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Lung transplantation is a life-saving therapy for adults with advanced lung diseases, such as interstitial lung disease and chronic obstructive pulmonary disease. The success of lung transplantation is limited by poor early and late outcomes. Primary graft dysfunction (PGD), a form of acute lung injury (ALI) occurring within 72 hours of lung transplantation, is the leading cause of death early after lung transplantation and contributes to chronic lung allograft dysfunction. We recently identified obesity as a novel risk factor for PGD. The mechanism underlying this association is not known, but obesity-related inflammation could contribute. Obesity is characterized by a chronic systemic inflammatory state due to the accumulation of pro-inflammatory adipose tissue macrophages (ATMs), T cells, and other immune cells. Adipocytes and ATMs secrete inflammatory mediators, chemoattractants, and adipokines, such as leptin, visfatin, and resistin, that could contribute to the development of ALI. We hypothesize that adipose tissue inflammation increases during lung transplant surgery and contributes to PGD, and that pro-inflammatory ATMs and T cells drive this process. To test our hypothesis, we propose leverage the existing infrastructure of the Lung Transplant Outcomes Group perform a prospective cohort study that includes (1) measurement of intrathoracic, visceral, and subcutaneous adipose tissue mass using quantitative CT imaging, (2) immunophenotyping of macrophages and T cells from intrathoracic adipose tissue and lymph nodes obtained immediately before and after lung transplantation, and (3) measurement of adipokines and cytokines in plasma and bronchoalveolar lavage (BAL) fluid and lymphocyte phenotypes in the circulating and lung compartments in participants at three lung transplant centers (Columbia, Penn, and Duke) to accomplish three Specific Aims: Specific Aim 1: Determine the associations of intrathoracic, visceral, and subcutaneous adipose tissue volume with the risk of PGD after lung transplantation; Specific Aim 2: Determine whether adipose tissue inflammation is associated with the risk of PGD; and Specific Aim 3: Determine whether plasma and BAL adipokine levels are associated with the risk of PGD. This application proposes to generate new knowledge on the role of adipose tissue inflammation in the development of PGD. The proposal is innovative in combining rigorous epidemiologic and translational approaches and the use of quantitative CT imaging of adipose tissue, which could help to improve the prediction of PGD risk and enhance transplant selection criteria. In addition, we propose to identify specific molecules that could be targeted in phase II clinical trials to decrease PGD risk and potentially improve outcomes after lung transplantation.
