Surgery, Columbia University Medical Center, New York, NY

[8]Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville, TN

[9]Department of Radiology, University of Iowa, Iowa City, IA

[10]Department of Surgery, University of Pennsylvania, Philadelphia, PA

[11]Columbia Center for Translational Immunology, Columbia University Medical Center, New York, NY

Corresponding Author: David J Lederer MD MS, Associate Professor of Medicine and Epidemiology, Columbia University Medical Center, 161 Fort Washington Avenue, Room 3-321A, New York, NY 10032, Phone: 212-305-8203, Fax: 212-305-8426, davidlederer@columbia.edu.

*These authors contributed equally to this work.

Author Contributions

Study Design: MRA, JMD, JDN, DT, DLF, JTG, SP, JDC, DJL

Data Acquisition, Analysis, Interpretation: MRA, JK, EE, JPS, JK, ML, TB, AM, MO, LK, MR, CW, GP, WL, SA, JS, FD, MB, EG, YT, LBW, WWH, JDC, DJL

First draft of the manuscript: MRA, JDC, DJL

Final Approval of the manuscript: All authors

[12]Department of Microbiology and Immunology, Columbia University Medical Center, New York, NY

[13]Duke University, Department of Medicine & Duke Clinical Research Institute, Durham, NC

[14]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

[15]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

[16]Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY

Abstract

Background: Obesity is associated with increased risk of primary graft dysfunction (PGD) after lung transplantation. The contributions of specific adipose tissue depots is unknown.

Methods: We performed a prospective cohort study of adult lung transplant recipients at four U.S. transplant centers. We measured cross-sectional areas of subcutaneous (SAT) and visceral adipose tissue (VAT) on chest and abdominal CT scans and indexed each measurement to height^2. We used logistic regression to examine associations of adipose indices and adipose classes with grade 3 PGD at 48 or 72 hours, and Cox proportional hazards models to examine survival. We used latent class analyses to identify patterns of adipose distribution. We examined associations of adipose indices with plasma biomarkers of obesity and PGD.

Results: 262 and 117 subjects had available chest CT scans and underwent protocol abdominal CT scans, respectively. In adjusted models, greater abdominal SAT index was associated with an increased risk of PGD (OR 2.0, 95% CI 1.03 to 4.1, p=.04) but not with survival time. VAT indices were not associated with PGD risk or survival time. Greater abdominal SAT index correlated with greater pre- and post-transplant leptin (r=.60, p<0.001, and r=0.42, p<0.001), pre-transplant IL-1RA (r=.25, p=0.04), and post-transplant ICAM-1 (r=.25, p=0.04). We identified three latent patterns of adiposity. The class defined by high thoracic and abdominal SAT had the greatest risk of PGD.

Conclusions: Subcutaneous, but not visceral, adiposity is associated with increased risk of PGD after lung transplantation.

Keywords

adipose tissue; primary graft dysfunction; lung transplantation

Introduction

Primary graft dysfunction (PGD), defined as acute lung injury within 72 hours of lung transplantation (1), affects 12 to 32% of all lung transplants, is a major cause of death within the first year after transplantation (2–5), and is a risk factor for bronchiolitis obliterans syndrome (6). There are no targeted therapies for PGD; treatment relies on supportive therapy focused on prevention of additional injury while awaiting lung recovery. A better understanding of risk factors for PGD will help identify patients at increased risk before transplant, as well as target pathways for prevention and treatment.

Obesity is a chronic pro-inflammatory state associated with changes in adipose tissue inflammation, and a risk factor for PGD after lung transplantation (7). Adipocyte hypertrophy, resulting from storage of excess fatty acids, produces interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) which along with increased free fatty acids (8–11), and increased leptin (12), recruits pro-inflammatory adipose tissue macrophages (ATMs) (8, 13). Pro-inflammatory ATMs produce interleukin-1 beta (IL1-β) which further stimulates adipocyte production of IL-6 and MCP-1 (14), a process that is decreased in the presence of interleukin-1 receptor antagonist (IL-1RA) (15). Visceral adipose tissue (VAT) contains a greater number of pro-inflammatory ATMs, although subcutaneous adipose tissue (SAT) in the obese also has an inflammatory phenotype with a similar number of ATMs (16) and increased T cell chemokines (17).

Subcutaneous and visceral adipose depots in both abdominal and thoracic compartments are associated with disease states and outcomes. Increased abdominal SAT is associated with increased cardio-metabolic risk factors (18, 19), incident heart failure (20), and acute kidney injury (21). Increased abdominal VAT is associated with decreased survival after liver transplantation (22, 23), while increased intrathoracic VAT has been associated with increased risks of atrial fibrillation (24), coronary artery disease (25, 26), systemic hypertension (25), and reduced right ventricular mass (27). The role of various adipose depots and obesity-related inflammation in PGD remains unknown.

Although obesity, as defined by the body mass index (BMI) is a poor surrogate for adipose depot distribution (28–34), it remains the primary metric used by centers to establish transplant candidacy. A better measure of obesity could identify novel targets for prevention and treatment and ultimately improve risk stratification prior to lung transplantation. Thus we examined associations between the size of various adipose tissue depots on computed tomography (CT) imaging and PGD risk after lung transplantation. We secondarily examined the association of both adipose indices and biomarkers of adiposity with PGD. Our a priori hypotheses specified that greater SAT and VAT in either compartment would be associated with an increased risk of PGD after lung transplantation.

Methods

Study Participants

The Lung Transplant Body Composition (LTBC) study is an NHLBI-funded multi-center prospective cohort study designed to examine the relationship between adiposity and PGD after lung transplantation. LTBC is nested within the Lung Transplant Outcomes Group (LTOG) study, which examines risk factors for PGD (2). Subjects were eligible for enrollment in LTBC if they were at least 18 years of age and undergoing lung transplant evaluation between 2011 and 2014 at the University of Pennsylvania, Columbia University, or Duke University. Additional subjects from the University of California at San Francisco who were enrolled in LTOG and had available clinically indicated chest CT scans were added to the cohort after LTBC enrollment had completed.

LTBC and LTOG studies were approved by Institutional Review Boards at all participating centers, and all participants provided informed consent prior to enrollment. Details of LTOG data collection and variable definitions have been previously described (2, 7, 35).

Measurement of Abdomen CT Adipose Tissue Area

A subset of LTBC participants consented to undergo a single slice (10 mm) abdominal CT scan at the level of the L4/L5 vertebrae using Siemens or GE scanners. Techniques used to identify abdominal subcutaneous and visceral adipose tissues have been previously described and are provided in the Supplement (21, 36) (Figure 1A–B).

Measurement of Chest CT Adipose Tissue Area

Clinically-indicated non-research pre-transplant unenhanced full inspiration CT scans were used for thoracic adipose quantification. Using a standardized anatomic space approach (37, 38), our group previously identified that the maximum correlation between total volume of thoracic SAT and single slice area of thoracic SAT is found at the mid-T8 vertebral level (Pearson's r= 0.97), and maximum correlation between total volume of thoracic VAT and single slice area of thoracic VAT is found at the mid-T7 vertebral level (Pearson's r= 0.86) (37). Using this technique, we identified the single slice cross-sectional area of thoracic VAT and thoracic SAT (Figure 1C–D). There was high interrater reliability with an intra-class correlation coefficient of .98 for thoracic SAT and .97 for thoracic VAT (Supplement Figures 1A–B). Readers were blinded to PGD status.

