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The Diabetic Parabiosis Model: Unlocking New Therapeutic Pathways in Diabetes Research

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ABSTRACT

Background: Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin production or function. Emerging evidence suggests that blood-borne components from healthy individuals can enhance glucose regulation and insulin sensitivity in diabetic subjects. The primary aim of our work is to provide a comprehensive, reproducible protocol for establishing a diabetic parabiosis model in rodents, which can serve as a foundation for future metabolic and pharmacological investigations.

Methods: Twenty four young female rats aged 2-4 months were used in this study. The animals were dived into three groups: isochronic diabetic, heterochronic diabetic and heterochronic non-diabetic. Five days after parabiosis surgical procedure, 50 mg/kg single dose of Streptozotocin (STZ) was administered intraperitoneally to diabetic groups. Blood glucose levels were measured from the tail vein 72 hours post-STZ, After eight weeks, rats were sacrificed and angiogenesis between parabionts was verified through dissection.

Result: The group with heterochronic diabetes parabiosis had significantly higher blood glucose levels than their non-diabetic peers. When compared to baseline values, blood glucose levels in diabetic groups were shown to be considerably higher following STZ delivery. There was no discernible difference between the diabetes groups. This study presents a detailed protocol for diabetic parabiosis, aiming to bridge basic research and clinical insights and to inspire novel therapeutic approaches for DM.

Key words: Diabetes mellitus, Endothelial dysfunction, Parabiosis, Streptozotocin.

INTRODUCTION

Diabetes mellitus (DM) is a chronic, metabolic disease characterized by elevated blood glucose levels due to defects in insulin production, insulin action, or both (American Diabetes, 2010; Carrizzo *et al.*, 2018; Darenskaya *et al.*, 2021) . More than 400 million people worldwide are affected from DM which has become epidemic proportions (Ciumarnean *et al.*, 2021). Although DM affects people of all ages, most forms of diabetes are chronic and all forms can be managed with medication and/or lifestyle changes. DM and its complications pose a serious challenge to human health and are becoming a global public health problem (Shaw *et al.*, 2010; Harding *et al.*, 2019). DM is subdivided into type I diabetes (T1D) and Type II diabetes (T2D). Although both types of diabetes involve abnormalities with the function of insulin, T1D and T2D vary in the pathogenesis (American Diabetes, 2010). T1D is a type of diabetes caused by damage to beta cells in the pancreas. T1D is most common in childhood and adolescence but can occur at any age, including old age. Consequently, individuals with T1D are reliant on insulin therapy for life (Ikegami *et al.*, 2022). T2D, is one of the most common type, is characterized by hyperglycemia, insulin deficiency and/or resistance. T2D has been closely linked to life style factors such as obesity, sedantary life style and poor dietary habits, alongside genetic predisposition (Coleman, 1978; Damanik and Yunir, 2021). Both T1D and T2D lead to serious long-term complications involving nearly all organ systems (Darenskaya *et al.*, 2021), particularly the cardiovascular (Eriksson and Nystrom, 2015; Rawshani *et al.*, 2017; Siasos, 2020), renal (Nabrdalik *et al.*, 2023) and nervous systems (American Diabetes, 2010). This underscores the importance of exploring new mechanisms, treatments and preventive strategies to address diabetes more effectively.

In recent years, parabiosis, the surgical joining of two organisms to form a shared circulatory, has attracted more interests. Since the first parabiosis surgery by Paul Bert in

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1864 (Conese *et al.*, 2017), based on Pubmed, at least 2274 articles have been published using this model (PubMed, 2025). Initially applied in 19th century, parabiosis enables for the exchange blood-borne factors between organisms, providing a unique insight info how circulating factors may influence physiology (Lagunas-Rangel, 2024).

Parabiosis studies frequently join young and aged animals in metabolic research to investigate aging processes, tissue regeneration and disease progression. Studies have indicated that certain rejuvenating factors present in young animals' blood can slow down or even reverse aging effects in older animals (Yang *et al.*, 2021). In our previous parabiosis study, we had shown that endothelial dysfunction and cardiac hypertrophy were reversed in heterochronic aged rats (Farisoglu *et al.*, 2022). This has encouraged the scientists to discover how parabiosis might be used to study or treatment of diseases beyond aging, involving metabolic disorders like diabetes.

