Geranylgeraniol Supplementation Mitigates Muscle Atrophy with Mitochondrial Quality Improvement in Diabetic Rats

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ABSTRACT

With diabetes, skeletal muscle mitochondrial quality control (mitochondrial fusion, fission & macro-autophagy) is impaired. Geranylgeraniol (GG) is shown to have a protective effect on preventing mitochondrial damage and muscle health; however, the effect of GG on a diabetic model is not known. **PURPOSE:** To determine the effect of GG on mitochondrial quality control and muscle cross-sectional area (CSA) in diabetic rats. **METHODS:** Thirty-five Sprague-Dawley rats were divided into three diet groups: control diet (CON), high-fat diet with 35 mg/kg body weight of streptozotocin (HFD), and HFD with 800 mg/kg body weight of GG (GG). Due to the limited sample, a total of 21 (CON: n = 7; HFD: n = 7; GG: n = 7) rats' muscle samples were used for this report. The soleus muscles were harvested after 7-weeks of feeding and were analyzed for OPA1, MFN2, DRP1, pDRP, PINK1, Parkin, LC3A, and LC3B protein content using western blot analysis. Muscle CSA were assessed using Image J. **RESULTS:** A significant ($p < 0.05$) condition effect was observed for MFN2, DRP, LC3A, and LC3B protein contents and muscle CSA. For mitochondrial fusion, GG (0.21 ± 0.08) had lower MFN2 than CON (0.43 ± 0.04; $p = 0.007$) and HFD (0.65 ± 0.08; $p = 0.010$). For mitochondrial fission, GG (0.26 ± 0.07) had lower DRP than HFD (0.59 ± 0.07; $p = 0.019$). For macro-autophagy, GG (1.08 ± 0.28) had lower LC3A than CON (2.81 ± 0.55; $p = 0.028$) and HFD (3.99 ± 0.57; $p = 0.010$); whereas GG (0.63 ± 0.21) had lower LC3B than HFD (1.93 ± 0.24; $p = 0.012$). No significant differences were observed for OPA1, pDRP, PINK1, Parkin, and LC3B/A. For muscle size, CON (10,092.88 ± 104.67μm2) had larger CSA than GG (7284.69 ± 70.91μm2, $p = 0.001$) and HFD (5615.59 ± 59.97μm2; $p = 0.001$), whereas GG (7284.69 ± 70.91μm2) had larger CSA than HFD (5615.59 ± 59.97μm2; $p = 0.001$). **CONCLUSION:** GG supplementation could prevent mitochondrial fragmentation (reduction in DRP), thus, potentially resulting in a decreased demand for mitochondrial fusion (reduction in MFN2). In addition, a greater rate of autophagosome degradation than formation (reduction in LC3A and LC3B) was observed (indicative of an increase in macro-autophagy). Improvement in mitochondrial quality could potentially contribute to attenuating the reduction of muscle size in diabetic rats with GG supplementation.