Plasma biomarkers

Plasma samples were obtained prior to and 24 hours after transplantation and stored at −80°C as previously published (39). Circulating biomarkers of obesity (leptin), coagulation (plasminogen activator inhibitor 1, PAI-1), cell adhesion (intracellular adhesion molecule-1, ICAM-1), innate immunity (long pentraxin-3, PTX3), inflammatory modulation (IL-1RA), and macrophage recruitment and T cell differentiation (IL-6), were chosen based on known associations with PGD and/or obesity (7, 39–45). Biomarker levels were measured on multiplex assays using Meso Scale Discovery platforms and were $\log_2$ transformed to normalize the distributions. Sample concentrations below the lower limit of detection were assigned values equal to halfway between zero and the lower limit of detection for the assay.

Primary Graft Dysfunction

All chest radiographs were collected at the time of transplantation and transmitted to the University of Pennsylvania where they were reviewed by two independent observers with adjudication as previously published (2, 35). The primary outcome was grade 3 PGD at 48 or 72 hours after transplantation defined as a PaO_2/FiO_2 ratio <200 with parenchymal opacities consistent with diffuse pulmonary edema (1, 35, 46, 47).

Analysis Approach

We operationalized adipose area in two fashions: (1) absolute cross-sectional area, and (2) area indexed to height-squared (m^2) (48). We $\log_2$ transformed the adipose measures to normalize distributions and allow estimation of associations per doubling of each

independent variable of interest. We evaluated the convergent and divergent validity of abdominal and thoracic adipose indices with other measures of body composition using Pearson correlation coefficients.

We used logistic regression models to examine associations between each independent variable of interest and PGD risk. We performed our primary analyses using generalized covariate balanced propensity scores to adjust for groups of covariates using a single propensity score (49–51) in order to avoid over-parameterized models. We performed multiple imputation with chained equation in ten datasets using the "MICE" package in R (51). We derived propensity scores in each imputed dataset and included the propensity scores as imputed covariates in our models. We used directed acyclic graphs (DAG) to identify the following confounders (Supplement Figure 2A–B), which we included in a "minimally adjusted" propensity score: intraoperative transfusion requirement, allograft ischemic time, intraoperative pulmonary artery systolic pressure, intraoperative use of extracorporeal support, and center. We also adjusted models by covariate groups defined as recipient characteristics (sex, pre-transplant diagnosis, lung allocation score (LAS), center), donor characteristics (total ischemic time, donor smoking), and operative characteristics (single vs. double lung transplantation, intraoperative use of cardiopulmonary bypass or extracorporeal membrane oxygenation, intraoperative transfusions greater than 1 liter of packed red blood cells). In order to demonstrate the durability of the effect estimates, (1) we performed sensitivity analyses with models adjusted for individual covariates, and (2) we have presented our results in a "model-building" format in which we sequentially adjusted for groups of covariates. We explored the use of non-linear terms for adipose indices using generalized additive models with the "GAM" function in R (52). In order to compare the relative contributions of the SAT index and BMI to PGD risk, we calculated R-squared values for models of PGD with: (1) minimally adjusted covariates, (2) minimally adjusted covariates plus BMI, and (3) minimally adjusted covariates plus the abdominal SAT index.

We evaluated the association between adipose depots associated with PGD and biomarkers of adiposity and PGD using Pearson correlation coefficients.

We performed latent class analysis to identify subgroups of subjects that were similar on observable characteristics (abdominal and thoracic SAT area, abdominal and thoracic VAT area, age, and sex) (53, 54). We compared the Bayesian Information Criteria to identify the optimal number of classes and the entropy to assess adequacy of fit. Each subject was assigned to the class to which they had the highest predicted probability of belonging.

We used multivariable adjusted Cox proportional hazards models to examine associations between adipose tissue area and survival time (time from transplantation to death) after transplantation. We confirmed the proportional hazards assumption by regressing Schoenfeld residuals over time.

All analyses were performed in STATA/IC version 15.1 (StataCorp, LP College Station, TX) (55) and R version 3.3.1 (R Foundation for Statistical Computing)

Results

Study Participants

Three-hundred fifty-six enrolled subjects underwent lung transplantation and had either an available chest CT or underwent single slice CT of the abdomen as part of the research protocol. Among these subjects, one was missing PGD assessment, 6 were missing chest imaging, and 21 were missing height, leaving 328 for inclusion in thoracic VAT analyses (Figure 2A). An additional 66 subjects had clinically-indicated chest CTs that cut off a portion of SAT, leaving 262 scans for inclusion in analyses of thoracic SAT. A total of 120 subjects consented to undergo abdominal imaging, of whom 117 had available measures for abdominal SAT and 116 had available measures for abdominal VAT (Figure 2B). Plasma biomarkers were available on a subset of 130 subjects. Due to availability of adequate plasma volume, some subjects did not have all biomarkers analyzed (Supplement Table 1).

Among the entire cohort, the median (interquartile range, IQR) age was 61 (53–66) years, 59% were male, 75% white, 9% African-American, 17% had chronic obstructive pulmonary disease (COPD), 64% had interstitial lung disease (ILD), and 53% required intraoperative mechanical support. The median LAS at time of transplantation was 41.6 (36.1 to 51.0) and the median BMI was 25.1 kg/m^2 (IQR 22.0 to 28.2). Donors were 83% male, 25% had a history of cigarette smoking, 42% were white, and 16% were African-American (Supplement Table 2). Among subjects with abdominal CT scans, there was a median (IQR) of 182 days (83-397) between the abdominal CT scan and transplantation. Among subjects with thoracic CT scans, there was a median (IQR) of 150 days (79-294) between the chest CT and transplantation. Twenty percent (n=70) developed grade 3 PGD at 48 or 72 hours after transplantation. The one-year mortality rate was 7.5 deaths per 100 person-years (95% CI 4.9 to 10.9). A total of sixty-three (18%) subjects died over a median 2.7 years after transplantation.

Compared to those in the thoracic SAT cohort, subjects in the abdominal SAT cohort were more likely to be white, more likely to have a male donor, more likely to have a donor with a history of smoking, more likely to have a white donor, and less likely to require intraoperative mechanical circulatory support (Table 1). Baseline characteristics by availability of plasma biomarkers and tertile of adipose measures are available in the Supplement (Supplement Tables 3–4).

Convergent and Divergent Validity of CT Measures of Adiposity

Abdominal and thoracic VAT and SAT indices were highly correlated with each other as well as BMI, waist circumference, hip circumference, and waist to hip ratio (Table 2). BMI was most closely correlated with SAT area in both the abdomen (r=.74) and chest (r=.68). Waist circumference was most closely correlated with VAT area in the abdomen (r=.74) and SAT area in the chest (r=.65). Hip circumference was most closely correlated with SAT area in the abdomen (r=.77) and chest (r=.65). Waist to hip ratio was most closely correlated with VAT area in the abdomen (r=.57) and chest (r=.47).

Subcutaneous adipose tissue

Among subjects with abdominal SAT measured, 23 (20%) developed grade 3 PGD at 48 or 72 hours after transplantation. Each doubling in the abdominal SAT index was associated with 1.9-fold increased odds of PGD in both minimally (OR 95% CI 1.02 to 3.4, p=.04, Table 3, Figure 3A) and fully adjusted models (OR 95% CI 1.1 to 3.4, p=.03). The association was similar in analyses adjusted for propensity scores for recipient characteristics, donor characteristics, and operative characteristics (Table 3) and in additional sensitivity analyses (Supplement Table 5–6). Results were similar when evaluating the association between abdominal SAT area (rather than index) and PGD risk (Supplement Table 7, Supplement Figure 3A).

