## EFFECTS OF METFORMIN AND AEROBIC EXERCISE TRAINING ON THE SKELETAL MUSCLE OF A MURINE MODEL

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**Introduction:** Metformin is an oral antidiabetic drug, which enhances glucose uptake by skeletal muscle, reducing insulin resistance and gluconeogenesis.
Recently, there is a growing interest in using metformin to treat aging and delay the onset of multiple age-related diseases. It has been demonstrated that aerobic exercise training and metformin independently have positive effects on the improvement of whole-body and peripheral insulin sensitivity. However, some evidences suggest that the addition of metformin to exercise does not induce an additive effect but instead inhibits the exercise-mediated improvements in insulin sensitivity.
Moreover, since insulin increases glucose uptake in skeletal muscle, and consequently, rises energy production, it has been inserted in the list of drugs banned by the World Anti-Doping Agency (WADA). The list of prohibited substances does not include oral antidiabetic drugs such as metformin, that could be used by healthy athletes in order to ameliorate and enhance their physical performance without falling into risks and/or side effects which would occur after insulin assumption. Furthermore, less is known about the effects of the antidiabetic drugs in the muscle, in reference to athletic performances. This study aimed to give information about the effects of metformin on the key regulators of training adaptation in skeletal muscle and evaluate if metformin was able to enhance muscular performances and then contribute to clarify whether metformin could be used combined to an exercise program to prevent or delay the deleterious effects of aging as well as this drug could be considered as a doping substance.

**Materials and methods:** Male Wistar rats were divided into sedentary rat group, which did not undergo physical exercise or metformin treatment; two control groups, treated or untreated with metformin; two trained groups, treated or untreated with metformin. Both control and trained groups were also submitted to a maximal speed run test in order to check rats' performances at the beginning, at a halfway point, and at the end of the entire experimental period. We analyzed serum parameters such as alanin aminotransferase (ALT), lactic dehydrogenase and levels of expression of adenosine monophosphate-activated protein kinase (AMPK), phospho- AMPK, acetyl coenzyme-A carboxylase (ACC), phospho-ACC, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, protein kinase B (AKT), phospho-AKT, microtubule-associated proteins 1A/1B light chain 3B and nucleoporin 62in total lysates of gastrocnemius muscles.

**Results:** Results show that food intake and body weight increase did not significantly change between groups. We have also seen that metformin assumption does not enhance physical performance level, which could be reached with training, but it speeds up the achievement of maximal performance preserving the training-induced muscle damage as suggested by the results obtained from the evaluation of some muscular lesion markers (ALT, LDH). Metformin and aerobic exercise training independently performed a positive effects on cell-signaling pathways involved in the control of energy production capacity. However, metformin seems to counteract physical training effects on skeletal muscle.

**Discussion and conclusion:** Our results show that metformin assumption does not increase physical performance that could be reached with training, but when associated to physical exercise metformin significantly speeds up the positive effects of training on the performance. Moreover, our findings suggest that combining metformin and exercise, may interfere with the improvement in some parameters of physiological function and do not interact synergistically. This study indicates that further research is needed before considering metformin as anti-aging drug.