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# Modulation of GLUT4 and FOXO1 Expression by SH-MSC and Alkaline Water in Experimental Type 2 Diabetes Mellitus

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**ORIGINAL ARTICLES**

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**ABSTRACT**

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterized by insulin resistance, which is associated with the dysregulation of glucose transporter 4 (GLUT4) and forkhead box protein O1 (FOXO1). The secretome from hypoxia-preconditioned mesenchymal stem cells (SH-MSC) and alkaline water have been proposed as potential therapies to modulate these molecular targets and improve glycemic control; however, their combined effects remain unexplored. Using an experimental post-test-only control group design, this study aimed to assess the possible additive effect of SH-MSC and alkaline water on the expression of GLUT4 and FOXO1 in Wistar rats with type 2 diabetes. Twenty-five male Wistar rats were split into five groups: healthy control (G1), T2DM control (G2), T2DM with metformin (G3), T2DM with SH-MSC (G4), and T2DM with SH-MSC and alkaline water (G5). Streptozotocin and nicotinamide were utilized to induce T2DM, and qRT-PCR was used to measure the expression of GLUT4 and FOXO1 in pancreatic tissue. One-way ANOVA and a post hoc LSD test were used for statistical analysis. The findings recognized that while GLUT4 expression was decreased, T2DM induction markedly increased fasting blood glucose levels and FOXO1 expression. SH-MSC treatment significantly upregulated GLUT4 and downregulated FOXO1 equated to the control T2DM group, and while the addition of alkaline water showed a further trend of improvement, this difference was not statistically significant. These findings suggest that SH-MSC therapy effectively improves glucose metabolism by modulating GLUT4 and FOXO1 expression, with the potential for alkaline water as an adjunctive therapy in T2DM management.

**Key Messages:**

- Combining SH-MSC with alkaline water resulted in greater molecular effects, although the difference was not statistically significant, suggesting a possible additive effect.
- Targeting key molecular in insulin sensitivity and glucose regulation is a novel approach, which could complement conventional T2DM therapies.
- The study supports the use of SH-MSC and alkaline water as adjunctive strategies in T2DM care, paving the path for further translational investigations.

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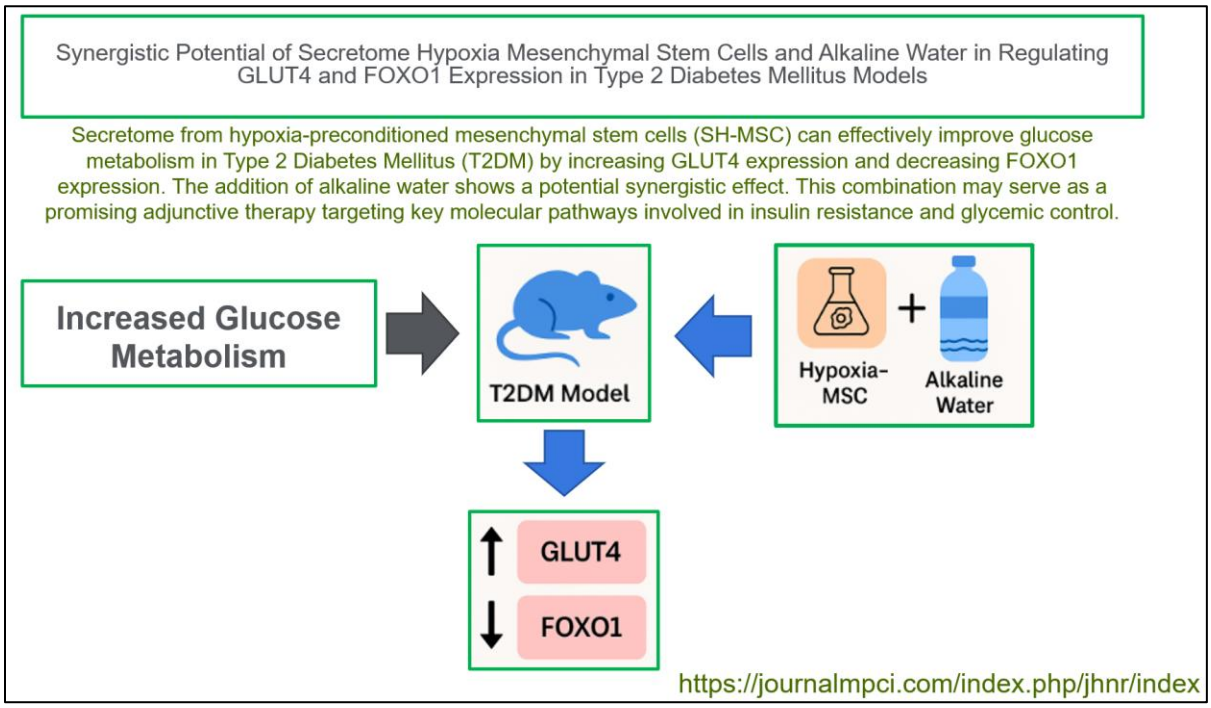
## GRAPHICAL ABSTRACT




## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic condition defined by insulin resistance and decreased glucose absorption (1,2), primarily caused by the dysregulation of glucose transporter 4 (GLUT4) and forkhead box protein O1 (FOXO1) (3–5). Disrupting in GLUT4 translocation to the plasma membrane reduces glucose uptake by adipose and muscle cells (6), while overexpression of FOXO1 exacerbates insulin resistance through increasing gluconeogenesis and oxidative stress (7). Treating these molecular abnormalities is critical for improving glycemic control and minimizing problems associated with T2DM (5,8,9).

Current T2DM treatment options, including metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors, have demonstrated efficacy in treating hyperglycemia (10). However, these treatments are frequently coupled with negative consequences such as hypoglycemia, gastrointestinal distress, and increased risk of infections (11,12). Therefore, there is an urgent need to investigate alternate therapy techniques that offer effective glycemic control while minimizing side effects.

Recent studies has highlighted the potential of SH-MSC as a novel treatment for metabolic disorders (13–16). SH-MSC, which is produced from mesenchymal stem cells (MSC) under hypoxic settings, contains bioactive compound such as cytokines and growth factors that regulate inflammatory responses, improve insulin sensitivity, and stimulate tissue regeneration (16–20). In parallel, alkaline water has been shown to have antioxidant properties that reduce oxidative stress, enhancing insulin signaling and glucose metabolism (21,22). Both SH-MSC and alkaline water may both provide therapeutic advantages in managing insulin resistance and associated metabolic disturbances.

Even though there is some evidence supporting the therapeutic effects of SH-MSC and alkaline water, their combined impact on GLUT4 and FOXO1 expression in T2DM remains unexplored. Understanding whether these interventions can enhance therapeutic effects by improving insulin signaling pathways may offer new insights for developing more effective and integrative strategies for diabetes management. The purpose of this study is to investigate the potentially enhanced effects of SH-MSC and alkaline water in modulating GLUT4 and FOXO1 expression in Wistar rats with T2DM. By exploring the molecular mechanisms behind these interventions, this study seeks to shed lights on the potential application of SH-MSC and alkaline water as adjunct therapy for T2DM management.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## METHODS

### Experimental Design

This study was carried out at the Stem Cell and Cancer Research (SCCR) Indonesia Laboratory. The SCCR Indonesia Laboratory produced SH-MSC and provided alkaline water. Animal maintenance, induction, and treatment were conducted at the Animal Model Research Center of SCCR Indonesia. The study was performed from November 2024 until January 2025.

The study used an experimental design, with a post-test only control group. A total of 25 male Wistar rats (aged 6–8 weeks and weighed 200–250 g) were randomly allocated into five groups: G1/Healthy Control (no treatment), G2/T2DM Control (Induced with streptozotocin and nicotinamide without further intervention), G3/T2DM + Metformin (Treated with metformin 45 mg/kg body weight per day via oral administration), G4/T2DM + SH-MSC (Received intraperitoneal injection of 500 µl SH-MSC on days 8, 15, and 22), and G5/T2DM + SH-MSC + Alkaline Water (Received SH-MSC as in K4, combined with oral administration of alkaline water 5 mL daily for 29 days).