Among subjects with available thoracic SAT measured, 45 (17%) developed grade 3 PGD at 48 or 72 hours after transplantation. We did not detect significant associations between either thoracic SAT index (Table 3, Figure 3B) or thoracic SAT area (Supplement Table 7, Supplement Figure 3B) and PGD risk in any models. In analyses of abdominal or thoracic SAT index among subjects with all 4 available scans, we did not detect a significant association between SAT index or SAT area and PGD or death after transplantation (Supplement Tables 6–7).

Addition of the abdominal SAT index to our models improved the fit of the minimally adjusted model by 55%, while the addition of BMI improved the fit by 36% (Supplement Table 8).

Visceral adipose tissue and PGD risk

Twenty-three subjects (20%) with measured abdominal VAT and 63 subjects (19%) with measured thoracic VAT developed PGD. We did not detect associations between thoracic VAT index, thoracic VAT area, abdominal VAT index, or abdominal VAT area and PGD risk in any models (Supplement Tables 9–11).

Latent class analysis

Latent class analyses identified 3 distinct groups (Supplement Table 12). Class 1 (n=22), referred to going forward as the high SAT group, was characterized by high thoracic and abdominal SAT; class 2 (N=46) had intermediate SAT, and class 3 (N=30) had low abdominal and thoracic SAT (Supplement Table 13). Although lacking precision in the estimates in this small under-powered post-hoc subgroup analysis, those in low and intermediate SAT groups had lower adjusted risk of PGD compared to those with high SAT (Supplement Table 14).

Post-transplant Survival

We did not observe an association between adipose measures and survival time (Supplement Tables 6–7, 9–10).

Biomarkers

Subjects with available biomarkers were more likely to be transplanted from a male donor or a white donor, and less likely to require intra-operative cardiopulmonary support but were

otherwise similar to those without available biomarkers (Supplement Table 3). Both abdominal and thoracic SAT indices were positively associated with pre-transplant leptin (abdominal SAT index r=.61 p<0.0001, thoracic SAT index r=.47, p<0.0001, Figure 4A–B), post-transplant leptin (abdominal SAT index r=.44, p<0.44, and thoracic SAT index r=.41, p<0.0001, Supplement Figure 4), and pre-transplant IL1-RA (abdominal SAT index r=.25, p=0.04, thoracic SAT index r=.28, p-=0.005, Figure 4C, Supplement Figure 5). Abdominal SAT index was significantly associated with post-transplant ICAM-1 levels (r=.25, p=0.04, Supplement Figure 6). There was no significant association between changes in leptin levels from pre- to post-transplant (Supplement Figure 4). There was no significant association between abdominal or thoracic SAT index and pre-transplant levels, post-transplant levels, or change in levels from pre- to post-transplant for IL-6 (Supplement Figure 7), PTX3 (Supplement Figure 8), or PAI-1 (Supplement Figure 9).

Discussion

We found that a greater quantity of abdominal SAT was associated with an increased risk of PGD after lung transplantation. Neither thoracic nor abdominal VAT measures seem to be associated with PGD risk despite these CT measures having strong construct validity as measures of adiposity. SAT adipose measures were also associated with higher plasma levels of leptin, IL-1RA, and ICAM-1. Based on post-hoc latent class analyses, those with both high thoracic and abdominal subcutaneous adiposity seemed to be at increased risk of PGD compared to those with intermediate or low subcutaneous adiposity. Overall, our findings support the hypothesis that subcutaneous, but not visceral, adipose tissue may play a role in the development of PGD after lung transplantation.

While VAT may be considered a more inflammatory tissue, SAT has an inflammatory phenotype with a similar number of adipose tissue macrophages (16) and increased T cell chemokines in obese compared to lean adults (17). Increased abdominal SAT is associated with increased cardio-metabolic risk factors (18, 19), incident heart failure in the elderly (20), and acute kidney injury after trauma (21). In addition to its inflammatory effects, obese adipose tissue is characterized by impaired clearance of reactive oxygen species and increased circulating free fatty acids (56, 57), both of which are associated with PGD risk (58). Furthermore, total SAT area is significantly greater than VAT area which may additionally account for the differential PGD effects between the two depots.

Adipose tissue is a major source of IL1-RA (15) consistent with our finding of increased IL1-RA with greater SAT. Exogenous IL-1RA attenuates ischemia-reperfusion injury in a rat model of myocardial ischemia (59) and decreases acute inflammation in a bleomycin mouse model of idiopathic pulmonary fibrosis (60). Greater IL-1RA does not seem to have had protective effects in patients with greater SAT, which may be related to corticosteroid administration (61,62), or maximal IL-1RA production at baseline. Alternately, greater IL-1RA may be a plasma marker of higher IL1-β production as has been suggested in critical illness (63). Further investigation of the role of adipose-mediated changes in IL1-RA production and IL1-β kinetics may identify a modifiable target for PGD prevention.

ICAM-1 is a pulmonary vascular endothelial marker associated with PGD risk (39). Obesity alters endothelial cell function via increased endoplasmic reticulum stress and decreased expression of endothelial junctional adherence proteins, resulting in increased circulating levels of vascular endothelial markers including ICAM-1, and increased vascular injury in response to lipopolysaccharide in mouse models (69, 70). The direct association between SAT and post-transplant ICAM-1 suggests that SAT may increase PGD risk through altered pulmonary endothelial cell function.

We identified a correlation between greater SAT and increased plasma leptin before and after transplantation. Leptin is produced by adipose tissue, may increase ATM recruitment (12), alters neutrophil chemotaxis (64,65), is increased in the BAL of patients with acute lung injury (66), and may increase macrophage-mediated cytokine production (67). Leptin resistance is protective from hyperoxia-induced lung injury and decreases both inflammation and fibrosis in a bleomycin-induced mouse model of acute lung injury (66, 68) suggesting that SAT-derived leptin may not only play a role in the pathogenesis of PGD but also link PGD to chronic lung allograft dysfunction.

Greater abdominal SAT may lead to misclassification of PGD through mechanical effects on the lungs including atelectasis and decreased chest wall compliance. However severe PGD is characterized by both radiologic changes and severe hypoxemia. Severe hypoxemia is unlikely to be caused by mechanical effects alone. Extensive work has validated the current diagnostic criteria for PGD (35, 46) suggesting that misclassification is unlikely to account for this association. Furthermore, prior latent class analysis evaluating sub-phenotypes of PGD identified classes that did not significantly differ by BMI as would be expected if chest wall compliance were leading to misclassification (47).

