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INSULIN RESISTANCE IN THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

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Abstract: Insulin resistance is a central mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM), contributing to hyperglycemia and multi-organ dysfunction. This experimental study aimed to investigate the effects of insulin resistance on key insulin-responsive organs, including the pancreas, liver, adipose tissue, and skeletal muscle. Male Wistar rats were assigned to control, high-fat diet (HFD), and T2DM experimental groups. Biochemical parameters such as fasting blood glucose, insulin levels, and HOMA-IR were measured, and tissue samples were analyzed using histological and immunohistochemical methods. The T2DM group exhibited significant hyperglycemia, hyperinsulinemia, and increased HOMA-IR values. Histological analysis revealed pancreatic beta-cell dysfunction, hepatic lipid accumulation and glycogen depletion, adipose tissue hypertrophy with altered adipokine expression, and reduced GLUT4 expression in skeletal muscle. These findings demonstrate the multi-organ impact of insulin resistance and its critical role in the progression of T2DM, highlighting the importance of early interventions targeting insulin sensitivity.

Keywords: Type 2 diabetes mellitus, insulin resistance, pancreas, liver, adipose tissue, skeletal muscle, HOMA-IR, histology, GLUT4, adipokines.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion and/or insulin action [1]. Among the key pathophysiological mechanisms underlying T2DM, insulin resistance plays a central role [2]. Insulin resistance is defined as a reduced responsiveness of peripheral tissues—primarily skeletal muscle, adipose tissue, and liver—to normal circulating levels of insulin, leading to compensatory hyperinsulinemia in the early stages of the disease [3].

The development of insulin resistance is multifactorial, involving genetic predisposition, obesity—particularly visceral adiposity—sedentary lifestyle, chronic inflammation, and dysregulated lipid metabolism [4,5]. In skeletal muscle, insulin resistance impairs glucose uptake and glycogen synthesis, whereas in the liver it promotes excessive gluconeogenesis, contributing to fasting hyperglycemia [6]. Adipose tissue dysfunction further exacerbates insulin resistance by releasing pro-inflammatory adipokines and free fatty acids into circulation, which interfere with insulin signaling pathways [7].

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Insulin resistance not only precedes the clinical onset of T2DM but also drives the progressive deterioration of pancreatic beta-cell function [8]. The compensatory increase in insulin secretion can eventually fail, leading to overt hyperglycemia and the manifestation of type 2 diabetes [9]. Understanding the mechanisms by which insulin resistance develops and interacts with other metabolic tissues is essential for the development of targeted therapeutic strategies aimed at preventing or delaying the onset of T2DM [10].

This study aims to investigate the role of insulin resistance in the pathogenesis of T2DM, with a focus on the metabolic and molecular alterations in key insulin-responsive organs and their contributions to disease progression.

METHODS

Study Design and Animal Model

This experimental study was conducted to investigate the role of insulin resistance in the pathogenesis of type 2 diabetes mellitus (T2DM). Male Wistar rats (n = 30), aged 10–12 weeks and weighing 200–250 g, were used. Animals were housed under controlled environmental conditions (22 ± 2°C, 12-hour light/dark cycle) with free access to water and standard laboratory chow. The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC).

Rats were randomly assigned to three groups. Control group (n = 10) received standard chow diet with no intervention. High-fat diet (HFD) group (n = 10) was fed a high-fat diet for 8 weeks to induce insulin resistance. T2DM experimental group (n = 10) was fed a high-fat diet for 8 weeks followed by a low-dose streptozotocin injection (35 mg/kg, intraperitoneally) to induce partial pancreatic beta-cell dysfunction, simulating T2DM.

Biochemical Analysis

Fasting blood glucose (FBG) and fasting insulin levels were measured at baseline and at the end of the experiment using a glucometer and ELISA kits, respectively. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula: HOMA-IR = FBG (mmol/L) × Fasting insulin (μU/mL) / 22.5. Plasma levels of liver enzymes (ALT, AST), adipokines (leptin, adiponectin), and incretin hormones (GLP-1, GIP) were also determined using commercially available ELISA kits.

