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1º SIMPÓSIO INTERNACIONAL de DOHaD e Pandemia: LIÇÕES DO COVID-19
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# DYSLIPIDEMIA CHANGES EXERCISE ENERGY EXPENDITURE IN MICE TRANSGENIC FOR HUMAN APOCIII

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**Abstract**

Hypertriglyceridemia is a predisposing factor for several metabolic diseases in the world today. Their cause is multifactorial, several factors are directly linked to the modification of plasma lipid metabolism, among them are genetics and exercise. The genic overexpression of apoCIII makes the animal hypertriglyceridemic and high levels of blood cholesterol, enabling further studies to be done on its metabolic profile. This study investigates how apoCIII overexpression and exercise modify the metabolism of genetically modified mice, especially their energy expenditure. We used 15-month-old male C57Bl/6 mice, subdivided into 4 groups: 2 NTG groups (non-transgenic mice that were submitted to training and their controls) and 2 CIII groups (transgenic Mice with basal triglyceridemia above 300mg/dL that were submitted to training and their controls). The exercised groups underwent for 8 weeks a moderate intensity training for 40 minutes 3 times a week. All animals were submitted to a stress test to evaluate performance and energy expenditure. The trained animals had higher energy expenditure during all stages of the test ($p<0.01$) and the area under curve of the EE showed that the trained animals had higher caloric consumption ($p<0.001$), while the animal CIII sed had a much higher energy expenditure than its control NTG sed ($p<0.001$). We conclude that dyslipidemia makes the CIII animal less fit for exercise, and trained animals have lower energy expenditure independent of dyslipidemia and produced more work.

**Keywords:** Dyslipidemia, Physical Exercise, Metabolism

## 1. Introduction

Hypertriglyceridemia is a dyslipidemia in which triglyceride concentrations increase severely, compromising metabolism in a way that enables the development of diseases such as obesity (1), diabetes (2), non-alcoholic hepatic steatosis (3) and it is considered a single factor for cardiovascular disease. Many factors can be linked with the occurrence of this dyslipidemia, like poor eating habits, sedentary lifestyle, alcoholism, smoking and genetic factors (4).

Transgenic mice overexpressing human apolipoprotein CIII (apoCIII) make it possible to improve metabolism studies, because gene modulation of apoCIII is an important factor regarding changes in lipid metabolism (5). Overexpression of apoCIII renders animals hypertriglyceridemic mainly by its action in retarding the removal of TG from lipoproteins, decreasing their affinity for Lipoprotein Lipase (LPL) and decreasing the uptake of VLDL and Chylomicrons Remnants via the hepatic receptor (6).

The aerobic exercise has high rate of lipid oxidation as energy substrate, moreover, for being executed at an intensity below the anaerobic threshold, it is capable of being sustained for long durations, which promotes an even greater oxidation of lipids. This study investigated the effect of 8 weeks of aerobic training on the metabolism and cardiopulmonary profile of dyslipidemic mice by overexpressing human apoCIII.

## 2. Material and methods

The colony of C57Bl/6 mice was established and reproduced according to internal guidelines. They are currently bred and kept in the animal house of the Department of Physiological Sciences (DFS-UEM), in a ventilated rack, isolated from other animals, with a 12-hour light and dark cycle, temperature at 23±1 ºC and free access to water and food (Nuvilab® balanced feed).

The genotyping consisted in measuring the baseline triglyceridemia after a 12-hour night fast. Animals with TG lower than 100 mg/dL were considered non-transgenic (NTG), and animals with TG higher than 300 mg/dL were considered transgenic (CIII). For the experiments, 36 male mice, mean age 12 months, were individually separated into 18 CIII and 18 NTG. Of these, 10 mice from each group were submitted to the aerobic training protocol (NTG Ex and CIII Ex), and the remaining 8 formed the control groups without training (NTG Sed and CIII Sed). Following the protocol approved by the Commission on Biosecurity (CTNBio No. 819/2013) and Ethics Committee on the Use of Animals in Experimentation - No. 020/2013 of the Maringá State University.

**2.1 Maximum effort test**

The test began with a warm-up (10 cm/s for 5 minutes), followed by a load increase of 9 cm/s every 3 minutes until the exhaustion of the animal (12). The test was performed on an individual treadmill suitable for rodents coupled to a gas analyzer to measure the oximetry and the Energy Expenditure (Panlab Harvard Apparatus®).

**2.2 Treadmill training protocol**

The training was performed on alternate days 3 times a week, always after 5 pm and had a total duration of 44 minutes, divided into: 2 minutes of warm-up (16 cm/s), 40 minutes of training (35cm/s) and 2 minutes of return to calm (16 cm/s) (13).

**2.3 Statistical analysis**

Results were expressed as mean ± standard deviation with significance of $p<0.05$. Data were processed using GraphPad Pism® statistical software (version 9.0). Shapiro-Wilk test for normality of data, followed by two-way ANOVA analysis of variance followed by Tukey's post hoc test.

