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Therapeutic Role of MSC-Secretome in Type 2 Diabetic Models: Correlation between Improved HOMA-IR and Attenuated Pancreatic-Hepatic Structural Alterations

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, β-cell dysfunction, and chronic hyperglycemia leading to multiorgan complications. Conventional therapies primarily target glycemic control but often fail to prevent progressive pancreatic and hepatic injury. This study investigated the therapeutic potential of hypoxic mesenchymal stem cell (MSC) secretome in improving insulin resistance and restoring tissue integrity in T2DM rat models. **Methods:** Male Wistar rats were induced with T2DM using a high-fat diet followed by streptozotocin–nicotinamide administration and subsequently treated intraperitoneally with MSC-secretome for four weeks. Fasting blood glucose, serum insulin levels, and HOMA-IR index were assessed, followed by histopathological evaluation of hepatic and pancreatic tissues. **Results:** The results showed that T2DM was significantly associated with elevated insulin levels and HOMA-IR values compared to the normal group, confirming insulin resistance. Treatment with MSC-secretome markedly reduced both parameters ($p < 0.001$), suggesting improved insulin sensitivity. Histological analyses revealed substantial hepatic and pancreatic degeneration in untreated diabetic rats, characterized by hepatocellular vacuolization, steatosis, and islet necrosis. **Conclusion:** Conversely, MSC-secretome treatment demonstrated remarkable restoration of lobular architecture, reduced lipid accumulation, and regeneration of pancreatic islets. These reparative effects are attributed to the secretome's bioactive components that regulate oxidative stress, inflammation, and cellular regeneration. In conclusion, hypoxic MSC-secretome administration effectively ameliorates insulin resistance and attenuates hepatic and pancreatic damage in T2DM rats, underscoring its potential as a novel non-cell-based therapeutic strategy for metabolic disorders

Keywords: Type 2 diabetes mellitus, Secretome, MSCs, Oxidative stress

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become one of the most serious public health issues in the world. This issue is driven largely by lifestyle factors such as lack of physical activity, poor sleep patterns, chronic stress, and unhealthy diets that increase prevalence of obesity. International Diabetes Federation (IDF) estimates that over 537 million people (aged 20-79 year) worldwide are currently living with diabetes, and this number is projected to rise continuously reaching around 783 million by 2045[1]. In 2022, recent global analyses showed that approximately 43% of adults were overweight and 16% were classified as obese, with obesity contributing substantially in some populations up to 80% to the burden of type 2 diabetes [2]. T2DM condition is characterized by insulin resistance and β-cell dysfunction, leading to chronic hyperglycemia and increased risk of complications like cardiovascular

disease, nephropathy, neuropathy, as well as organ-specific damage such as fatty liver disease (non-alcoholic fatty liver disease, NAFLD) and progressive pancreatic dysfunction.

The high risk of complications in T2DM represents a critical consideration to determine the most appropriate therapy. Current standard therapies, such as lifestyle interventions, oral hypoglycemic drugs, and insulin administration, primarily focus on regulating blood glucose levels. However, these strategies frequently do not delay the progression of the disease or protect against organ damage, especially in individuals with obesity-related metabolic disturbances. Persistent hyperglycemia and chronic inflammatory responses can further promote liver fat accumulation (hepatic steatosis) and inhibit the regeneration of pancreatic β-cells, this leads to a vicious cycle of impairing glycemic control and progressive organ injury.

This limitation has prompted the exploration of innovative therapeutic approaches, such as use of the mesenchymal stem cell (MSC) secretome. Secretome of mesenchymal stem cells (MSCs) is a complex mixture of molecules including cytokines, growth factors, and extracellular vesicles that has the potential to address these underlying mechanisms. Different from conventional therapies that primarily target glycemic control, MSC-derived secretomes have been shown to modulate immune responses, reduce inflammation, enhance tissue repair, and improve insulin sensitivity, offering a promising therapeutic approach to prevent or ameliorate T2DM-related complications, including hepatic and pancreatic damage[3]. This regenerative potential positions secretome-based therapies as a novel strategy to manage both metabolic dysfunction and organ-specific injury in T2DM. Therefore, this study aims to analyze the effect of hypoxic secretome MSCs on the stage of insulin resistance through the observation of insulin levels and HOMA-IR values, as well as their correlation with the improvement of hepatic and pancreatic histopathological structures in T2DM rat's model

MATERIALS AND METHODS

Animals and Experimental Design

Male Wistar rats (Rattus norvegicus), 8–10 weeks old and weighing 190–220 g, were obtained from the Animal Model Research Center, Stem Cell and Cancer Research Indonesia. Animals were housed under controlled conditions (22 ± 2 °C, 12 h light/dark cycle) with ad libitum access to food and water.