T2DM was induced by administering nicotinamide via intraperitoneal injection (15 mg/kg body weight), followed by STZ (50 mg/kg body weight) in sodium citrate buffer (0.1 M, pH 4.5). Confirmed diabetes in rats by measuring fasting blood glucose levels on day 7 post-induction, with rats exhibiting glucose levels >126 mg/dL included in the study. The SH-MSCs used in this study were isolated from rat umbilical cord (UC) tissue. Prior to administration, the cells were characterized by surface marker analysis, which showed positive expression of CD29 and CD90 and negative expression of CD31 and CD45, consistent with the mesenchymal stem cell identity. Their multipotency was further confirmed by successful osteogenic differentiation, indicated by calcium deposits stained with Alizarin Red, and adipogenic differentiation was demonstrated by lipid droplets stained with Oil Red O. The alkaline water (Sigma-Aldrich, USA) used in this study had a pH of 8.5.

### GLUT4 and FOXO1 Expression Analysis Using RT-PCR Method

Pancreatic tissue samples were collected from all groups and kept at -80°C until day 30 for analysis. TRIzol® reagent (Invitrogen Life Technologies) was used to extract total RNA from pancreatic tissue according the manufacturer's protocol. The obtained RNA was then converted into complementary DNA (cDNA) using the iScript cDNA Synthesis Kit (Bio-Rad iScript gDNA Clear cDNA Synthesis Kit Catalog). The cDNA synthesis process was carried out using a Reverse Transcriptase PCR (RT-PCR) thermal cycler C1000 (Bio-Rad). Quantitative real-time PCR (qRT-PCR) was utilized to determine the expression levels of GLUT4 and FOXO1. The RT-PCR reaction amplified GLUT4 and FOXO1 using the designed primers (Table 1).

**Table 1. GLUT4 and FOXO1 Primary Design**

| Gene | Sequences |
|---|---|
| **GLUT4** | *F 5'-ACA TAC CTG ACA GGG CAA GG-3'* |
| | *R 5'-CGC CCT TAG TTG GTC AGA AG-3'* |
| **FOXO1** | *F 5'-CTC AGG TGG TGG AGA CCG A-3'* |
| | *R 5'-GAG CTG GTT CGA GGA CGA AA-3'* |

The mRNA expression levels of *FOXO1* and *GLUT4* genes were measured in relation to the housekeeping gene *GAPDH*. The relative expression levels were estimated using the comparative ΔΔCt or ddCt methods.

### Statistical Analysis

Data were analysed using one-way ANOVA, followed by a post hoc LSD test for group comparisons. The results were expressed as mean ± standard deviation (SD), with significance set at $p < 0.05$.

### CODE OF HEALTH ETHICS

Ethical approval for this study was obtained from the Medical/Health Research Ethics Commission, Faculty of Medicine, Sultan Agung Islamic University in Semarang, Indonesia (No. 10/I/2025/Komisi Bioetik).



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## RESULTS

### Validation of Type 2 Diabetes Mellitus Model in Wistar Rats

The induction of T2DM in Wistar rats using streptozotocin (STZ) caused in a significant increase in fasting blood glucose (FBG) levels, confirming the formation of the diabetic model. Table 2. shows that the levels of FBG in the diabetic control group reached 450.29 mg/dL, certainly higher than the healthy control group (105 mg/dL).