There are several limitations to the current study. First, our patient population is predominantly normal or overweight with few obese patients, which may limit generalizability of our findings particularly with greater degrees of adiposity present in the general population. However, despite our limited BMI range, we identified an increased risk associated with increased abdominal SAT suggesting that subcutaneous adipose area identifies additional PGD risk even among patients who appear low risk by BMI. Additionally, the population selected represents the overall transplant population and our approach, including the delay between imaging and transplantation, is pragmatic in the setting of unpredictable transplant timing thus making it particularly relevant to this question. Whether there are changes in adiposity prior to lung transplantation is unknown. Second, we have a relatively small cohort with few events, limiting the ability to evaluate effect modification by classic risk factors including cardiopulmonary bypass, diagnosis, and donor smoking. Notably, our main effect estimates remain significant even when including a large number of covariates in the model suggesting a durable effect despite small sample size. Third, we were only able to evaluate circulating biomarkers as a measure of systemic inflammation. This may fail to identify local effects of adipose-mediated inflammation. Fourth, measurement of single slice cross-sectional area of adipose may not entirely reflect total adiposity. Prior work has demonstrated a significant correlation between single slice cross-sectional area and total volume of adipose (37, 38); additionally, our measures of adipose were highly correlated with traditional measures of body composition suggesting

that we are measuring the tissue of interest. Fifth, the divergent findings in abdominal and thoracic subcutaneous adipose could also reflect either (1) different populations rather than differential effects of the two distinct anatomic adipose depots or (2) differences in adipose measurement related to the use of clinically-indicated rather than protocolized research thoracic CT scans. Reassuringly, on clinically observable characteristics, the two groups appear similar. Sixth, both abdominal and thoracic imaging were only available on a subgroup of 98 subjects thus limiting interpretation of our latent class models. Seventh, while our analyses reflect the results of our a priori hypotheses, there remains a small risk of a false positive finding given the multiple comparisons made. Finally, our study was not designed to evaluate the role of abdominal SAT measurement in pre-operative risk stratification, while our data suggest that abdominal SAT may better model PGD risk compared to BMI, additional work is required before this could be integrated into routine clinical assessment.

The reason that SAT, but not VAT, appears to contribute to PGD risk remains unclear but may be related to (1) the larger volume of total SAT, (2) differences in systemic effects of SAT including increased reactive oxygen species and free fatty acids, (3) anatomic differences in drainage or changes in compliance, or (4) we have failed to detect an association between VAT and PGD where one truly exists.

In summary, we have shown that greater abdominal subcutaneous adipose tissue area was associated with increased risk of PGD after lung transplantation independent of known PGD risk factors in a multi-center prospective cohort study. We have also highlighted the potential utility of measuring body composition through advanced imaging techniques, rather than non-specific measurements such as BMI, in order to better understand mechanisms linking body composition and outcomes in lung transplantation. Further research is required to establish the mechanisms by which adipose tissue affects the pulmonary parenchyma including the potential role of changes in free fatty acid levels, reactive oxygen species, local changes in inflammation, and pulmonary endothelial cell injury. Additionally, future studies should focus on the role of abdominal SAT in risk stratification prior to lung transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We gratefully acknowledge our research coordinators for their work on patient recruitment, data acquisition and specimen storage, and our patients for their participation in the study. We additionally acknowledge the methodological input of A. Russell Localio PhD.

Funding Information:

Supported by National Institutes of Health/NHLBI Grants: R01 HL114626, R01 HL087115, K24 HL115354, K24 HL 131937, K23 HL121406, K23 HL111115, T32 HL105323, K23 HL 116656, R03 HL135227, R01 DK066525, T32 DK07328, R01 HL134851, VA ORD IK2 CX001034 and with the support of RWJ AMFDP 70640 and the Stony-Wold Herbert Foundation

References

1. Snell GI, Yusen RD, Weill D, et al.: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2017;36:1097–103. [PubMed: 28942784]
2. Diamond JM, Lee JC, Kawut SM, et al.: Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527–34. [PubMed: 23306540]
3. Christie JD, Sager JS, Kimmel SE, et al.: Impact of primary graft failure on outcomes following lung transplantation. Chest 2005;127:161–5. [PubMed: 15653978]
4. Christie JD, Bavaria JE, Palevsky HI, et al.: Primary graft failure following lung transplantation. Chest 1998;114:51–60. [PubMed: 9674447]
5. Christie JD, Kotloff RM, Ahya VN, et al.: The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 2005;171:1312–6. [PubMed: 15764726]
6. Daud SA, Yusen RD, Meyers BF, et al.: Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2007;175:507–13. [PubMed: 17158279]
7. Lederer DJ, Kawut SM, Wickersham N, et al.: Obesity and primary graft dysfunction after lung transplantation: the Lung Transplant Outcomes Group Obesity Study. Am J Respir Crit Care Med 2011;184:1055–61. [PubMed: 21799077]
8. Gustafson B, Hammarstedt A, Andersson CX, Smith U: Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27:2276–83. [PubMed: 17823366]
9. Zha BS, Zhou H: ER Stress and Lipid Metabolism in Adipocytes. Biochem Res Int 2012;2012:312943. [PubMed: 22400114]
10. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr.: Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808. [PubMed: 14679176]
11. Curat CA, Miranville A, Sengenes C, et al.: From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. Diabetes 2004;53:1285–92. [PubMed: 15111498]
12. Dib LH, Ortega MT, Fleming SD, Chapes SK, Melgarejo T: Bone marrow leptin signaling mediates obesity-associated adipose tissue inflammation in male mice. Endocrinology 2014;155:40–6. [PubMed: 24169547]
13. Andersson CX, Gustafson B, Hammarstedt A, Hedjazifar S, Smith U: Inflamed adipose tissue, insulin resistance and vascular injury. Diabetes Metab Res Rev 2008;24:595–603. [PubMed: 18756581]
14. Gao D, Madi M, Ding C, et al.: Interleukin-1beta mediates macrophage-induced impairment of insulin signaling in human primary adipocytes. Am J Physiol Endocrinol Metab 2014;307:E289–304. [PubMed: 24918199]
15. Juge-Aubry CE, Somm E, Giusti V, et al.: Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. Diabetes 2003;52:1104–10. [PubMed: 12716739]
16. Kralova Lesna I, Kralova A, Cejkova S, et al.: Characterisation and comparison of adipose tissue macrophages from human subcutaneous, visceral and perivascular adipose tissue. J Transl Med 2016;14:208. [PubMed: 27400732]
17. Wu H, Ghosh S, Perrard XD, et al.: T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. Circulation 2007;115:1029–38. [PubMed: 17296858]
18. Newton RL Jr., Bouchard C, Bray G, et al.: Abdominal adiposity depots are correlates of adverse cardiometabolic risk factors in Caucasian and African-American adults. Nutr Diabetes 2011;1:e2. [PubMed: 23154294]