Parabiosis provides a novel way to studying the systemic nature of diabetes in research. By pairing diabetic and non-diabetic animals, researchers are able to evaluate how healthy blood-borne factors affect insulin sensitivity, pancreatic function and glucose regulation (Pietramaggiori *et al.*, 2009). Early research indicates that factors present in the blood of healthy organisms may improve glucose homeostasis and increase insulin sensitivity in diabetic individuals (Fushimi *et al.*, 1980). This implies that certain circulating factors could be modulating metabolic process and reducing some of the damaging consequences of diabetes.

Parabiosis studies have identified a number of blood-borne factors that may affect metabolic health. One important factor is growth differentiation factor 11 (GDF11), a protein whose regenerative capabilities have shown promise in aging research (Lagunas-Rangel, 2024). Other posibble alternatives include particular cytokines (Xiao *et al.*, 2014), extracellular vesicles (Lagunas-Rangel, 2024) and microRNAs [22] that may regulate insulin signaling pathways, beta-cell survival or inflamation. By understanding these factors, potential therapeutic targets for reversing or mitigating diabetes-related pathologies can be revealed. Research on precise mechanisms which these factors function in diabetic individuals is still crucial. Scientists propose that parabiosis-induced alterations could be mediated by oxidative stress reduction, improved pancreatic beta cell function, or immune response modulation (Salpeter *et al.*, 2013; Morrison *et al.*, 2019).

The aims of this methodological article is to open new horizons in diabetes research by providing a comprehensive description of the diabetic parabiosis method, including its procedures, pratical applications and potential implications for future studies.

MATERIALS AND METHODS

Animals

The experimental procedures were carried out between 2024-2025 at the Department of Physiology, Faculty of Medicine, Near East University, using 24 young female rats (2-4 months old). Animals were classified into three groups: isochronic diabetic, heterochronic diabetic and heterochronic non-diabetic. The Near East University Ethics Committee for Animal Experimentation authorized all methods and procedures (Approval number: 2024/172) and all animals were used in compliance with the Guide for the Care and Use of Laboratory Animals. The rats were obtained from the Near East University Experimental Animals Care and Production Unit and housed in a room maintained at a temperature of 23±2°C, with a 12-hour light/12-hour dark cycle and provided with unrestricted access to water and commercial rat chow.

The parabiosis protocol is implemented as follows

This protocol describes step by step methodical process of establishing reliable parabiotic models in rats for diabetes research, with a focus on a surgical proficiency and animal care.

Pre-surgical preparation

Socialization and housing

Rats destinated for parabiosis should be co-housed in same cage for least two weeks before surgery in order to promote peaceful coexistence and leþsen post-operative stress.

Anesthesia

The combination of xylazine (10 mg/kg) and ketamine (100 mg/kg) is administered intraperitoneally as anesthetic.

Preparation of surgical instruments and sutures

The surgical tools utilized during surgical operation are shown in Fig 1A. Non-absorbable silk suture (3-0) is used for joint connections, while an absorbable (3-0) silk suture is used for skin closure.

Hair removal and aseptic preparation

- Position the rats side by side (Fig 1B) and remove hair from the left side of one rat and the right side of the other. Shaving extends approximately 1 cm above the elbow and 1 cm below the knee on each rat.
- Ophthalmic ointment is applied to prevent corneal drying and shaved areas are disinfected with Betadine before and after shaving (Fig 1C-D).

Positioning and draping

The rats are placed with their shaved parts facing upward and a sterile drape covers them, leaving only the surgery field exposed to maintain asepsis (Fig 1D).

Surgical procedure

Incision and skin separation

The shaved side of each rat is cut longitudinally with a sharp pair of scissors, extending from 0.5 cm above the elbow to 0.5 cm below the knee. Curved forceps are used to separate the skin from the subcutaneous fascia along the entire incision (Fig 2A).

Joint connections

- The left elbow of one rat is sutured to the right elbow of the other. Similarly, the knee joints are exposed through dissection and joined.
- The skin is continually sutured from the elbow to the knee following joint ligation. The ventral skin connection is completed with a double surgical knot and a dorsal knot is tied to finalize the attachment (Fig 2B-D). The sutures' strenght is controled to ensure stability.

