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Peer Review

Review of: "Development of a High-Fat Diet and Low-Dose Streptozotocin-Induced Rat Model for Type 2 Diabetes Mellitus"

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This manuscript presents a comprehensive and methodically sound study that establishes a robust rodent model of type 2 diabetes mellitus (T2DM) using a high-fat diet (HFD) in combination with low-dose streptozotocin (STZ). The authors have succeeded in developing a metabolic condition that closely resembles human T2DM, with clear documentation of hyperglycemia, dyslipidemia, renal markers, and insulin resistance. The approach adopted reflects thoughtful consideration of experimental modeling, and the overall presentation is clear, methodical, and well-structured.

One of the major strengths of this study lies in its thoughtful modification of the STZ dosage protocol, which improves animal survival while preserving the model's fidelity. Instead of following the conventional two-dose 30 mg/kg regimen, the authors judiciously reduced the STZ concentration to 25 mg/kg, administered five days apart. This decision reflects a nuanced understanding of the pharmacological dynamics of STZ and effectively balances the induction of β-cell dysfunction with animal welfare and survival, which is commendable.

The use of multiple biochemical parameters, including fasting blood glucose (FBG), HbA1c, total cholesterol, creatinine, and HOMA-IR, adds depth and credibility to the study's findings. These markers allow a multidimensional view of the metabolic alterations characteristic of T2DM. The significant elevation of all these indicators in the diabetic group (DC) confirms the effectiveness of the model and supports its use for future investigations into therapeutic interventions or pathophysiological mechanisms.

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Moreover, the study design adheres to ethical research practices and incorporates clear procedural details regarding animal care, housing, and handling. The description of the diet formulation—including macronutrient distribution and caloric content—adds transparency and reproducibility to the methodology. This level of rigor in documenting both dietary and pharmacological protocols strengthens the reproducibility of the model and invites further use by the research community.

The discussion section demonstrates a strong command of the literature, synthesizing complex information about the biochemical effects of STZ, HFD-induced insulin resistance, and metabolic stress pathways. The authors provide mechanistic insights into how lipotoxicity, chronic inflammation, and oxidative stress contribute to β-cell dysfunction and systemic insulin resistance—creating a physiological state that mirrors human T2DM. These elements elevate the manuscript from a purely empirical report to a reflective and theory-grounded contribution to the field.

The study is also commendable for including HOMA-IR as a validated and widely accepted indicator of insulin resistance. The observed elevation of this index in the diabetic group not only supports the induction of insulin resistance but also provides a quantitative baseline for future pharmacological or dietary interventions. Including this metric improves the translational value of the model for preclinical research, where insulin sensitivity is a central therapeutic target.

That said, a few areas offer potential for enhancement. The sample size (n=6 per group), while acceptable for preliminary research, limits the statistical power and generalizability of the findings. Expanding the number of animals in future studies would increase robustness and allow for subgroup analyses, including possible sex differences or age-related responses. Additionally, the inclusion of a third experimental group—such as an HFD-only group without STZ—could help isolate the independent effects of the diet and enhance mechanistic interpretation.

Furthermore, while the metabolic profiling is well-executed, the study lacks dynamic metabolic assessments such as the oral glucose tolerance test (OGTT) or insulin tolerance test (ITT). These evaluations are instrumental in establishing glucose disposal capacity and insulin responsiveness. Their inclusion would further validate the diabetic phenotype and strengthen the functional characterization of the model.

Finally, incorporating molecular analyses such as Western blotting or qPCR for insulin signaling markers (e.g., IRS-1, GLUT4, Akt) would provide deeper insights into the molecular architecture of insulin resistance and β-cell dysfunction. This mechanistic layer would elevate the impact of the study and potentially identify biomarkers or therapeutic targets for further exploration.

In conclusion, the authors have developed a practical and biologically relevant model of T2DM that balances scientific rigor with humane methodology. The study offers substantial value to researchers aiming to explore diabetic pathophysiology or test pharmacological agents in vivo. While there are areas that could be enriched in future iterations, particularly in terms of molecular depth and dynamic glucose testing, the foundational framework is solid and thoughtfully implemented. The manuscript reflects a careful, ethical, and well-informed approach to experimental diabetes modeling and represents a meaningful contribution to the field.

Declarations

Potential competing interests: No potential competing interests to declare.