19. Fox CS, Massaro JM, Hoffmann U, et al.: Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39–48. [PubMed: 17576866]
20. Nicklas BJ, Cesari M, Penninx BW, et al.: Abdominal obesity is an independent risk factor for chronic heart failure in older people. J Am Geriatr Soc 2006;54:413–20. [PubMed: 16551307]
21. Shashaty MG, Kalkan E, Bellamy SL, et al.: Computed tomography-defined abdominal adiposity is associated with acute kidney injury in critically ill trauma patients*. Crit Care Med 2014;42:1619–28. [PubMed: 24776609]
22. Hamaguchi Y, Kaido T, Okumura S, et al.: Impact of Skeletal Muscle Mass Index, Intramuscular Adipose Tissue Content, and Visceral to Subcutaneous Adipose Tissue Area Ratio on Early Mortality of Living Donor Liver Transplantation. Transplantation 2017;101:565–74. [PubMed: 27926595]
23. Terjimanian MN, Harbaugh CM, Hussain A, et al.: Abdominal adiposity, body composition and survival after liver transplantation. Clin Transplant 2016;30:289–94. [PubMed: 26717257]
24. Stojanovska J, Kazerooni EA, Sinno M, et al.: Increased epicardial fat is independently associated with the presence and chronicity of atrial fibrillation and radiofrequency ablation outcome. Eur Radiol 2015;25:2298–309. [PubMed: 25764090]
25. Rosito GA, Massaro JM, Hoffmann U, et al.: Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. Circulation 2008;117:605–13. [PubMed: 18212276]
26. Mahabadi AA, Massaro JM, Rosito GA, et al.: Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. Eur Heart J 2009;30:850–6. [PubMed: 19136488]
27. Wenger DS, Kawut SM, Ding J, et al.: Pericardial Fat and Right Ventricular Morphology: The Multi-Ethnic Study of Atherosclerosis- Right Ventricle Study (MESA-RV). PLoS One 2016;11:e0157654. [PubMed: 27311062]
28. Singer JP, Peterson ER, Snyder ME, et al.: Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med 2014;190:1012–21. [PubMed: 25233138]
29. Shah NR, Braverman ER: Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. PLoS One 2012;7:e33308. [PubMed: 22485140]
30. Martin V, Davila-Batista V, Castilla J, et al.: Comparison of body mass index (BMI) with the CUN-BAE body adiposity estimator in the prediction of hypertension and type 2 diabetes. BMC Public Health 2016;16:82. [PubMed: 26817835]
31. Sardinha LB, Lohman TG, Teixeira PJ, Guedes DP, Going SB: Comparison of air displacement plethysmography with dual-energy X-ray absorptiometry and 3 field methods for estimating body composition in middle-aged men. Am J Clin Nutr 1998;68:786–93. [PubMed: 9771855]
32. Romero-Corral A, Somers VK, Sierra-Johnson J, et al.: Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond) 2008;32:959–66. [PubMed: 18283284]
33. Flegal KM, Shepherd JA, Looker AC, et al.: Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. Am J Clin Nutr 2009;89:500–8. [PubMed: 19116329]
34. Kuk JL, Janiszewski PM, Ross R: Body mass index and hip and thigh circumferences are negatively associated with visceral adipose tissue after control for waist circumference. Am J Clin Nutr 2007;85:1540–4. [PubMed: 17556690]
35. Christie JD, Bellamy S, Ware LB, et al.: Construct validity of the definition of primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2010;29:1231–9. [PubMed: 20655249]
36. Pou KM, Massaro JM, Hoffmann U, et al.: Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234–41. [PubMed: 17709633]

37. Tong Y, Udupa JK, Torigian DA, et al.: Chest Fat Quantification via CT Based on Standardized Anatomy Space in Adult Lung Transplant Candidates. PLoS One 2017;12:e0168932. [PubMed: 28046024]
38. Tong Y, Udupa JK, Torigian DA: Optimization of abdominal fat quantification on CT imaging through use of standardized anatomic space: a novel approach. Med Phys 2014;41:063501. [PubMed: 24877839]
39. Shah RJ, Bellamy SL, Localio AR, et al.: A panel of lung injury biomarkers enhances the definition of primary graft dysfunction (PGD) after lung transplantation. J Heart Lung Transplant 2012;31:942–9. [PubMed: 22694851]
40. Ljung L, Olsson T, Engstrand S, Wallberg-Jonsson S, Soderberg S, Rantapaa-Dahlqvist S: Interleukin-1 receptor antagonist is associated with both lipid metabolism and inflammation in rheumatoid arthritis. Clin Exp Rheumatol 2007;25:617–20. [PubMed: 17888220]
41. Hamilton BC, Kukreja J, Ware LB, Matthay MA: Protein biomarkers associated with primary graft dysfunction following lung transplantation. Am J Physiol Lung Cell Mol Physiol 2017;312:L531–L41. [PubMed: 28130262]
42. Diamond JM, Lederer DJ, Kawut SM, et al.: Elevated plasma long pentraxin-3 levels and primary graft dysfunction after lung transplantation for idiopathic pulmonary fibrosis. Am J Transplant 2011;11:2517–22. [PubMed: 21883907]
43. Diamond JM, Meyer NJ, Feng R, et al.: Variation in PTX3 is associated with primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2012;186:546–52. [PubMed: 22822025]
44. Mathur A, Baz M, Staples ED, et al.: Cytokine profile after lung transplantation: correlation with allograft injury. Ann Thorac Surg 2006;81:1844–9; discussion 9-50. [PubMed: 16631683]
45. Moreno I, Vicente R, Ramos F, Vicente JL, Barbera M: Determination of interleukin-6 in lung transplantation: association with primary graft dysfunction. Transplant Proc 2007;39:2425–6. [PubMed: 17889209]
46. Cantu E, Diamond JM, Suzuki Y, et al.: Quantitative Evidence for Revising the Definition of Primary Graft Dysfunction after Lung Transplant. Am J Respir Crit Care Med 2018;197:235–43. [PubMed: 28872353]
47. Shah RJ, Diamond JM, Cantu E, et al.: Latent class analysis identifies distinct phenotypes of primary graft dysfunction after lung transplantation. Chest 2013;144:616–22. [PubMed: 23429890]
48. Shah RV, Murthy VL, Abbasi SA, et al.: Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. JACC Cardiovasc Imaging 2014;7:1221–35. [PubMed: 25440591]
49. Hill J: Reducing bias in treatment effect estimation in observational studies suffering from missing data. Institute for Social and Economic Research Policy: Working Paper 2004;Working Paper 04-01.
50. Fong C, Ratkovic M, Hazlett C, Yang X, Imai K: CBPS: Covariate Balancing Propensity Score. R package version 0.12 ed; 2016.
51. van Buuren S, Groothuis-Oudshoorn K: mice: Multivariate Imputation by Chained Equations in R. 2011;45:1–67.
52. Hastie T: GAM: Generalized Additive Models. R package version 1.14 ed; 2016.
53. Conaway M: Latent Class analysis In: P A, T C, editors.Encyclopedia of Biostatistics. Hoboken, NJ: John Wiley & Sons Inc; 2005.
54. Collins LM, Lanza ST: Latent Class and Latent Transition Analyis: With Applications in the Social, Behavioral, and Health Sciences. Hoboken, NJ: Wiley & Sons Inc; 2009.
55. StataCorp: Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC; 2017.
56. Grenier-Larouche T, Galinier A, Casteilla L, Carpentier AC, Tchernof A: Omental adipocyte hypertrophy relates to coenzyme Q10 redox state and lipid peroxidation in obese women. J Lipid Res 2015;56:1985–92. [PubMed: 26239051]
57. Furukawa S, Fujita T, Shimabukuro M, et al.: Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752–61. [PubMed: 15599400]