Hydration

To prevent dehydration, 0.5 ml of 0.9% NaCl is administered subcutaneously to each rat.

Post-operative care

Recovery monitoring

The rats are placed on a heated pad until full recovery from anesthesia.

Analgesia

Post-operative pain management is provided with Meloxicam (1 ml/kg) administered subcutaneously at 12 and 24 hours post-surgery, continuing for two days.

Infection prevention

Trimethoprim (0.4 mg/ml) and Sulfamethoxazole (2 mg/ml) are added to the drinking water for ten days as a part of the Prophylactic treatment.

Dietary support

Moistened food pellets are placed on the cage floor to make it easier to obtain food during adaptation to the parabiotic process.

Healing

Within 1-2 weeks, rats will typically achieve coordinated movement with surgically joined forelimbs and hindlimbs. Images of the healed incision sites after eight weeks are shown in Fig 3A and 3B.

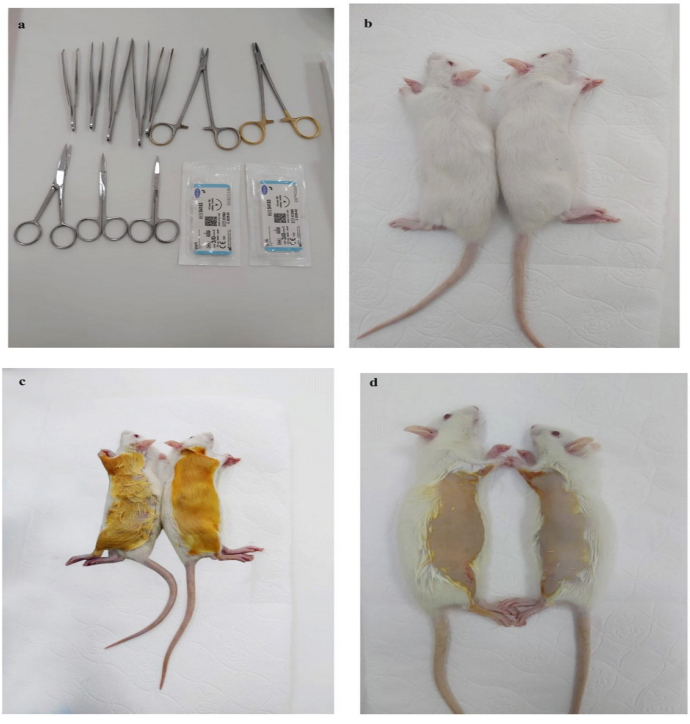
Streptozotocin (STZ) administration for diabetes induction

STZ injection

Five days post-surgery, a single intraperitoneal dose of Streptozotocin (STZ) at 50 mg/kg is administered to induce diabetes in the experimental groups (Khajuria *et al.*, 2018; Tasci *et al.*, 2024). To counter potential hypoglycemia following STZ injection, 30% dextrose is provided in the drinking water.

Blood glucose measurement

Blood glucose levels are monitored 72 hours post-STZ injection by collecting a blood sample from the tail vein and measuring glucose levels using a blood glucose test strip. Blood glucose levels before and after STZ injection was shown in Fig 4.



A. Frequently used surgical instruments. B. The rats are placed side by side before shaving. C. Betadine before shaving. D. After shaving, the rats are placed side by side.

Fig 1: Pre-surgical Preparation.

Validation of circulatory chimerism

Blood chimerism occurs 10-14 days after surgery. The methods used to test for blood chimerisation are.

Glucose fluctuation method

Ten days post-parabiosis, circulatory chimerism by measuring glucose levels in donor and recipient parabionts are assessed. The parabionts with 2,2,2-tribromoethanol (0.1 mL/10 g, intraperitoneal) are anesthetized. Glucose (100 µL at 1.2 g/kg) is injected through tail vein and Blood samples is collected from both parabionts at multiple time points pos-injection (1, 5, 10, 15, 20, 30, 40, 50 and 60 minutes). Glucose levels are then monitored with glucometer test strips.

Evan's blue counterstain as positive control

To confirm blood mixing between parabionts, Evan's Blue (200 µL of 0.5%) is injected intraperitoneally. After two hours, the parabionts are euthanized and serum samples are collected via cardiac puncture. Following centrifugation and dilution (1:50 with 0.9% NaCl), serum evans blue absorbance is measured at 620 nm.

