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Regulation of the GLUT4 Translocation Pathway in Diabetic Skeletal Muscle: Comparative Effects of Aerobic and Resistance Training on AS160 and GLUT4 Gene Expression in Type 2 Diabetic Mice

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1. Round 1

1.1 Reviewer 1

Reviewer:

In the paragraph beginning with “Exercise training is among the most effective non-pharmacological strategies for improving insulin sensitivity,” the literature review remains descriptive rather than analytical. The authors should critically compare the mechanisms through which aerobic and resistance training influence insulin signaling pathways, particularly AMPK, Akt, mTOR, and mitochondrial adaptations, to better justify the comparative design of the present investigation.

The final paragraph of the Introduction states that “fewer studies have directly compared aerobic and resistance training in the same experimental design.” This important claim should be supported by a more systematic synthesis of previous comparative studies, including their methodological limitations, inconsistent findings, and unresolved questions. Doing so would more clearly establish the research gap addressed by the present study.

Table 4 reports highly significant group effects for both genes; however, confidence intervals for estimated differences are not provided. Reporting 95% confidence intervals alongside p-values and partial eta-squared values would improve the interpretability and robustness of the findings.

In the Results section, the authors conclude that the soleus muscle exhibited a stronger response than the EDL muscle. Because the soleus and EDL differ substantially in fiber composition and metabolic profile, it would be valuable to quantify the magnitude of these differences through interaction contrasts rather than relying solely on the significance of the group × muscle interaction term.

Authors revised the manuscript and uploaded the updated document.

1.2 Reviewer 2

Reviewer:

In the Materials and Methods section, the sentence “Fifty male C57BL/6 mice were used” lacks justification regarding sample size determination. The manuscript should include a power analysis or statistical rationale explaining how the sample size was selected to ensure adequate power for detecting differences in gene expression outcomes.

In the paragraph describing diabetes induction, the authors indicate that a “low-dose streptozotocin was administered intraperitoneally,” but the exact dose (mg/kg), preparation method, solvent, injection volume, and number of injections are not reported. These methodological details are essential for reproducibility and should be clearly specified.

The aerobic training protocol states that mice exercised at approximately “12–15 m/min” and “60–75% of aerobic capacity.” However, no method is provided to explain how aerobic capacity was assessed or estimated. The authors should clarify whether maximal running tests, published conversion models, or pilot data were used to determine exercise intensity.

In the resistance training protocol, the sentence “Load was attached to the tail and increased progressively according to body weight and performance” is insufficiently detailed. The manuscript should specify initial loading percentages, progression rates, number of climbs per session, rest intervals, and criteria used for increasing resistance to improve methodological transparency.

The Real-Time PCR section reports that gene expression was normalized to GAPDH using the 2^-ΔΔCt method; however, no information is provided regarding primer sequences, amplification efficiency, annealing temperatures, or validation of GAPDH stability across experimental conditions. These details should be included, preferably in a supplementary table.

The statistical analysis section indicates that “two-way mixed analysis of variance” was used. However, the manuscript does not report verification of the sphericity assumption or whether corrections were applied when assumptions were violated. The authors should provide a more complete description of assumption testing and statistical decision-making procedures.

Table 1 reports fasting blood glucose values exceeding 300 mg/dL in the exercise-trained diabetic groups at study completion. Because exercise is known to improve glycemic control, it is surprising that blood glucose remained markedly elevated. The authors should clarify whether these values were measured before or after the intervention and discuss the physiological implications of persistent hyperglycemia despite training.

In Table 2, the authors report that GLUT4 expression increased to “2.54 ± 0.33” in the soleus muscle after aerobic training. However, no direct statistical comparison between aerobic and resistance training is presented. The manuscript should include Bonferroni-adjusted pairwise comparisons between training modalities and report corresponding effect sizes to support claims of aerobic superiority.

The Results section states that “the GLUT4 response was stronger than the AS160 response.” This conclusion is based primarily on descriptive observations. A formal statistical comparison of the magnitude of changes between genes should be conducted or, alternatively, the conclusion should be presented more cautiously.

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Authors revised the manuscript and uploaded the updated document.

2. Revised

Editor's decision after revisions: Accepted.

Editor in Chief's decision: Accepted.

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