**Table 2. The DMT2 Rat Validation Results**

| Data | Healthy Rat | STZ-Induced Rat |
|---|---|---|
| Fasting Blood Glucose | 105 mg/dL | 450.29 mg/dL |
| Homa-IR | 0.77 | 20.91 |

### GLUT4 Gene Expression

GLUT4 expression also exhibited a normal distribution (Shapiro-Wilk test; $p>0.05$) and homogeneous variance test (Levene's test, $p>0.05$). The expression levels varied significantly among the groups ($p<0.001$). The healthy control group (G1) exhibited baseline expression (1.00 ± 0.00). In the untreated diabetic control group (G2), GLUT4 expression was elevated (9.05 ± 3.45), likely reflecting an insufficient compensatory response to hyperglycaemia, whereas G3 showed a slight increase (12.37 ± 6.09). The treatment groups G4 (21.70 ± 10.57) and G5 (27.97 ± 10.93) demonstrated a marked upregulation of GLUT4 expression. Post hoc LSD analysis indicated that G4 had significantly higher GLUT4 expression than G2 ($p<0.05$), but no statistically significant difference was observed between G4 and G3 ($p>0.05$). G5 exhibited significantly increased GLUT4 expression compared to both G2 and G3 ($p<0.05$) but was not statistically significantly different from G4 ($p>0.05$). This shows that the combination of SH-MSCs and alkaline water enhanced GLUT4 expression, potentially improving glucose uptake efficiency. Table 3 shows the GLUT4 gene expression data.

**Table 3. Results of GLUT4 Expression**

| Variable | Group | | | | | |
|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | Sig. (P) |
| GLUT4 Mean ± SD | 1.00±0.00 | 9.05±3.45 | 12.37±6.09 | 21.70±10.57 | 27.97±10.93 | |
| Shapiro Wilk | | | | | | >0.05 |
| Lavene test | | | | | | >0.05 |
| One Way ANOVA | | | | | | <0.00 |

These results show that the combination of alkaline water and SH-MSC injection did not significantly increase GLUT4 expression compared to SH-MSC injection alone. This suggests that, while both treatments contribute to increased GLUT4 expression, the addition of alkaline water does not provide a substantial incremental effect beyond SH-MSC therapy. Figure 1 shows a visualization of GLUT4 expression levels.

The healthy control group (G1) exhibited the lowest GLUT4 expression, while the untreated diabetic group (G2) had low GLUT4, indicating decreased glucose transport. Metformin treatment (G3) significantly increased GLUT4 expression compared to G2, and the combination of SH-MSCs and alkaline water (G5) further increased GLUT4 levels. However, no significant difference was seen between G4 and G5, indicating that the addition of alkaline water had no significant incremental effect beyond SH-MSC therapy alone. These data suggest that SH-MSCs and alkaline water contribute to improved glucose absorption by upregulating GLUT4 expression, potentially improving insulin sensitivity



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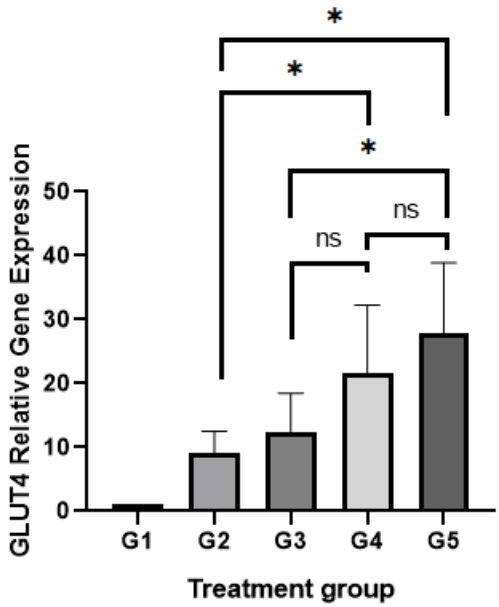