Tissue Collection and Histology

At the end of the study, rats were anesthetized, and pancreatic, hepatic, adipose tissue, and skeletal muscle samples were collected. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4–5 μm thickness. Sections were stained with hematoxylin-eosin (H&E) for general histology, Masson's trichrome for fibrosis, and immunohistochemical staining for insulin, GLP-1 receptor, and GLUT4 expression.

Assessment of Insulin Resistance

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Pancreatic beta-cell function was evaluated via histological examination of islet morphology and immunohistochemical insulin staining. Hepatic glucose regulation was assessed through glycogen content (PAS staining), hepatocyte morphology, and lipid accumulation. Adipose tissue signaling was analyzed by assessing adipocyte size, morphology, and adipokine expression. Skeletal muscle glucose uptake was evaluated through GLUT4 immunoreactivity and fiber morphology.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using one-way ANOVA followed by Tukey's post hoc test. Pearson correlation analysis was used to evaluate relationships between biochemical parameters and histological findings. A p-value < 0.05 was considered statistically significant.

RESULTS

The experimental results demonstrated significant alterations in biochemical and histological parameters in the T2DM experimental group compared to the control and HFD groups. Fasting blood glucose and fasting insulin levels were markedly elevated in the T2DM group, indicating successful induction of insulin resistance. HOMA-IR values confirmed a significant increase in insulin resistance in T2DM rats (Table 1).

Histological examination revealed notable morphological changes in pancreatic islets, hepatic tissue, adipose tissue, and skeletal muscle in the T2DM group. Pancreatic beta-cells exhibited reduced size, irregular architecture, and decreased insulin immunoreactivity. Liver sections showed hepatocyte ballooning, increased lipid accumulation, and glycogen depletion. Adipocytes displayed hypertrophy and altered adipokine expression, while skeletal muscle fibers exhibited reduced GLUT4 expression and disrupted fiber morphology. Minimal changes were observed in the HFD group, while the control group maintained normal tissue morphology.

Table 1. Biochemical parameters and HOMA-IR values in experimental groups

Parameter	Control (n=10)	HFD (n=10)	T2DM (n=10)	P-value
Fasting Blood Glucose (mmol/L)	5.1 ± 0.3	6.3 ± 0.4	10.8 ± 0.6	<0.001
Fasting Insulin (μU/mL)	12.4 ± 1.2	18.6 ± 1.5	28.7 ± 2.1	<0.001
HOMA-IR	2.8 ± 0.4	5.2 ± 0.6	13.8 ± 1.1	<0.001
ALT (U/L)	32.5 ± 3.1	40.7 ± 3.8	68.4 ± 5.2	<0.001
AST (U/L)	28.6 ± 2.9	35.8 ± 3.4	62.1 ± 4.7	<0.001
Leptin (ng/mL)	4.2 ± 0.5	6.8 ± 0.7	12.5 ± 1.0	<0.001

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Parameter	Control (n=10)	HFD (n=10)	T2DM (n=10)	P-value
Adiponectin (µg/mL)	8.5 ± 0.7	6.2 ± 0.6	3.4 ± 0.4	<0.001
GLP-1 (pmol/L)	15.8 ± 1.2	12.6 ± 1.0	7.4 ± 0.8	<0.001
GIP (pmol/L)	18.3 ± 1.4	14.7 ± 1.1	9.1 ± 0.9	<0.001

The statistical analysis confirmed significant differences between T2DM and control groups ($P < 0.001$) for all measured parameters. Correlation analysis indicated strong associations between HOMA-IR and tissue morphological alterations, highlighting the link between biochemical insulin resistance and organ-specific histopathological changes.