58. Diamond JM, Porteous MK, Roberts LJ, 2nd, et al.: The relationship between plasma lipid peroxidation products and primary graft dysfunction after lung transplantation is modified by donor smoking and reperfusion hyperoxia. J Heart Lung Transplant 2016;35:500–7. [PubMed: 26856667]
59. Suzuki K, Murtuza B, Smolenski RT, et al.: Overexpression of interleukin-1 receptor antagonist provides cardioprotection against ischemia-reperfusion injury associated with reduction in apoptosis. Circulation 2001; 104:1308–I3.
60. Gasse P, Mary C, Guenon I, et al.: IL-1R1/MyD88 signaling and the inflammasome are essential in pulmonary inflammation and fibrosis in mice. J Clin Invest 2007;117:3786–99. [PubMed: 17992263]
61. Kerr KM, Auger WR, Marsh JJ, et al.: Efficacy of methylprednisolone in preventing lung injury following pulmonary thromboendarterectomy. Chest 2012;141:27–35. [PubMed: 21835900]
62. Langereis JD, Oudijk EJ, Schweizer RC, Lammers JW, Koenderman L, Ulfman LH: Steroids induce a disequilibrium of secreted interleukin-1 receptor antagonist and interleukin-1beta synthesis by human neutrophils. Eur Respir J 2011 ;37:406–15. [PubMed: 20650986]
63. Meyer NJ, Reilly JP, Anderson BJ, et al.: Mortality Benefit of Recombinant Human Interleukin-1 Receptor Antagonist for Sepsis Varies by Initial Interleukin-1 Receptor Antagonist Plasma Concentration. Crit Care Med 2018;46:21–8. [PubMed: 28991823]
64. Ubags ND, Vernooy JH, Burg E, et al.: The role of leptin in the development of pulmonary neutrophilia in infection and acute lung injury. Crit Care Med 2014;42:e143–51. [PubMed: 24231757]
65. Kordonowy LL, Burg E, Lenox CC, et al.: Obesity is associated with neutrophil dysfunction and attenuation of murine acute lung injury. Am J Respir Cell Mol Biol 2012;47:120–7. [PubMed: 22427537]
66. Jain M, Budinger GR, Lo A, et al.: Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferator-activated receptor-gamma. Am J Respir Crit Care Med 2011;183:1490–8. [PubMed: 21317313]
67. Gainsford T, Willson TA, Metcalf D, et al.: Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A 1996;93:14564–8. [PubMed: 8962092]
68. Bellmeyer A, Martino JM, Chandel NS, Scott Budinger GR, Dean DA, Mutlu GM: Leptin resistance protects mice from hyperoxia-induced acute lung injury. Am J Respir Crit Care Med 2007;175:587–94. [PubMed: 17185651]
69. Shah D, Romero F, Duong M, et al.: Obesity-induced adipokine imbalance impairs mouse pulmonary vascular endothelial function and primes the lung for injury. Sci Rep 2015;5:11362. [PubMed: 26068229]
70. Shah D, Romero F, Guo Z, et al.: Obesity-Induced Endoplasmic Reticulum Stress Causes Lung Endothelial Dysfunction and Promotes Acute Lung Injury. Am J Respir Cell Mol Biol 2017;57:204–15. [PubMed: 28277743]

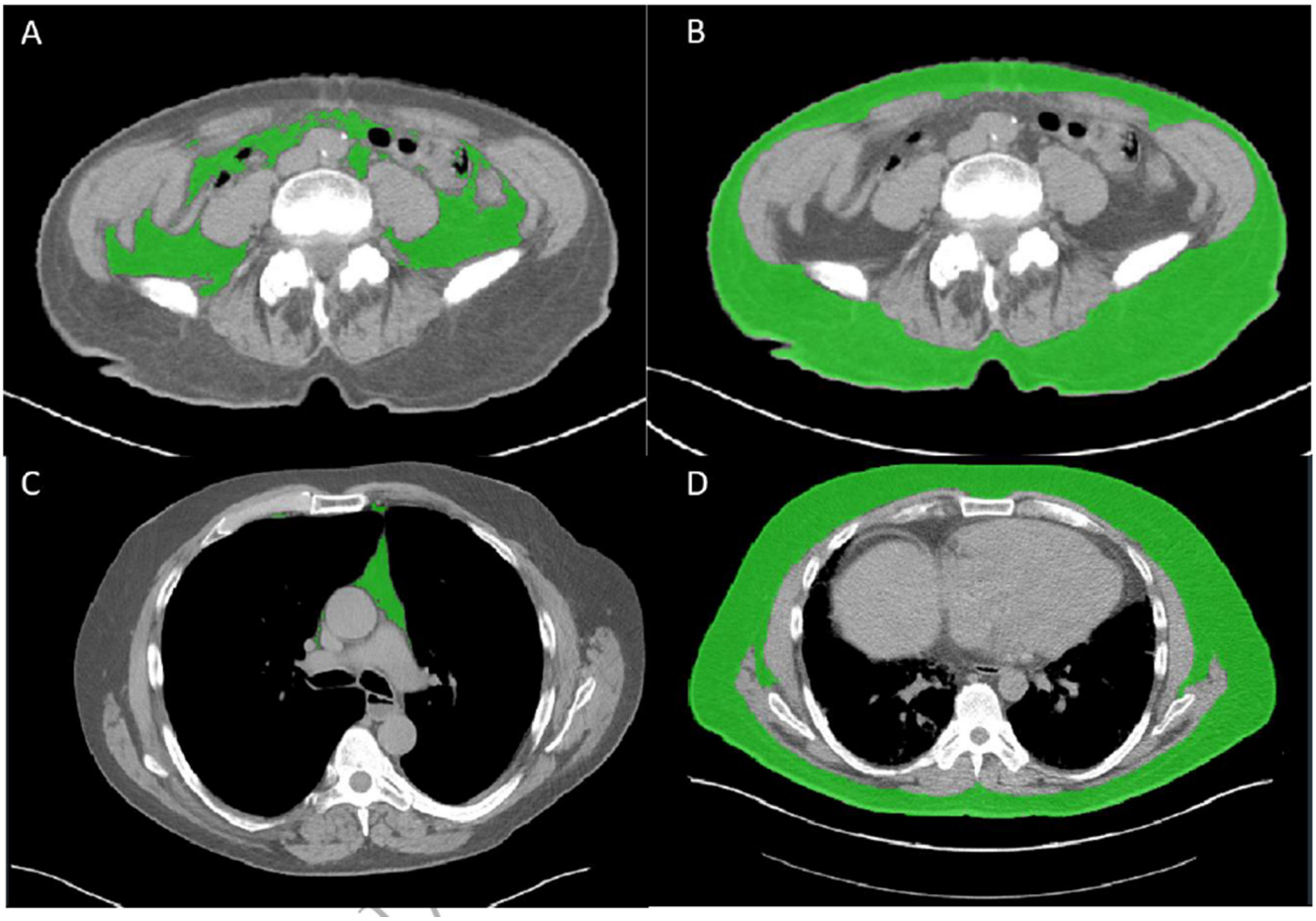

Figure 1:
Selected axial images from computed tomography scan of (A) abdominal visceral adipose tissue at L4/L5 vertebral level, (B) abdominal subcutaneous adipose tissue at L4/L5 vertebral level, (C) thoracic visceral adipose tissue at mid-T7 vertebral body, and (D) thoracic subcutaneous adipose tissue at mid-T8 vertebral body.