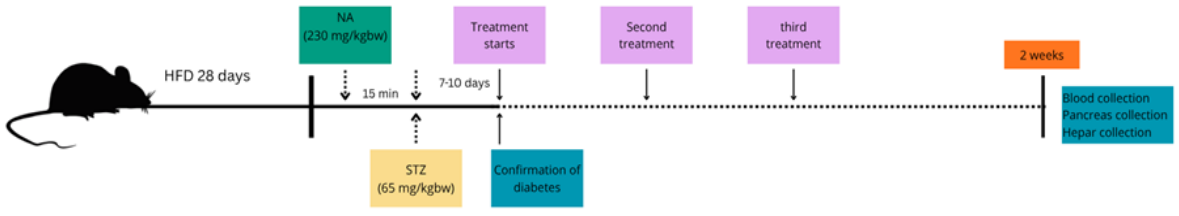

Figure 1. Diagrams showing representative flow charts of T2DM was induced by combining a high-fat diet (HFD) and streptozotocin (STZ)–nicotinamide (NA) administration.

Induction of Type 2 Diabetes Mellitus

Rats were first fed an HFD containing 45% fat, 20% protein, and 35% carbohydrates for four weeks to induce insulin resistance. On day 29, rats received a single intraperitoneal (i.p.) injection of nicotinamide (NA; 230 mg/kg BW) dissolved in normal saline, followed 15 min later by STZ (65 mg/kg BW) freshly prepared in 0.1 M cold citrate buffer (pH 4.5). After 72 h, fasting blood glucose (FBG) was measured via tail vein sampling using a glucometer. Rats with FBG levels between 150–250 mg/dL were considered diabetic and included in the study

MSC-Secretome Preparation and Administration

The mesenchymal stem cell (MSC) secretome was obtained from conditioned medium of cultured rat umbilical cord-derived MSCs (passage 3–5). After 48 h of serum-free incubation, the conditioned medium was collected, centrifuged at 3000 rpm for 15 min, and filtered through a 0.22 µm filter to remove debris. The supernatant (secretome) was aliquoted and stored at −80 °C until use. Treatment was administered via intraperitoneal injection at a dose of 250 µL, once weekly for four consecutive weeks. The vehicle control group received the same volume of phosphate-buffered saline (PBS).

Biochemical Analyses

At the end of the treatment period, fasting blood glucose (FBG) and fasting insulin levels were measured. Blood was collected from the retro-orbital plexus after overnight fasting. Serum insulin concentrations were determined using an ELISA kit (e.g., Rat Insulin ELISA Kit, [Manufacturer]).
The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated using the formula:

$$\text{HOMA-IR} = \frac{\text{FBG (mg/dL)} \times \text{Fasting Insulin (µU/mL)}}{405}$$

Histological Analysis of Pancreas and Liver

Pancreatic and hepatic tissues were excised, fixed in 10% neutral-buffered formalin, dehydrated, embedded in paraffin, and sectioned at 5 µm thickness. Sections were stained with hematoxylin and eosin (H&E) for histopathological examination under a light microscope. Pancreatic assessment focused on the morphology of the islets of Langerhans and degree of cellular degeneration, using a semi-quantitative scoring system (0–4). Hepatic assessment included evaluation of hepatocellular architecture, steatosis, and inflammatory infiltration. Histological scoring was performed blindly by two independent observers.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Statistical differences among groups were analyzed using one-way ANOVA followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant. All analyses were performed using GraphPad Prism 9.

RESULT AND DISCUSSION

Treatment Effect of Secretome-Mesenchymal Stem Cell on Insulin Secretion and Insulin Resistence

Based on these results as shown in Table 1, a strong correlation was observed between insulin levels and HOMA-IR values across each group. The T2DM group exhibited a marked increase in both insulin levels (13.00 ± 0.78 µIU/mL) and HOMA-IR values (8.85 ± 0.77) compared to the Normal group (3.01 ± 0.45 µIU/mL and 0.80 ± 0.14, respectively). This significant elevation ($p < 0.001$) confirms the presence of insulin resistance in the T2DM group. On the other hand, the Secretome-MSC treated T2DM group demonstrated a reduction in both insulin levels (7.38 ± 0.41 µIU/mL) and HOMA-IR values (2.71 ± 0.55) relative to the untreated T2DM group