After 8 weeks, the rats were sacrificed and angiogenesis between the parabiosis pair was exposed by dissection. Image of angiogenesis is presented in Fig 5.

Statistical analysis

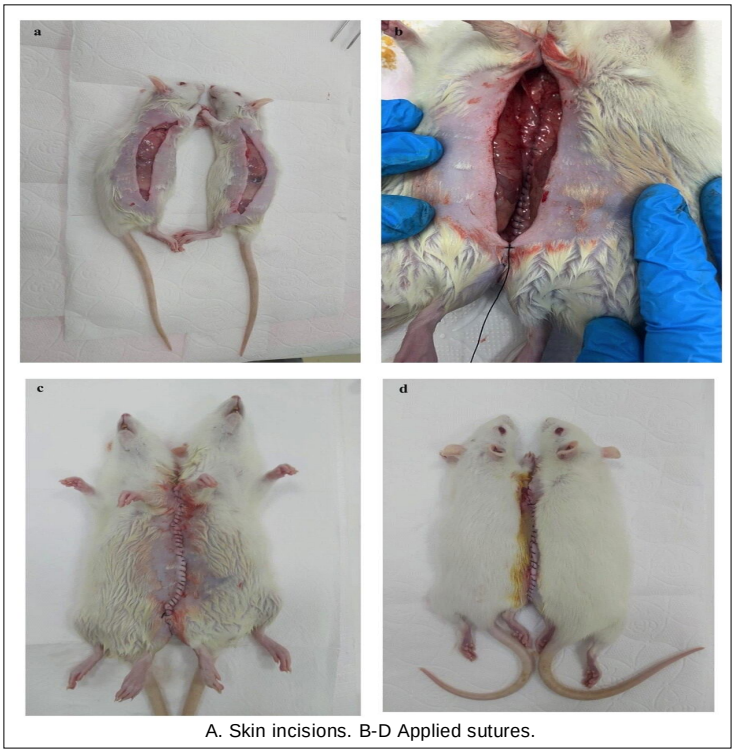
The results obtained in our study were expressed as mean ±standard error of the mean (SEM). To evaluate the blood glucose levels before and after STZ administration, two-way repeated measures analysis of variance (ANOVA) was perfomed, followed by Tukey's post hoc test.

RESULTS AND DISCUSSION

The present study explores the application of parabiosis as a model for investigating systemic metabolic effects, specifically in the context of diabetes. By pairing diabetic and non-diabetic organisms, this model allows researchers to observe how blood-borne factors influence glucose homeostasis, insulin sensitivity and pancreatic function in diabetic subjects. This approach addresses the urgent need for innovative strategies to combat diabetes and offers insights into how circulatory factors might alleviate some of the physiological consequences associated with the disease.

Chimerization between the animals is completed within 14 days. The STZ injection was adminitrated five days following parabiosis surgery after allowing sufficient time for the animals 'wounds to heal' (da Silva *et al.*, 2021). This timing provides that administration of STZ before the completion of chimerisation allows one of the heterochronic parabionts to become diabetic and the other to become non-diabetic.

Following 5 days of STZ injection, the H-diabetic parabiosis group exhibited significantly higher blood glucose levels (616±55 mg/dL, $p<0.001$) compared to their non-diabetic counterparts (H-Non-diabetic: 117±16 mg/dL). Following STZ administration, blood glucose levels (I-Diabetic: 541±53 mg/dL, H-Diabetic: 616±55 mg/dL, $p<0.001$) increased markedly relative to baseline values (I-Diabetic: 130±13 mg/dL, H-Diabetic: 106±13 mg/dL) in all diabetic groups . However, no significant difference was observed between the diabetic groups.



A. Skin incisions. B-D Applied sutures.

Fig 2: Surgical procedure.