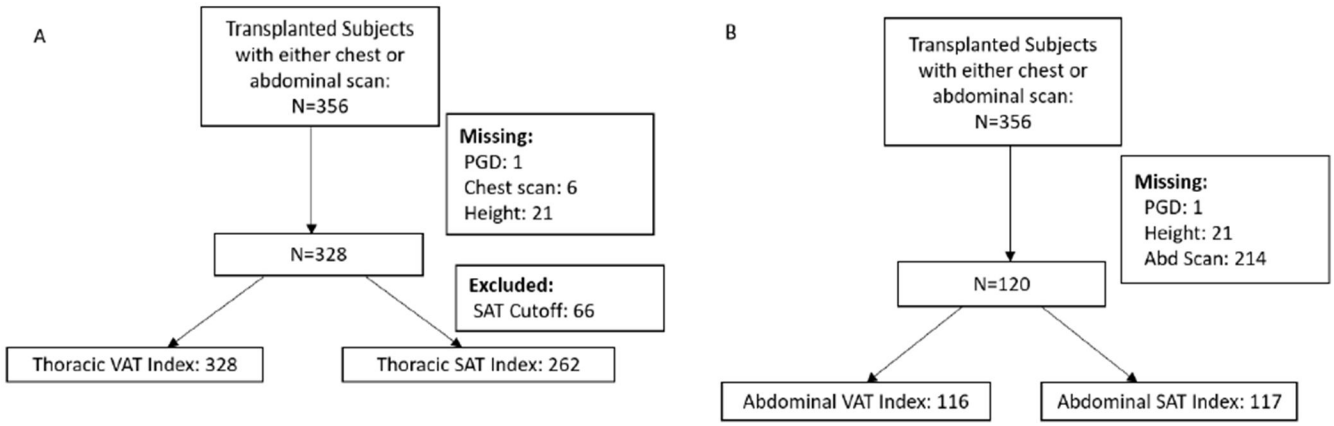

Figure 2:

Study flow for (A) thoracic measures, and (B) abdominal measures.

Footnote:

Definition of abbreviations: PGD=primary graft dysfunction; VAT Index = visceral adipose tissue area/height^2; SAT Index= subcutaneous adipose tissue area/height^2.

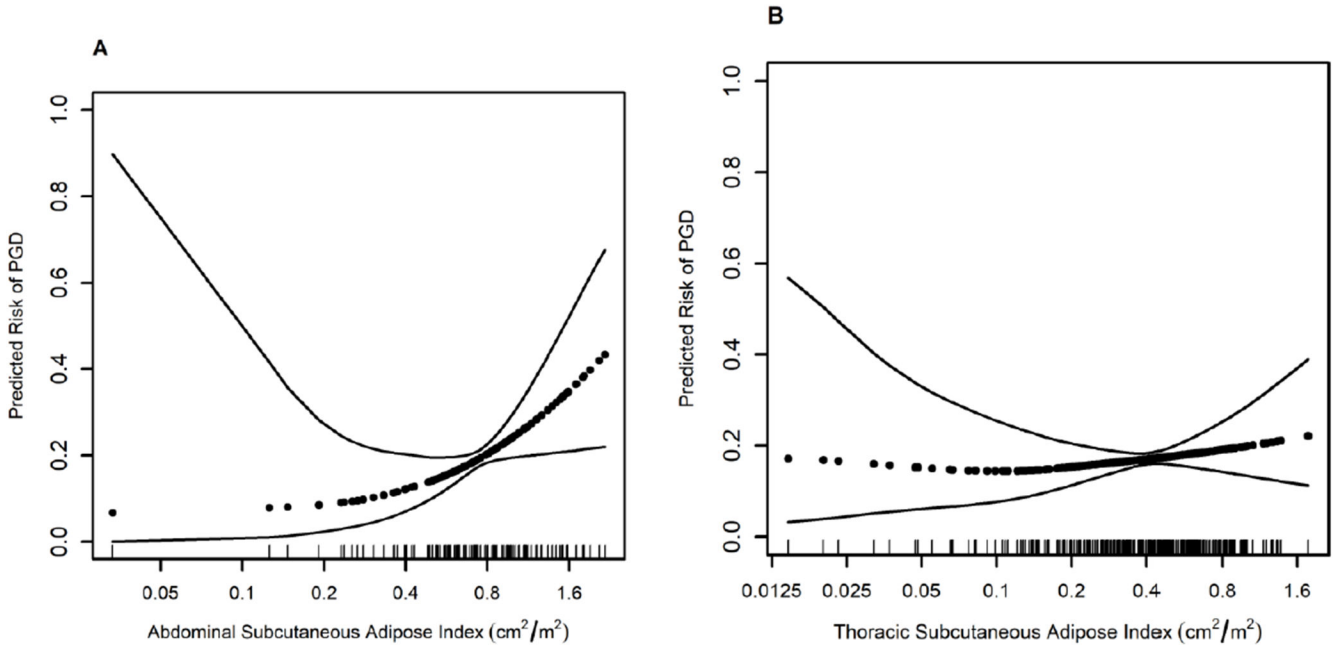

Figure 3:

Continuous association between (A) Abdominal Subcutaneous Adipose Index and grade 3 PGD at 48 or 72 hours, and (B) Thoracic Subcutaneous Adipose Index and grade 3 PGD at 48 or 72 hours. P values for association are (A) p=0.045, and (B): p=0.54. Values differ from main analyses due to differences in modeling technique. Dark dotted black line represents the effect estimates. Surrounding thin lines represent 95% confidence bands. Each vertical line in the rug plot along the x axis represents a single study subject.

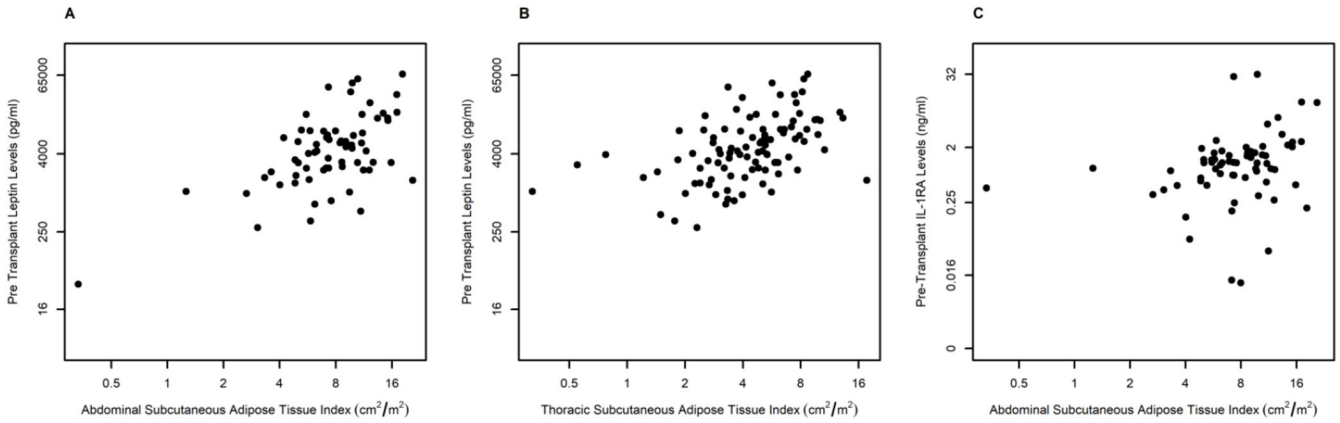

Figure 4:

Scatter plots of (A) abdominal subcutaneous adipose index and pre-transplant leptin levels, (B) thoracic subcutaneous adipose index and pre-transplant leptin levels, and (C) abdominal subcutaneous adipose index and pre-transplant IL1-RA levels. Pearson correlation coefficients are (A) r= 0.61, p<0.0001, (B) r=0.47, p<0.0001, and (C) r=0.25, p=0.04.

