



ROLE OF SKELETAL MUSCLE MACROPHAGES IN INACTIVITY-INDUCED INSULIN RESISTANCE

Nikol Yonemura (Paul Reidy, Alec McKenzie, Ziad Mahmassani, Paul LaStayo, Alex Yu
Kuei Lin, Micah Drummond)

Department of Health, Kinesiology, and Recreation

Background: The population of older adults aged 65 and over is drastically increasing and by 2030, 6 out of 10 will be diagnosed with more than one chronic condition and will account for a greater proportion of hospitalizations than ever before. Hospitalizations as a result of injury, disease, and/or surgery tend to decrease physical mobility and therefore, affect older adults' ability to maintain physical activity during and after hospitalization. Subsequently, older adults are likely to adopt a sedentary lifestyle, increasing the risk of skeletal muscle and metabolic dysfunction (e.g. impaired glucose disposal, insulin resistance). A novel mechanism that may contribute to physical inactivity-induced insulin resistance is accumulation of inflammation via macrophage infiltration of skeletal muscle. It is currently unknown if proliferation of skeletal muscle macrophages is related to physical inactivity induced insulin sensitivity changes in older adults. My goal is to elucidate the effects of two weeks of physical inactivity on anti-inflammatory macrophages within older adult skeletal muscle and examine the potential relationship between macrophages and insulin resistance.

Methods: Twelve healthy older adult subjects, ages 60-85, were recruited into this study. After screening, subjects performed a hyperinsulinemic-euglycemic clamp combined with muscle biopsies to determine insulin sensitivity. Subjects underwent 2-weeks of reduced activity, and following the reduced activity period, participants completed another hyperinsulinemic-euglycemic clamp and then a final clamp after 2-weeks of ambulatory recovery. Muscle biopsies at pre, post, and recovery time points were cut into 8 μ m sections and mounted on glass slides for staining. For macrophage quantification, samples were immunolabeled with the following markers: DAPI, CD206, and CD68. Immunofluorescent stained sections were imaged on an automated Nikon Ti-E inverted widefield microscope using a high sensitivity Clara CCD camera at 20x magnification. Difference between groups was determined by an ANOVA with Tukey post hoc tests as necessary in GraphPad Prism.

Results: Insulin sensitivity decreased after two weeks of reduced activity ($p < 0.05$) and increased to higher than baseline levels after two weeks of normal activity ($p < 0.05$). Only the macrophage population that was positive for all three stains (CD68⁺ CD206⁺ DAPI⁺) increased after 14 days of reduced activity ($p < 0.05$) and there was a positive relationship between this mixed macrophage content and insulin sensitivity.

Conclusion: Skeletal muscle macrophages increase after 2-weeks of reduced activity in older adults. In contrast to our hypothesis, there was a positive relationship between skeletal muscle macrophages and insulin sensitivity. Further studies need to be conducted to evaluate other types

of macrophages, and whether changes in blood flow may affect macrophage populations during reduced activity and its positive relationship to insulin sensitivity.