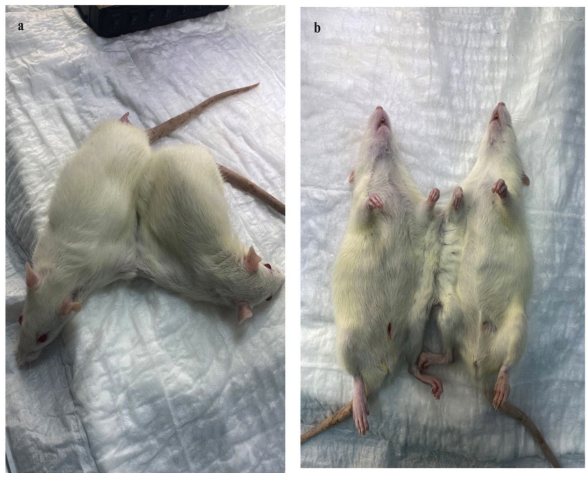
The surgical and post-operative protocols for establishing parabiotic pairs, as well as the methods for validating blood chimerism, should be carefully designed to ensure reliable data and effective blood exchange between animals. The rigorous process of validating blood chimerism, including glucose fluctuation tests, Evan's Blue staining (Liu *et al.*, 2020) and flow cytometry (Rodriguez *et al.*, 2022), is essential in ensuring that shared circulation is achieved and sustained. These protocols lay a foundation for reliable parabiotic models that can be applied not only in diabetes research but also in studies on aging (Rodriguez *et al.*, 2022), immune function (Feng *et al.*, 2018) and other systemic diseases (Eggel and Wyss-coray, 2014).

In addition, our findings highlight the role of angiogenesis in long-term parabiotic pairs, as evidenced by the growth of new blood vessels in the parabiotic connection after eight weeks. This vascular development is crucial for maintaining efficient blood exchange and suggests that the parabiotic connection becomes functionally integrated over time, allowing for more consistent metabolic interactions between paired animals. This angiogenesis could play a role in the observed improvements in diabetic parabionts by providing a more stable platform for the exchange of beneficial blood-borne factors.

Surgical complications remain a significant concern throughout all stages of parabiosis studies (Conboy *et al.*, 2013). Parabiotic disharmony-often indicated by lethargy or death-can arise due to immune rejection or from non-cohesive pairing, often due to mismatched weights or aggressive interactions (Yang *et al.*, 2021). Selecting genetically similar animals and ensuring less than a 20% weight difference can reduce these risks (Rodriguez *et al.*, 2022). Additionally, due to males tend to show increased aggression, pairing with long-term cage mate or a naïve parabiont at the time of presurgery period may be more effective

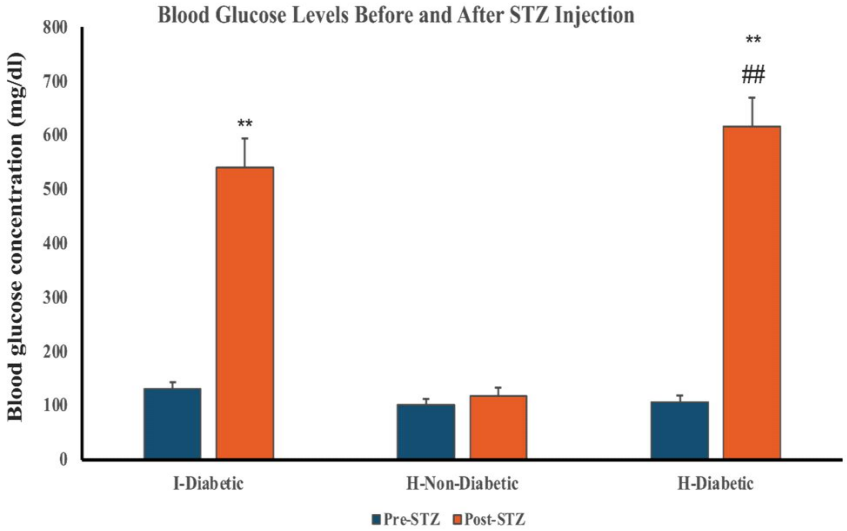
Anesthesia is another important consideration, especially in parabiosis where two animals must be sedated simultaneously. Differences in anesthetic requirements based on sex, age, weight and strain are significant; females are more sensitives to xylazine and ketamine coctail compare with males (Levin-Arama *et al.*, 2016). Supplementary ketamine or isoflurane can be applied for maintaining proper anesthesia, as prolonged xylazine use may lead to respiratory complications (Levin-Arama *et al.*, 2016).