**3. Results and discussion**

The estimation of energy expenditure showed that the sedentary groups had higher energy expenditure at the beginning, in the middle, and had a higher peak in the stress test. When comparing between groups, the NTG Sed group had the lowest energy expenditure in the test (Fig. 1).

The energy expenditure curve corroborates with the, also showing that the exercised animals walked longer distances with lower energy expenditure, however, the analysis of variance of the area under the curve identified that training influenced a lower energy expenditure, while dyslipidemia influenced an increase in energy expenditure (Fig. 2).

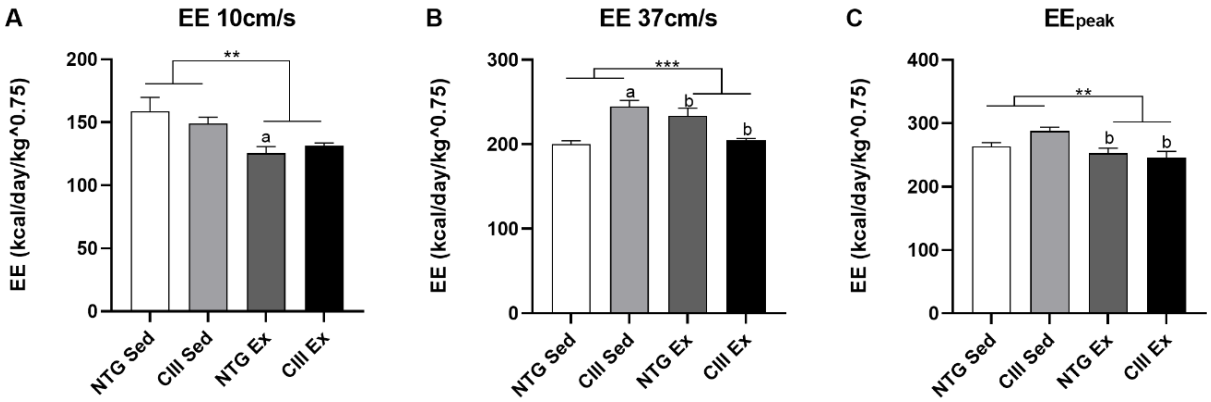


**Figure 1 –** Energy Expenditure of groups NTG and CIII with and without training Values are in mean ± SEM. Statistical analysis: two-way ANOVA, followed by post-hoc test of Tukey. * = p<0,05; ** = p<0,01; ***=p<0,0001; a = vs NTG Sed; b=vs CIII Sed.

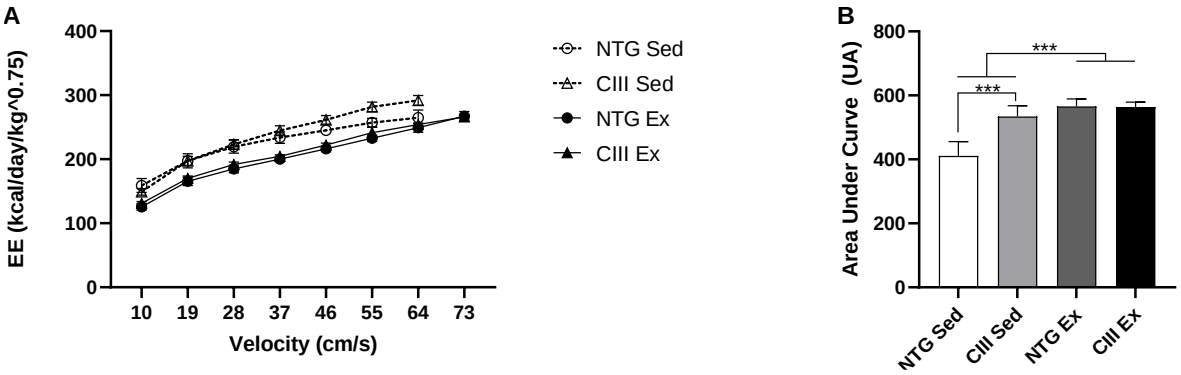


**Figure 2 –** Area under curve of Energy Expenditure of NTG and CIII with and without training Values are in mean ± SEM. Statistical analysis: two-way ANOVA, followed by post-hoc test of Tukey. * = p<0,05; ** = p<0,01; ***=p<0,0001; a = vs NTG Sed; b=vs CIII Sed.

## 4. Conclusion

We conclude that animal CIII has much higher energy expenditure than animal NTG for the same effort test, making it less physically able. Aerobic training improves exercise performance, leading the trained animals to have a lower energy expenditure during all stages

of training; moreover, they produce more work by sustaining the exercise longer, with a total caloric consumption of the session significantly higher than sedentary animals.

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