Table 1. Results of Insulin Level and HOMA-IR Values

Group	Insulin Levels (µIU/mL) Mean ± SD	HOMA-IR Values Mean ± SD	*Sig. (p-value)*
Normal	3.01 ± 0.45	0.80 ± 0.14	<0.001
T2DM	13.00 ± 0.78	8.85 ± 0.77	<0.001
T2DM with Secretome-MSC treatment	7.38 ± 0.41	2.71 ± 0.55	<0.001

Data are expressed as mean ± standard eror. Number of animals in each group is eight.

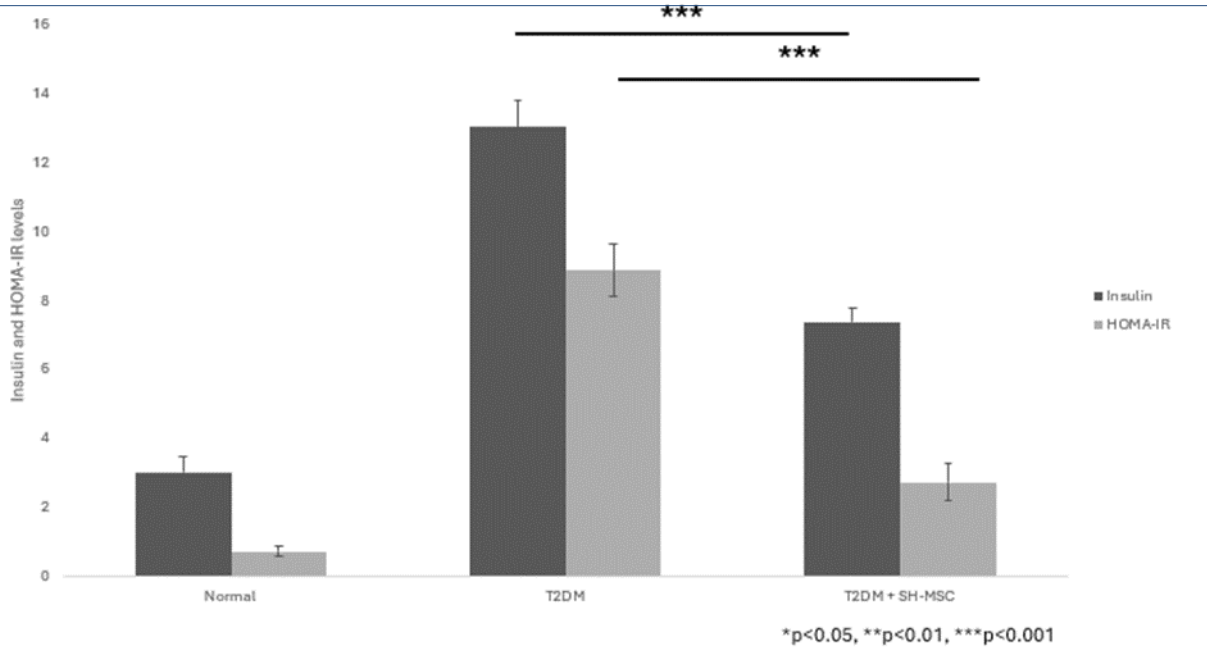

Figure 2. The Insulin and HOMA-IR levels of blood serum in each group. Data are expressed as the mean ± standard error of the mean, *p value <0.001.

Effect of Secretome Hypoxia Mesenchymal Stem Cells on Hepatic Morphology in Type 2 Diabetic Mellitus.

Histological analysis was taken of liver sections from three groups of rats (Fig 2) in the normal group, hepatic tissue exhibited a well-preserved lobular architecture with distinct central veins and radiating hepatic cords. Hepatocytes appeared polygonal with centrally located nuclei and clear cytoplasm, while the sinusoidal spaces were regular and unobstructed. In the T2DM group, liver sections revealed marked centrilobular degeneration characterized by cytoplasmic vacuolization and mild sinusoidal dilation, indicating hepatic steatosis and cellular stress induced by hyperglycemia. Group treatment with secretome hypoxic MSCs showed notable restoration of hepatic morphology, evidenced by reduced lipid accumulation, reorganization of hepatic cords, and fewer degenerative changes. These findings are consistent with previous reports showing that secretome hypoxia-MSC can ameliorate hepatic steatosis and restore normal hepatocellular structure by modulating lipid metabolism and oxidative stress pathways.

