ABSTRACT
IMMUNE CELL AND MUSCLE BIOENERGETICS IN PERSONS WITH MULTIPLE SCLEROSIS

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The pathology of Multiple Sclerosis (MS) is immune-mediated, associated with excessive lymphocyte activity, and dysregulated immune cell metabolism. Biomarkers readily detected in the blood have superior utility in research and the clinical laboratory for their pathological, diagnostic, and prognostic value as well as translatability. There is a need for additional biomarkers of disease status in MS. Therefore, the purpose of this dissertation was to determine whether peripheral blood immune cell (PBMC) metabolism differed between people with MS and non-MS controls, and whether PBMC bioenergetics correlated to muscle energetics and clinical end points including clinical, psychosocial, and functional outcomes.

Specific cellular preparation techniques were used to measure physiologically relevant profiles of oxidative and glycolytic metabolism parameters. PBMC metabolism was measured using extracellular flux analysis in people with and without MS matched for age, sex, body composition, and menopausal status. People with MS were of mild to moderate disability status. A functional and *in vivo* measure of muscle mitochondrial oxidative capacity was measured in the forearm flexor muscles. Clinical and functional endpoints included are commonly used in clinical and research settings.

Extracellular flux analysis detected distinct bioenergetic profiles in PBMCs between people with MS and non-MS controls. PBMC bioenergetic rates, especially glycolytic adenosine triphosphate (ATP) production rates, are greater in people with MS, particularly in those with worse functional and clinical disease status. Additionally, PBMC bioenergetics were found to relate to indices of forearm muscle energetics, clinical, psychosocial, and functional parameters. Some relationships were disease specific, while others were not. Thus, it appears that measurement of PBMC bioenergetics via extracellular flux analysis could serve as a potential diagnostic, disease activity, and clinical end point biomarker of MS. Further research is needed to validate this marker, but this exploratory study provided a foundation for an additional biomarker candidate in MS care.