**Figure 1. Relative expression of the GLUT4 gene among different treatment groups. ns= not significant, *= p<0.05**.

**FOXO1 Gene Expression**

The FOXO1 gene expression followed a normal distribution, as confirmed by the Shapiro-Wilk test ($p > 0.05$). The Levene's test also revealed homogeneity of variance ($p>0.05$), which allowed for parametric statistical analysis. The treatment groups showed a significant difference ($p<0.001$). The FOXO1 expression was highest in the untreated diabetic control group G2 (15.36 ± 2.14), followed by G3 (8.94 ± 5.61), G4 (6.92 ± 3.27), and G5 (2.82 ± 1.50). The healthy control group (G1) showed baseline FOXO1 expression (1.00 ± 0.00). The post hoc LSD analysis showed that FOXO1 expression in G4 was significantly different from G2 ($p<0.05$) but not from G3 ($p>0.05$), while G5 had statistically significantly lower expression than both G2 and G3 ($p<0.05$) but not statistically significantly different from G4 ($p>0.05$). This demonstrates that the combination of SH-MSCs and alkaline water did not further inhibit FOXO1 expression when compared to SH-MSCs alone.

**Table 4. Results of FOXO1 Expression**

| Variable | Group | | | | | |
|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | Sig. (P) |
| FOXO1 Mean±SD | 1.00±0.00 | 15.36±2.14 | 8.94±5.61 | 6.92±3.27 | 2.82±1.50 | |
| Shapiro Wilk | | | | | | >0,05 |
| Lavene test | | | | | | >0,05 |
| One Way ANOVA | | | | | | <0,00 |

The diabetic control group (G2) exhibited the highest FOXO1 expression, suggesting enhanced gluconeogenesis and insulin resistance. Treatment with SH-MSCs (G4) statistically significant reduced FOXO1 expression compared to G2, while the combination of SH-MSCs and alkaline water (G5) further suppressed FOXO1 levels. However, no significant difference was observ ed between G4 and G5, indicating that the addition of alkaline water does not provide a substantial additional effect beyond SH-MSC therapy alone. These results suggest that SH-MSCs and alkaline water contribute to enhance glucose metabolism by downregulating FOXO1 expression, which reduces hepatic glucose synthesis and increases insulin sensitivity.



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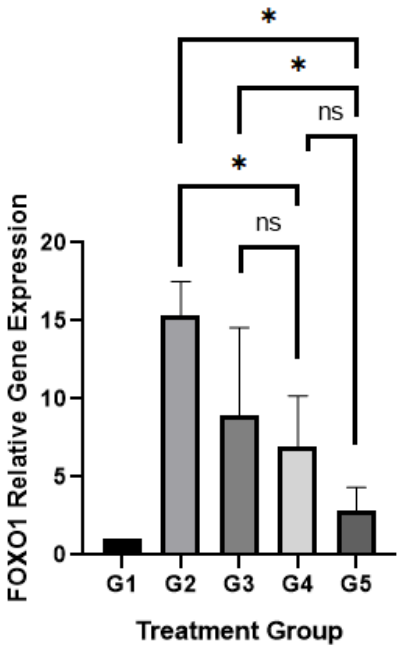


Figure 2. Relative expression of the FOXO1 gene among different treatment groups. ns= not significant, *= $p<0.05$.

## DISCUSSION

The presented research provides substantial proof that the combination SH-MSC and alkaline water offers significant therapeutic potential in modulating glucose metabolism in T2DM via influencing FOXO1 and GLUT4 expressions. The study found that administrating SH-MSC alone reduced FOXO1 expression (6.92±3.27) and a significantly upregulation of GLUT4 expression (21.70±10.57) compared to the untreated T2DM group (G2), which had higher FOXO1 expression (15.36±2.14) and relatively lower GLUT4 levels (9.05±3.45). The pronounced FOXO1 overexpression in the G2 group is consistent with the pathophysiology of T2DM (23), wherein insulin resistance promotes hepatic gluconeogenesis, exacerbating hyperglycemia (24,25). Although GLUT4 expression increased in this group, it is most likely a compensatory response that remains insufficient to effectively combat insulin resistance and impaired glucose uptake in peripheral tissues (26).

