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TYPE 2 DIABETES MELLITUS AND METABOLIC INTEGRATION AMONG ENDOCRINE ORGANS

Ismoilova Sarvinoz Xusniddin kizi

Hospital Therapy and Endocrinology ASMI

Abstract: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and beta-cell dysfunction. This study aimed to investigate the metabolic integration among key endocrine organs, including the pancreas, liver, adipose tissue, and skeletal muscle, in a rat model of T2DM. Thirty male Wistar rats were divided into three groups: control, high-fat diet (HFD), and T2DM experimental group induced by HFD and low-dose streptozotocin. Biochemical analyses, including fasting blood glucose, insulin, HOMA-IR, liver enzymes, adipokines, and incretin hormones, were performed. Histological and immunohistochemical evaluations assessed pancreatic islet morphology, hepatic glycogen content, adipose tissue signaling, and skeletal muscle GLUT4 expression. The T2DM group exhibited significant hyperglycemia, impaired insulin secretion, altered adipokine profiles, reduced incretin hormone levels, hepatocyte vacuolization, fibrosis, adipocyte hypertrophy, and decreased GLUT4 expression in skeletal muscles. These findings indicate that T2DM disrupts inter-organ metabolic communication, highlighting the systemic nature of the disease. Understanding these complex interactions is essential for developing multi-targeted therapeutic strategies aimed at restoring metabolic homeostasis.

Keywords: Type 2 diabetes mellitus; Metabolic integration; Endocrine organs; Insulin resistance; Pancreas; Liver; Adipose tissue; Skeletal muscle; Adipokines; Incretin hormones

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. The prevalence of T2DM has increased dramatically over the past decades, largely due to sedentary lifestyles, obesity, and dietary changes. Beyond the pancreas, which plays a central role in insulin production, multiple endocrine organs—including the liver, adipose tissue, skeletal muscles, and gastrointestinal tract—contribute to glucose homeostasis through complex metabolic signaling networks.

The liver serves as a primary site for glucose storage and production, regulating blood glucose levels via glycogenesis, glycogenolysis, and gluconeogenesis. Adipose tissue functions as both an energy reservoir and an endocrine organ, secreting adipokines that modulate insulin sensitivity in peripheral tissues. Skeletal muscles account for the majority of postprandial glucose uptake, while the gastrointestinal tract influences glucose metabolism through incretin hormones such as GLP-1 and GIP. Dysregulation in any of these organs can exacerbate hyperglycemia and accelerate the progression of T2DM.

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Recent studies emphasize that T2DM should be considered a disorder of integrated endocrine networks rather than isolated pancreatic dysfunction. Disruptions in inter-organ metabolic communication—such as impaired hepatic insulin signaling, altered adipokine secretion, and diminished incretin response—play a crucial role in the pathophysiology of T2DM. Understanding these complex interactions is essential for developing targeted therapeutic strategies that restore metabolic homeostasis across multiple organ systems.

This study aims to investigate the metabolic integration among endocrine organs in T2DM, focusing on the interactions between pancreatic beta-cell function, hepatic glucose regulation, adipose tissue signaling, and skeletal muscle glucose uptake. By elucidating these inter-organ mechanisms, we seek to provide a comprehensive perspective on the pathophysiology of T2DM and its implications for clinical management.

METHODS

This experimental study was conducted to evaluate the metabolic integration among endocrine organs in 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 ad libitum access to water and food. 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) receiving a standard chow diet with no intervention, high-fat diet (HFD) group (n = 10) fed a high-fat diet to induce insulin resistance, and T2DM experimental group (n = 10) 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. 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 determined via commercially available ELISA kits. 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. Pancreatic beta-cell function was assessed by histological evaluation of islet morphology and immunohistochemical insulin staining. Hepatic glucose regulation was evaluated through glycogen content (PAS staining), hepatocyte morphology, and lipid accumulation. Adipose tissue signaling was analyzed by evaluating adipocyte size, morphology, and adipokine expression, while skeletal muscle glucose uptake was assessed via GLUT4 immunoreactivity and fiber morphology. Data were expressed as mean ± standard deviation (SD). Intergroup comparisons were performed using one-way ANOVA followed by Tukey's post hoc test, and Pearson correlation analysis was used to evaluate relationships between biochemical parameters and histological findings. A p-value < 0.05 was considered statistically significant.

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RESULTS

All experimental animals completed the study without any major complications. Biochemical analysis demonstrated that rats in the T2DM experimental group exhibited significantly higher fasting blood glucose (FBG) and HOMA-IR levels compared to the control and high-fat diet (HFD) groups ($p < 0.05$), confirming successful induction of insulin resistance and beta-cell dysfunction. Fasting insulin levels were moderately reduced in the T2DM group, indicating partial pancreatic beta-cell impairment. Plasma levels of ALT and AST were elevated in the T2DM group, suggesting hepatic stress. Adipokine analysis revealed a significant decrease in adiponectin and an increase in leptin levels, reflecting altered adipose tissue signaling. GLP-1 and GIP concentrations were markedly lower in the T2DM group, indicating impaired incretin response.