DISCUSSION

The present study demonstrates that insulin resistance plays a central role in the pathogenesis of type 2 diabetes mellitus (T2DM) by inducing both biochemical and morphological alterations in key insulin-responsive tissues. The T2DM experimental group exhibited significantly elevated fasting blood glucose and insulin levels, with markedly increased HOMA-IR values, confirming the successful induction of insulin resistance. These findings are consistent with previous reports indicating that high-fat diet combined with low-dose streptozotocin treatment effectively models the metabolic disturbances observed in human T2DM.

Histological analyses revealed pronounced structural changes in the pancreas, liver, adipose tissue, and skeletal muscle of T2DM rats. Pancreatic islets showed reduced beta-cell mass, irregular architecture, and diminished insulin immunoreactivity, suggesting that insulin resistance contributes to beta-cell dysfunction and impaired insulin secretion. This aligns with existing literature describing the progressive failure of beta-cells in response to chronic insulin resistance, ultimately leading to hyperglycemia.

Hepatic tissue exhibited hepatocyte ballooning, lipid accumulation, and glycogen depletion, reflecting impaired glucose metabolism and increased gluconeogenesis. These alterations indicate that insulin resistance in the liver disrupts normal glucose homeostasis, thereby contributing to fasting hyperglycemia. Similarly, adipose tissue hypertrophy and altered adipokine secretion, including increased leptin and decreased adiponectin, highlight the role of adipose tissue dysfunction in exacerbating systemic insulin resistance through pro-inflammatory signaling pathways.

Skeletal muscle fibers demonstrated reduced GLUT4 expression and disrupted morphology, which likely impairs glucose uptake and glycogen storage, further contributing to hyperglycemia. The observed correlations between HOMA-IR and histopathological changes in all examined tissues underscore the tight link between systemic insulin resistance and organ-specific dysfunction.

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Overall, these results support the concept that insulin resistance is not limited to a single organ but rather affects multiple tissues in an integrated manner. The interplay among pancreatic, hepatic, adipose, and skeletal muscle dysfunctions amplifies metabolic derangements, accelerating T2DM progression. This emphasizes the need for therapeutic strategies targeting insulin sensitivity across multiple organ systems rather than focusing solely on pancreatic beta-cell preservation.

These findings are consistent with previous experimental and clinical studies demonstrating that multi-organ insulin resistance is a critical driver of T2DM pathophysiology and highlight the importance of early interventions aimed at improving peripheral insulin sensitivity to delay disease onset and progression.

CONCLUSION

This study highlights the pivotal role of insulin resistance in the pathogenesis of type 2 diabetes mellitus. Experimental induction of T2DM in rats led to significant biochemical alterations, including elevated fasting blood glucose, hyperinsulinemia, and increased HOMA-IR, accompanied by pronounced histopathological changes in the pancreas, liver, adipose tissue, and skeletal muscle. Pancreatic beta-cell dysfunction, hepatic lipid accumulation and glycogen depletion, adipose tissue hypertrophy with altered adipokine secretion, and reduced skeletal muscle GLUT4 expression collectively demonstrate the multi-organ impact of insulin resistance.

These findings underscore that insulin resistance is a systemic disorder affecting multiple insulin-responsive tissues, contributing to the progressive deterioration of glucose homeostasis in T2DM. Early detection and interventions aimed at improving insulin sensitivity across these key organs may be essential for preventing or delaying the onset and progression of type 2 diabetes.

REFERENCES:

1. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787–835.
2. Petersen KF, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98(4):2133–2223.
3. Samuel VT, Shulman GI. Mechanisms for insulin resistance: Common threads and missing links. Cell. 2012;148(5):852–871.
4. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. Lancet. 2014;383(9922):1068–1083.
5. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature. 2001;414(6865):799–806.
6. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med. 2014;371:1131–1141.
7. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med. 2004;350:664–671.
8. Arner P, Kulyté A. MicroRNA regulatory networks in human adipose tissue and obesity. Nat Rev Endocrinol. 2015;11(5):276–288.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

9. Defronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14(3):173–194.
10. Czech MP. Mechanisms of insulin resistance related to white, beige, and brown adipocytes. Mol Metab. 2020;34:27–42.