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Abstract
Psoriatic arthritis (PsA) is a systemic inflammatory disease that affects between 0.1 and 1% of the worldwide population. Higher body mass index (BMI), a surrogate for adiposity, has been strongly linked to psoriatic arthritis (PsA) risk and disease manifestations. In addition, treatment responses are blunted in PsA patients who are overweight or obese. Together, these findings suggest a mechanistic role for adipose tissue in the pathobiology of PsA. Activated macrophages and T cells, and their associated cytokines, contribute to the disease manifestations of PsA. Similarly, cellular infiltration of adipose tissue macrophages (ATMs) accompanies fat gain, with T-cells and other immune cells present and contributing to inflammatory function. Despite these compelling links, no studies have explored direct measures of adiposity in PsA, and none have yet evaluated adipose tissue inflammatory features in PsA in relation to disease manifestations and treatment responses. Additionally, inheritance of certain HLA-B and C alleles is associated with specific phenotypic manifestations of PsA, the penetrance of which may be conditioned on an individual's level of adiposity. However, these gene-obesity interactions have received little prior investigation. Within this context, we propose the following aims:

Aim 1. To compare measures of adipose inflammation, from tissue obtained from periumbilical subcutaneous adipose aspiration, between patients with PsA, RA, and controls without rheumatic diseases and evaluate the associations of adipose inflammatory tissue characteristics and metabolism with PsA phenotypic characteristics. *Hypothesis: ATM content (ATMc) and other adipose inflammatory characteristics in PsA will be higher than otherwise similar non-rheumatic disease controls, and will be similar to RA. Adipose T cells, especially $CD8^+$ T cells, will be higher in PsA. Even after controlling for BMI, ATMc and other adipose inflammatory characteristics will be associated with PsA disease activity and severity characteristics.*

Aim 2. To quantify the effects of adipose partitioning and adipose tissue inflammation on treatment response in PsA. *Hypothesis: PsA patients with more visceral fat and/or higher levels of adipose inflammation will have a lower response to pharmacotherapies compared with patients with lower visceral fat and lower adipose inflammation, independent of BMI.*

Aim 3. To examine the interactions of adiposity and candidate HLA-B and C alleles and haplotypes on phenotypic characteristics of PsA using two well characterized Northern European PsA cohorts comprising over 500 PsA patients. *Hypothesis: The associations of HLA-B and C alleles with PsA phenotypic characteristics will differ depending on strata of BMI. Synergistic effects will be observed for PsA patients with higher BMI who possess alleles associated with greater severity, while protective alleles will demonstrate diminished effects in PsA patients with higher BMI.*

Relevance
Psoriatic arthritis (PsA) is one of the most common forms of inflammatory arthritis. Its manifestations can be severe and disabling, and affected individuals often have a reduced lifespan and a lower quality of life. Understanding how adipose tissue contributes to these manifestations of PsA may identify novel targets for intervention to allow PsA patients live longer, happier, and more productive lives.

Research Category and Classification:
Clinical Research

Keywords:
Psoriatic arthritis, adipose tissue inflammation, gene-environment interaction