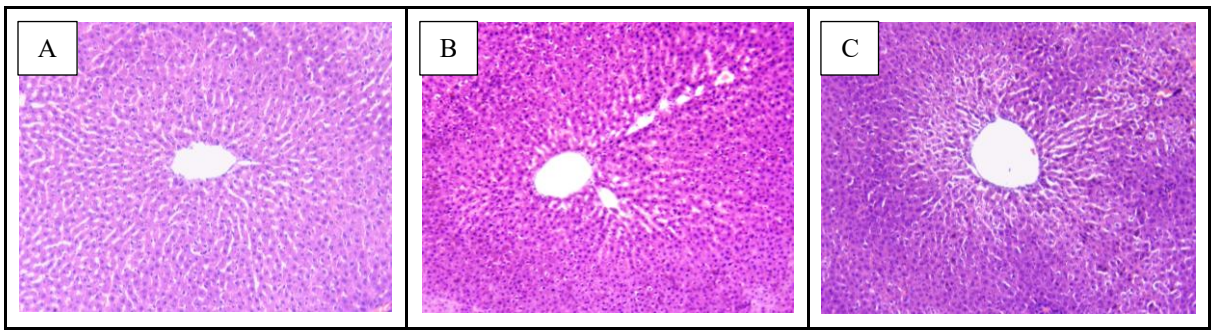

Figure 3. Micrograph of Rat Hepatic Tissue (hematoxylin and eosin stain, 400x). A: Normal group; B: Type 2 Diabetic Mellitus (T2DM); C: Type 2 Diabetic Mellitus with Secretome Hypoxia-MSC treated group (T2DM with SH-MSC)

Effect of Secretome Hypoxia Mesenchymal Stem Cells on Pancreatic Morphology in Type 2 Diabetic Mellitus.

The histopathological evaluation of pancreatic tissue was performed to assess the structural alterations induced by type 2 diabetes and the potential reparative effect of hypoxic mesenchymal stem cells (MSCs) secretome treatment. Hematoxylin and eosin (H&E) staining was used to observe changes in the morphology of the islets of Langerhans and surrounding exocrine acinar cells under light microscopy at 400× magnification. In the normal group (Fig 3A), the pancreatic sections revealed a well-organized architecture with distinct and compact islets of Langerhans surrounded by intact exocrine acinar cells. The cellular arrangement was uniform, and nuclei appeared round and clearly defined, indicating normal pancreatic histology. In the T2DM group showed evident structural disorganization within the islets of Langerhans (Fig 3B). The islets appeared shrunken and irregular with reduced cellular density. Cytoplasmic vacuolization and nuclear pyknosis were observed, accompanied by mild inflammatory infiltration, suggesting necrotic and degenerative changes consistent with diabetes-induced pancreatic injury. In the T2DM with SH-MSC group (Fig 3C), histological restoration of the islet structure was evident. The islets showed improved cellular organization with more preserved boundaries and decreased degenerative changes. The exocrine portion appeared comparable to that of the normal group.

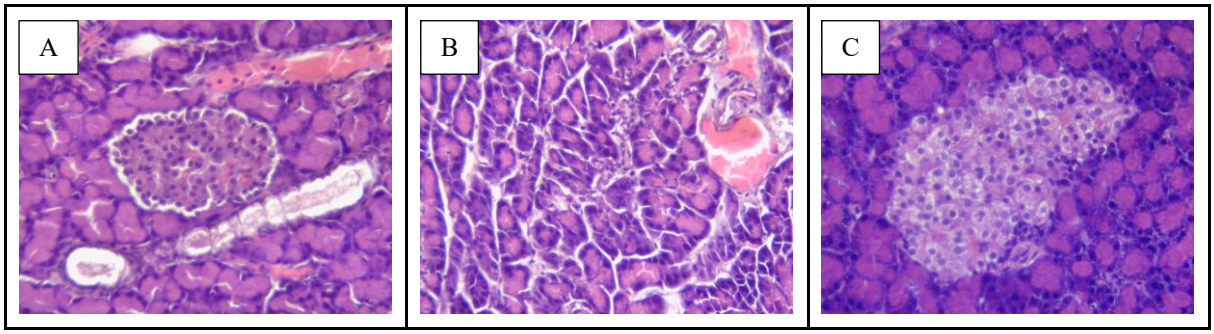

Figure 4. Micrograph of Rat Pancreatic Tissue (hematoxylin and eosin stain, 400x). A: Normal group; B: Type 2 Diabetic Mellitus (T2DM); C: Type 2 Diabetic Mellitus with Secretome Hypoxia-MSC treated group (T2DM with SH-MSC).