Table 1:

Overall subject characteristics for chest and abdomen cohorts

	Abdominal SAT cohort (n=117)	Thoracic SAT Cohort (n=262)
Recipient Variables		
Age, years	62 (48-68)	62 (53-67)
Male gender	71 (61)	164 (63)
LAS at transplantation	39.5 (35.0 to 44.7)	40.3 (35.7–47.7)
Diagnosis		
COPD	24 (21)	53 (20)
Interstitial lung disease	63 (54)	156 (60)
Sarcoidosis	5 (4)	10 (4)
Cystic fibrosis	15 (13)	25 (10)
Pulmonary arterial hypertension	3 (3)	7 (3)
Other	7 (6)	11 (4)
Race		
White	101 (86)	214 (82)
African American	11 (9)	24 (9)
Other	5 (4)	15 (6)
Height, cm	172.7 (162.6 to 177.8)	172.0 (164.0-177.8)
Weight, kg	75.1 (60.3 to 83.9)	74.2 (61.5-83.3)
BMI, kg/m^2	24.9 (21.5 to 27.9)	24.7 (21.5-27.6)
BMI Category		
<18.5	11 (9)	26 (10)
18.5-25	49 (42)	115 (44)
25-30	39 (33)	83 (32)
30-35	16 (14)	36 (14)
>35	2 (2)	2 (1)
Abdominal VAT area (cm^2)	85.5 (44.0 to 133.6)	88.1 (44.9-139.0)
Abdominal VAT Index (cm^2/m^2)	30.0 (16.0 to 45.3)	30.2 (16.5-47.2)
Abdominal SAT area (cm^2)	220.6 (160.4 to 316.1)	215.2 (154.7-313.0)
Abdominal SAT Index (cm^2/m^2)	72.2 (53.7 to 109.9)	71.4 (52.2-104.5)
Thoracic VAT area (cm^2)	11.4 (5.3-22.4)	13.5 (6.7-23.7)
Thoracic VAT Index (cm^2/m^2)	4.1 (1.9-7.7)	4.5 (2.3-8.1)
Thoracic SAT area (cm^2)	119.5 (75.2-193.8)	122.3 (75.6-176.0)
Thoracic SAT Index (cm^2/m^2)	40.5 (25.6-66.8)	42.1 (25.4-61.2)
Donor Variables		
Gender, male	73 (62)	128 (49)
Any smoking history	49 (42)	75 (29)
Race		
White	78 (67)	122 (47)
African American	27 (23)	39 (19)
Other	12 (10)	91 (35)

	Abdominal SAT cohort (n=117)	Thoracic SAT Cohort (n=262)
Procedure Variables		
Ischemic time, minutes	369 (301 to 420)	340 (271-402)
Transplant type - double	79 (68)	177 (68)
PRBC > 1 L	16 (14)	41 (16)
CPB or ECMO	43 (37)	124 (47)
PASP, mmHg	38 (31 to 47)	38 (30-47)
Center		
Center A	47 (40)	57 (22)
Center B	19 (16)	61 (23)
Center C	51 (44)	62 (24)
Center D	NA	82 (31)

Continuous variables are presented as median (interquartile range). Categorical variables are presented as percentages. Percentages may not exactly equal 100% because of rounding.

Missing data for abdominal cohort: 5 are missing donor smoking, 10 are missing pulmonary artery systolic pressure, 11 are missing transfusion, 4 missing abdominal VAT measurement, 6 are missing thoracic SAT measurement, 5 are missing thoracic VAT measurement.

Missing data for chest cohort: 2 are missing sex, 9 are missing race, 62 are missing donor sex, 10 are missing donor smoking, 14 are missing total ischemic time, 32 are missing pulmonary artery systolic pressure, 17 are missing transfusion, 4 are missing use of CPB or ECMO, 161 are missing abdominal SAT measures, , 162 are missing abdominal VAT measurements.

Definition of abbreviations: LAS = lung allocation score at transplantation; COPD = chronic obstructive pulmonary disease; VAT = visceral adipose tissue area; VAT index = visceral adipose tissue area divided by height^2; SAT= subcutaneous adipose tissue area; SAT index= subcutaneous adipose tissue area divided by height^2; CPB = intraoperative use of cardiopulmonary bypass; ECMO = intraoperative use of extracorporeal membrane oxygenation; PRBC = packed red blood cells; PASP = pulmonary artery systolic pressure.

Table 2:

Convergent and divergent validity of adipose area and indexed adipose area with other measures of body composition. Values represent Pearson correlation coefficients.

	Abdomen				Chest			
	VAT Area	**VAT Index**	**SAT Area**	**SAT Index**	**VAT Area**	**VAT Index**	**SAT Area**	**SAT Index**
Abdomen VAT Area	1							
Abdomen VAT Index	0.99*	1						
Abdomen SAT Area	0.62*	0.64*	1					
Abdomen SAT Index	0.56*	0.60*	0.98*	1				
Chest VAT Area	0.62*	0.59*	0.43*	0.36*	1			
Chest VAT Index	0.62*	0.60*	0.46*	0.40*	0.99*	1		
Chest SAT Area	0.66*	0.68*	0.87*	0.87*	0.52*	0.53*	1	
Chest SAT Index	0.60*	0.64*	0.85*	0.88*	0.46*	0.49*	0.99*	1
Body mass index	0.58*	0.59*	0.74*	0.71*	0.47*	0.47*	0.67*	0.65*
Waist Circumference	0.74*	0.71*	0.69*	0.62*	0.61*	0.59*	0.65*	0.57*
Hip Circumference	0.58*	0.56*	0.77*	0.72*	0.43*	0.42*	0.69*	0.62*
Waist to Hip Ratio	0.57*	0.55*	0.25*	0.19	0.47*	0.46*	0.25*	0.20*
Six-minute walk distance	0.02	−0.01	−0.06	−0.10	0.12	0.10	−0.18*	−0.21

Definition of abbreviations: VAT = visceral adipose tissue area; VAT Index = visceral adipose tissue area divided by height^2; SAT= subcutaneous adipose tissue area; SAT Index = subcutaneous adipose tissue area divided by height^2

Waist circumference was available for 181 subjects, hip circumference was available for 182 subjects, waist to hip ratio was available for 181 subjects, six-minute walk distance was available on 239 subjects.

* $p \leq 0.05$

Table 3:

Associations between subcutaneous adipose tissue index and grade 3 primary graft dysfunction at 48 or 72 hours.

	All subjects with available SAT Index					
	Abdomen (N=117)			Chest (N=262)		
Model	**OR per doubling of SAT index**	**95% CI**	**P**	**OR per doubling of SAT index**	**95% CI**	**P**
PGD models						
Minimally Adjusted ¥	1.9	1.02 to 3.4	.04	1.1	0.8 to 1.5	.53
Adjusted for recipient variables ≠	1.9	1.1 to 3.4	.03	1.1	0.8 to 1.5	.63
+ Donor $	1.9	1.03 to 3.6	.04	1.1	0.8 to 1.5	.64
+ Operative §	2.0	1.1 to 3.6	.04	1.1	0.8 to 1.5	.53

Definition of abbreviations: SAT index = subcutaneous adipose tissue area divided by height^2, CI = confidence interval, OR = odds ratio.

¥Minimally Adjusted Characteristics are transfusion requirement, allograft ischemic time, pulmonary artery systolic pressure, intraoperative use of cardiopulmonary bypass or extracorporeal membrane oxygenation, center

≠Recipient Characteristics are diagnosis, gender, pulmonary artery systolic pressure, lung allocation score, center

$Donor Characteristics are allograft ischemic time, donor smoking

§Operative Characteristics are use of extracorporeal support, transplant type, intraoperative transfusions >1L packed red blood cells