



Mid Atlantic Regional Chapter of the American College of Sports Medicine

Annual Scientific Meeting, November 1st – 2nd, 2019
Conference Proceedings

International Journal of Exercise Science, Volume 9, Issue 8



High-fat Diets and Exercise Modulate Colon Inflammation and Proliferative Status in Male and Female Mice

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Increased abdominal adiposity and diets high in total fats are risk factors for colorectal cancer (CRC) and inflammatory bowel disease (IBD) development. In contrast, aerobic exercise has shown to significantly reduce the risk of CRC development in both men and women as well as attenuate symptoms associated with IBD. **PURPOSE:** We aimed to examine the impact of a high-fat diet (HFD) and exercise on predictors of CRC and IBD, which include proliferation index (PI) and colon inflammation. **METHODS:** 56 (n=7/group) 6-week old C57BL/6NTac male and female mice were weighed and randomly assigned to one of 4 groups: (1) control-diet sedentary (CDS, 10% fat diet, Research Diets); (2) very high-fat diet sedentary (VHFS, 60% fat, Research Diets); (3) control-diet exercise (CDX); and (4) very high-fat diet exercise (VHFX) for 12 weeks. Mice had *ad libitum* access to food and water. Exercised mice had free access to a running wheel in their cages. Food intake was monitored every other day and body weights once per week. After 12 weeks animals were sacrificed and colon sections were prepared for immunohistochemistry for cyclooxygenase-2 (COX-2), a marker of inflammation; F4/80, a marker of tissue-resident macrophages; and proliferating cell nuclear antigen (PCNA), a marker of proliferation. PI was calculated as the ratio of immunoreactive nuclei for PCNA to total nuclei counted per crypt. F4/80 stained cells were counted and normalized to total area of mucosa measured. Comparisons were made using one and three-way ANOVAs. **RESULTS:** COX-2 expression was increased in VHFS animals and reduced in both exercised (CDX and VHFX) groups in males and females. Both female VHF diet groups (VHFS and VHFX) reduced F4/80 counts compared to CDX (p=0.057, 0.045). VHF fed animals (male and female) had a significant decrease in F4/80 cells compared to CD fed animals (0.782 vs 1.283, p=0.023). Female mice had a 7.6% lower PI compared to males (44.4 vs 51.9, p=0.046) and sedentary mice had a 17.9% higher PI compared to exercised mice (58.9 vs 41.0, p=0.000). **CONCLUSION:** Exercise attenuates HFD-induced colon inflammation in male and female mice. HFDs may modulate the expression of murine macrophage populations in female mice only. Since a higher PI is indicative of disease risk, our results suggest that females have a lower risk of CRC while being sedentary increases it.