DISCUSSION

The data indicates that individuals with T2DM have significantly higher insulin levels and HOMA-IR values compared to normal individuals, confirming the presence of insulin resistance in T2DM. Treatment with Secretome-MSC showed that decrease both insulin levels and HOMA-IR values in T2DM patients, suggesting a potential improvement in insulin sensitivity. The high statistical significance ($p < 0.001$) supports the reliability of these findings. These results suggest that Secretome-MSC treatment may have a beneficial effect on insulin resistance in individuals with T2DM. This may occur because MSC secretome possesses immunomodulatory properties, that to shift macrophage phenotypes toward anti-inflammatory (M2) polarization, suppress proinflammatory cytokines (e.g. TNF-α, IL-6) and reduce chronic low-grade inflammation. Some studies report that MSC-derived secretome increases phosphorylation of Akt (protein kinase B) and enhances translocation of glucose transporter GLUT4 to the membrane in insulin-resistant cells 3. These changes restore effective insulin signaling downstream of the insulin receptor, thereby lowering circulating insulin needs and HOMA-IR.

Histopathological evaluation revealed that type 2 diabetes mellitus induced substantial degenerative alterations in both hepatic and pancreatic tissues, consistent with the metabolic

dysregulation caused by persistent hyperglycemia. In T2DM rats, hepatic parenchyma exhibited cytoplasmic vacuolization, sinusoidal dilation, and centrilobular degeneration, which are characteristic features of hepatic steatosis and oxidative injury. These pathological manifestations are consistent with previous findings reporting that prolonged hyperglycemia disrupts lipid metabolism and mitochondrial function, leading to excessive reactive oxygen species (ROS) formation and hepatocellular necrosis (Ragavan & Krishnakumari, 2006; Lenzen, 2008). The observed morphological changes likely reflect the cumulative impact of oxidative stress, lipid peroxidation, and inflammatory cytokine activation within hepatic tissue.

Administration of hypoxic mesenchymal stem cell (MSC) secretome demonstrated a pronounced hepatoprotective effect by reducing intracellular lipid accumulation and restoring lobular organization. The improvement observed may be attributed to the bioactive constituents of the secretome—including growth factors, cytokines, and extracellular vesicles—which are known to regulate antioxidant enzyme systems, suppress inflammatory cascades, and stimulate hepatocyte regeneration (Yun et al., 2019; Kim et al., 2020). The hypoxic preconditioning of MSCs has been reported to enhance the secretion of paracrine mediators, particularly exosomes enriched with angiogenic and anti-apoptotic molecules, thereby augmenting their cytoprotective efficacy (Hu et al., 2016).

Similarly, pancreatic histoarchitecture in diabetic rats exhibited marked shrinkage and necrosis of the islets of Langerhans, nuclear pyknosis, and reduced cellular density—pathological features consistent with β-cell degeneration and oxidative stress-mediated apoptosis. These findings corroborate previous histological studies that described inflammation, necrosis, and islet atrophy as hallmarks of diabetes-induced pancreatic damage (Cheekati et al., 2017; Ragavan & Krishnakumari, 2006). In contrast, animals treated with hypoxic MSC secretome displayed partial restoration of islet integrity, decreased necrotic foci, and improved cellular organization, indicating reparative and anti-inflammatory actions mediated by paracrine signaling pathways. Collectively, these findings suggest that hypoxic MSC secretome mitigates hyperglycemia-induced oxidative damage by modulating redox balance, suppressing inflammation, and promoting hepatic and pancreatic tissue regeneration.

CONCLUSION

The present study demonstrates that administration of hypoxic mesenchymal stem cell (MSC) secretome exerts a protective and restorative effect on hepatic and pancreatic tissues in type 2 diabetic rats. The treatment effectively attenuated histopathological damage characterized by hepatocellular degeneration and islet necrosis. These findings indicate that the bioactive components of hypoxic MSC secretome play a critical role in mitigating oxidative stress, reducing inflammation, and promoting cellular regeneration. Thus, hypoxic MSC secretome represents a promising non-cell-based therapeutic approach for improving hepatic and pancreatic integrity in metabolic disorders such as type 2 diabetes mellitus.

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Competing Interests

The authors declare that there is no conflict of interest.

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