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Summary/Abstract

Obesity is an established risk factor for the development of rheumatoid arthritis (RA), and has been implicated as the primary source of the recent rise in RA incidence. However, the immunologic contribution of adipose tissue to the RA disease state has received little prior investigation. Parallels between inflamed adipose tissue and the inflamed synovium of RA are striking, and the cytokines, chemokines, and adipokine hormones produced act via paracrine and endocrine mechanisms to perpetuate cellular activation, elaborate additional inflammatory mediators, increase cardiometabolic risk factors, and accelerate atherogenesis. Paralleling this, higher systemic inflammation, insulin resistance, and a marked propensity toward accelerated atherosclerosis are prominent features of RA, suggesting a potential role for adipose inflammation in the RA disease process.

From preliminary data, we observed higher levels of multiple measures of adipose inflammation in RA patients compared with matched controls. Higher levels of adipose inflammation were strongly correlated with RA disease activity, circulating inflammatory markers, insulin resistance, and atherosclerosis, suggesting that RA adipose tissue is a contributor to the defining features and key comorbid sequelae of RA. Moreover, we observed robust associations in the frequency and inflammatory gene expression profiles of circulating intermediate “inflammatory” monocytes and memory effector T cell subsets with inflammatory characteristics of RA adipose tissue, suggesting an interface between inflamed adipose tissue and circulating immune effectors. However, whether these features are modifiable with RA pharmacotherapies and whether non-invasive measures of adipose inflammation [such as 18fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning] are correlated with the disease features of RA are unknown. Within this context, we propose to:

1. Quantify the changes in measures of adipose tissue inflammation occurring with disease modifying antirheumatic drug (DMARD) therapy in RA patients, under the hypothesis that DMARD responsiveness will be associated with a decrease in adipose tissue macrophage content and decreases in other secondary measures of adipose inflammation.

2. Delineate the associations of the immunophenotypic characteristics of subsets of peripheral blood mononuclear cells (PBMCs) characteristic of RA (i.e. circulating intermediate monocytes and/or terminally differentiated memory/effector T-cells) with adipose tissue inflammation in RA.

3. Evaluate the associations of adipose FDG uptake with measures of adipose tissue inflammation from adipose aspiration, RA characteristics, and vascular inflammation.

Completion of these aims will define unique contributions of adipose tissue to the key pathobiologic features of RA, establish treatment responsiveness, and identify novel methods for screening and prediction.