Wound healing complications, such as dehiscence, may arise both internally (at joint sites) and externally (along



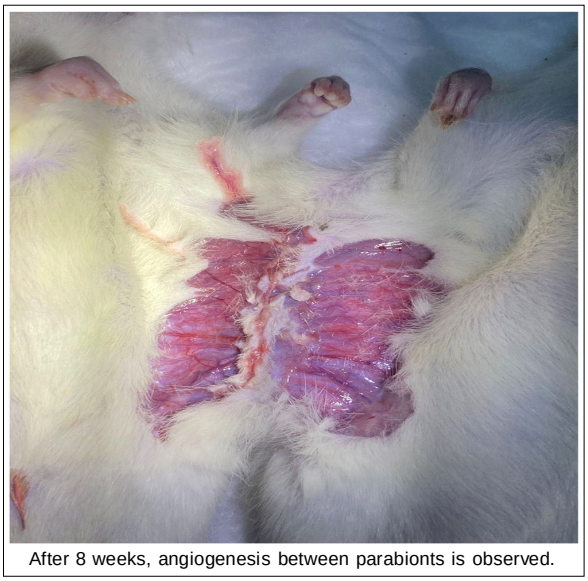
A,B. Appearance of the parabiosis pair at 8 weeks.

Fig 3: Post-operative recovery.



I-Diabetic, isochronic diabetic group; H-Diabetic, heterochronic diabetic group; H-Non-dibetic, Heterochronic non-diabetic group. ** p<0,001, difference from own Pre-SZT values, ## p<0,001, difference compare with I-Diabetic group.

Fig 4: Blood glucose levels before and after STZ injection.



After 8 weeks, angiogenesis between parabionts is observed.

Fig 5: Angiogenesis.

skin incisions). Use of topical agents and careful surgical techniques, including layered suturing, are essential to prevent and manage dehiscence. Persistent dehiscence or signs of infection, such as inflammation and discharge, may necessitate antibiotic intervention or surgical revision, particularly in severe cases. Elbow dehiscence, more consequential than knee separation, should be promptly repaired to avoid skin and vascular constriction (Rodriguez *et al.*, 2022).

Additional postoperative issues like dehydration and weight loss are common. Daily monitoring and supportive care, including subcutaneous antibiotics, nutrient supplements and moisture-enriched food, can alleviate some of these complications. Skin irritation around sutures, especially from scratching, can also occur; nail trimming and carprofen may help manage these symptoms. Another important point, in heterochronic diabetic and isochronic diabetic groups, %30 dextrose should be added to drinking water to prevent animals from hypoglisemia for two days following STZ injection.

STZ is naturally occuring nitrosourea compound that selectively destroys pancreatic b cells, thereby inducing insulin-deficient diabetes in experimental animals (Vijay *et al.*, 2019; Erkiliç and Bayraktar, 2025). This STZ-induced diabetic models provides a reliable platform for investigating metabolic alterations and testing potential therapeutic interventions.

Recent advances in metabolic cross-circulation studies highlight that parabiosis can serve as a bridge between basic physiology and pharmacological research, potentially identifying circulating molecules for antidiabetic therapy development.

The improved glucose regulation observed in diabetic parabionts may be attributed to circulating rejuvenating factors, such as GDF11, extracellular vesicles and specific miRNAs circulating rejuvenating factors, (Lagunas-Rangel, 2024) These molecules could modulate pancreatic b cells function, enhance insulin signaling and reduce oxidative stress.

CONCLUSION

Our study underscores the value of parabiosis as a tool for diabetes research, providing a unique perspective on the systemic nature of the disease. By enabling the exploration of blood-borne factors, parabiosis opens new research avenues for developing targeted therapies aimed at improving metabolic health. This model holds promise for advancing our understanding of diabetes and related metabolic disorders, offering insights that may lead to novel interventions and more effective management of diabetes in the future.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Declaration of generative AI and AI-Assisted technologies in the writing process

This study utilized AI-based tools for grammar checking and language enhancement to improve clarity and readability.

Informed consent

The Near East University Ethics Committee for Animal Experimentation authorized all methods (Approval number: 2024/172) and procedures and all animals were used in compliance with the Guide for the Care and Use of Laboratory Animals. The rats were obtained from the Near East University Experimental Animals Care and Production Unit.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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