Administration of SH-MSC alone (G4) effectively mitigated metabolic dysregulation by suppressing FOXO1 expression, a key regulator of gluconeogenesis (27), while concurrently enhancing GLUT4 expression, thereby promoting insulin sensitivity and facilitating glucose uptake (28). The observed upregulation of GLUT4 is attributable to the bioactive components within SH-MSC secretome, as well as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), which have been shown to affect insulin signaling pathways and increase GLUT4 translocation to the plasma membrane (29,30). These findings align with prior research demonstrating the capacity of SH-MSC-derived factors to regulate metabolic pathways integral to glucose homeostasis and insulin responsiveness (15,16,31).

Notably, the combination of SH-MSC with alkaline water (G5) further potentially enhanced the therapeutic benefits, as evidenced by a greater reduction in FOXO1 expression (2.82±1.50) and a more pronounced increase in GLUT4 expression (27.97±10.93) compared to SH-MSC monotherapy. Granting these differences were not statistically significant, the findings suggest a potential additive effect of alkaline water in augmenting the metabolic benefits of SH-MSC, potentially through its antioxidative properties and its role in maintaining intracellular pH homeostasis (21,32), both of which contribute to mitigating oxidative stress and chronic inflammation, two critical factors underlying insulin resistance (33). Oxidative stress is recognized as a key driver in the progression of T2DM, and by scavenging reactive oxygen species (ROS)(34), alkaline water may enhance insulin signaling by altering the PI3K/Akt pathway, a fundamental mechanism involved in GLUT4 translocation and glucose uptake in peripheral tissues (35).



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Statistical analysis revealed that the metabolic improvements perceived in the SH-MSC and alkaline water group (G5) were statistically significantly greater than the standard therapy group (G3, metformin-treated), indicating the superior efficacy of this combination therapy in restoring glucose homeostasis. Although the differences between SH-MSC monotherapy (G4) and SH-MSC combined with alkaline water (G5) did not reach statistical significance, the observed trend toward further enhancement in GLUT4 expression and greater suppression of FOXO1 expression in the G5 group suggests that the combination therapy may confer potential additive effect. This supports the premise that alkaline water contributes to improved metabolic efficiency, potentially through its capacity to modulate glucose-metabolizing enzymes and reduce insulin resistance via PI3K/Akt-mediated GLUT4 translocation (35,36).

This study provides solid evidence that SH-MSC therapy effectively modulates glucose metabolism by downregulating FOXO1 and upregulating GLUT4, improving insulin sensitivity and glucose utilization in T2DM. While the statistical analysis revealed no significant difference in GLUT4 and FOXO1 expression between SH-MSC monotherapy (G4) and the combined treatment with alkaline water (G5, the observed trend toward higher GLUT4 expression and greater FOXO1 suppression in G5 suggests a potential additive or synergistic effect. However, since no statistical significance was attained, this trend should be regarded with caution and does not provide clear proof of synergy. These findings indicate the need for further studies that adjusts variables such as dosage and treatment period to establish whether the observed benefits are supported. Furthermore, the combined therapy in G5 exhibits a promising trend toward enhanced metabolic regulation, bolstering its potential as a novel adjunctive strategy for T2DM treatment. Nonetheless, further research, including long-term studies and clinical trials in human subjects, is needed to validate these findings and explore their broader applicability. Given the growing global prevalence of type 2 diabetes mellitus (T2DM), this study highlights the therapeutic potential of SH-MSC and alkaline water as a multifaceted intervention that targets both insulin resistance and oxidative stress, presenting a potential strategy for enhanced metabolic regulation and improved glycemic control.

## CONCLUSION

This study shows that SH-MSC therapy effectively improves glucose metabolism in T2DM by decreasing FOXO1 expression and increasing GLUT4 expression, thereby improving insulin sensitivity and glucose uptake. The combination of SH-MSC and alkaline water shows a promising tendency to further amplify these effects, most likely by lowering oxidative stress and improving insulin signaling. This approach appears to offer superior metabolic benefits than metformin, indicating its potential as an adjunctive therapy for T2DM management. Further research is needed to improve dosage, treatment duration, and therapeutic application, as well as to validate these findings in human investigations.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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