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Peer Review

Review of: "Development of a Type 2 Diabetes Mellitus Model in Rats with Administration of High-Fat Diet and Streptozotocin"

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General Comments

The submitted manuscript aims to develop and validate a Type 2 Diabetes Mellitus (T2DM) model in rats using a combination of a high-fat diet (HFD) and low-dose streptozotocin (STZ). This approach is well-recognized and widely used to simulate the dual pathophysiology of insulin resistance and β-cell dysfunction observed in human T2DM. The manuscript is clearly written, adheres to ethical standards, and provides meaningful results. However, there are a few inconsistencies and omissions that should be addressed before final acceptance.

Major Points

1. Experimental Model Design

The study uses an HFD + STZ protocol, which is standard for inducing T2DM in rodents. The authors modify an existing approach by using a slightly reduced STZ dose (25 mg/kg) given twice at five-day intervals. This adjustment appears beneficial in reducing mortality, but the novelty of this modification is somewhat limited unless better contextualized in light of previous literature.

- **Suggestion:** Strengthen the novelty claim by referencing recent T2DM model papers that used varying STZ dosages (cite PMID: 31676315). A brief comparative discussion would be valuable.

2. Metabolic Parameter Evaluation

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The model's success is evaluated using fasting blood glucose, serum cholesterol, creatinine, HbA1c, and HOMA-IR. The first four parameters were elevated in the diabetic group, clearly indicating a diabetic phenotype.

However, an unexpected outcome arises in the HOMA-IR values: the diabetic group shows **lower HOMA-IR** than the normal control group, which contradicts the expected increase in insulin resistance.

Concern: This inconsistency should be carefully examined. Either there is a mislabeling in the results table, or there is a miscalculation that requires correction.

- **Suggestion:** Include insulin levels in a supplementary table or clarify how HOMA-IR was calculated (See the article PMID: 31676315)

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3. Insulin Resistance and β-cell Dysfunction Validation

The manuscript correctly identifies the need to replicate both insulin resistance and β-cell impairment. However, no glucose tolerance test (GTT) or insulin tolerance test (ITT) is conducted—tests that would provide direct and functional validation of insulin resistance.

Suggestion: While these tests may not have been feasible in the current study, the authors should acknowledge this limitation and suggest it as a direction for future work.

4. Data Presentation and Sample Size

All results are clearly presented and statistically analyzed. However, the sample size (n=6/group) is on the lower end for preclinical animal studies. This limits statistical power and increases the risk of Type II errors.

Suggestion: Consider increasing the sample size or discussing this limitation explicitly.

5. Ethical and Practical Merits

The study reports **zero mortality**, good animal health, and ethical compliance—all commendable. This speaks to the practicality and reproducibility of the model, which is valuable for future preclinical testing.

Minor Issues

- A few typographical errors are present (e.g., “morbidity developed during the process” should read more clearly).
- Formatting of Table 1 could be improved for clarity—labels for HOMA-IR should indicate units or explain their significance.
- Several references are cited without complete formatting (e.g., reference #4 lacks author names).

Conclusion and Recommendation

This is a solid manuscript addressing a relevant topic in experimental diabetes research. The methodology is ethically sound, and the results support the central claims. However, due to the discrepancy in HOMA-IR data, the limited sample size, and the lack of functional insulin resistance testing, **I recommend *minor revision*** before acceptance.

Declarations

Potential competing interests: No potential competing interests to declare.