

Effects of Exercise and Nexrutine® on Biomarkers of Cachexia in TRAMP Mice

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ABSTRACT

Cachexia is a major adverse effect of prostate cancer (PCa) and leads to functional impairment and poor quality of life. The pathophysiology of cachexia is complex and includes an imbalance of anabolic and catabolic factors. Oncologists often encourage nutritional and physical interventions to improve cancer outcomes. However, it is unclear how these interventions affect the pathophysiology of PCa-induced cachexia. **PURPOSE:** To test the hypothesis that exercise and Nexrutine® (a natural product derived from the bark of the Amur cork tree) can modulate cachexia in a transgenic adenocarcinoma of mouse prostate (TRAMP) model. **METHODS:** Ten-week old TRAMP mice were randomized into three groups, voluntary wheel running (VWR; n=7), Nexrutine® (Nex; 600 mg/kg; n=6) and control (Con; n=6), and studied over an eight-week time frame. Grip strength was measured at 0, 5 and 8 weeks. At weeks 5 and 8, animals were euthanized and gastrocnemius muscle was dissected, weighed and snap frozen until analysis. A 1-2 mm piece of muscle was homogenized in 1 mL of phosphate buffered saline, sonicated and centrifuged for 5 minutes at 5,000 rpm. Supernatant was collected to measure insulin-like growth factor (IGF)-1 and myostatin with commercially available ELISA kits. A multivariate analysis of variance was performed using Tukey's post hoc test with significance set at $p < 0.05$. Data are presented as mean \pm SE. **RESULTS:** VWR mice ran an average of 7.16 KM/day. No significant differences were observed between groups with respect to body mass, muscle mass and grip strength at either of the time points. Analysis revealed a significant difference in IGF-1 concentrations between groups ($F=4.3$; $p=0.01$). Post hoc analysis showed at 5 weeks, IGF-1 was significantly greater in the VWR group (78.3 ± 6.5 pg/ml) compared to Con (47.9 ± 6.5 pg/ml; $p=0.007$) and Nex (41.5 ± 6.5 pg/ml; $p=0.002$), respectively. This increase was transient with no difference at 8 weeks. A trend is visible for group mean differences between the VWR and Nex group ($p=0.70$), but not the Con group. Though not significant, myostatin was markedly greater at 5 weeks in the VWR group (241.4 ± 180.4 pg/ml) compared to the Nex (153.4 ± 78.2 pg/ml; $\Delta 44.6\%$) and Con groups (118.1 ± 22.1 pg/ml; $\Delta 68.5\%$), respectively. **CONCLUSIONS:** The results of this pilot study suggest that exercise can increase intramuscular IGF-1 during the early stages of PCa development. However, the benefits of exercise in modulating IGF-1 may be neutralized with the marked increase in myostatin. Longitudinal studies need to be carried out to better understand IGF-1 and myostatin's influence on the onset and progression of PCa-induced cachexia.