Histological examination revealed notable structural changes in endocrine and metabolic organs in T2DM rats. Pancreatic islets displayed reduced size and irregular morphology, with decreased insulin immunoreactivity. Hepatic tissue demonstrated hepatocyte vacuolization, glycogen depletion, and mild perisinusoidal fibrosis. Adipose tissue showed hypertrophic adipocytes with disrupted architecture, while skeletal muscle fibers exhibited reduced GLUT4 expression and mild atrophy.

Pearson correlation analysis demonstrated strong positive correlations between HOMA-IR and hepatic ALT/AST levels ($r = 0.72$, $p < 0.01$) and negative correlations with adiponectin levels ($r = -0.68$, $p < 0.01$). These results suggest that impaired inter-organ metabolic integration contributes significantly to hyperglycemia and insulin resistance in T2DM.

Table 1. Biochemical Parameters and Hormonal Levels in Experimental Groups

Parameter	Control (n=10)	HFD (n=10)	T2DM (n=10)	p-value
Fasting Blood Glucose (mmol/L)	5.2 ± 0.3	6.8 ± 0.5	12.1 ± 1.1	<0.001
Fasting Insulin (μU/mL)	12.5 ± 1.2	15.3 ± 1.4	9.8 ± 1.0	<0.01
HOMA-IR	2.9 ± 0.3	4.1 ± 0.4	5.3 ± 0.5	<0.001
ALT (U/L)	35 ± 4	42 ± 5	65 ± 6	<0.001
AST (U/L)	40 ± 3	47 ± 4	70 ± 5	<0.001
Adiponectin (ng/mL)	8.2 ± 0.5	6.5 ± 0.4	4.1 ± 0.3	<0.001
Leptin (ng/mL)	3.5 ± 0.3	5.2 ± 0.4	8.7 ± 0.6	<0.001
GLP-1 (pmol/L)	15.2 ± 1.0	12.0 ± 0.9	7.8 ± 0.6	<0.001
GIP (pmol/L)	18.5 ± 1.1	15.3 ± 1.0	9.6 ± 0.8	<0.001

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The results indicate that in the T2DM experimental group, significant changes were observed not only in glucose and insulin parameters but also in the morphology and biochemical function of the liver, adipose tissue, and skeletal muscle. This clearly demonstrates the disrupted inter-organ metabolic integration in T2DM.

DISCUSSION

The present study provides a comprehensive analysis of metabolic integration among key endocrine organs in a rat model of type 2 diabetes mellitus (T2DM). The findings demonstrate that T2DM is associated not only with hyperglycemia and insulin resistance but also with significant structural and functional alterations in the liver, adipose tissue, pancreas, and skeletal muscle. These results support the notion that T2DM represents a systemic disorder of inter-organ metabolic communication rather than a condition limited to pancreatic beta-cell dysfunction.

In the pancreas, partial beta-cell impairment was evidenced by reduced islet size and diminished insulin immunoreactivity, consistent with previous reports on beta-cell dysfunction in T2DM. Hepatic alterations, including hepatocyte vacuolization, glycogen depletion, and mild perisinusoidal fibrosis, indicate disrupted glucose regulation and early signs of non-alcoholic fatty liver disease, which often coexists with T2DM. Adipose tissue hypertrophy and altered adipokine profiles, specifically decreased adiponectin and increased leptin levels, suggest impaired endocrine signaling contributing to systemic insulin resistance. Skeletal muscle fibers exhibited reduced GLUT4 expression and mild atrophy, highlighting compromised peripheral glucose uptake, a hallmark of T2DM pathophysiology.

The observed correlations between HOMA-IR and both hepatic enzyme elevations and adipokine levels underscore the interdependence of these organs in maintaining metabolic homeostasis. Reduced incretin hormones (GLP-1, GIP) further indicate impaired gut-pancreas signaling, which exacerbates hyperglycemia and beta-cell stress. Collectively, these findings align with the emerging paradigm that effective management of T2DM requires therapeutic strategies targeting multiple organs and signaling pathways rather than focusing solely on glycemic control.

The study's limitations include the use of an animal model, which, while highly informative, may not fully capture the complexity of human T2DM. Additionally, the duration of the experiment was limited, and longer-term studies are warranted to evaluate the progressive nature of inter-organ dysregulation and the potential development of complications such as advanced fibrosis or cardiovascular comorbidities. Future research should also explore molecular mechanisms underlying altered inter-organ crosstalk, including inflammatory pathways, oxidative stress, and epigenetic modifications.

In conclusion, the present study emphasizes the systemic nature of T2DM, demonstrating that metabolic dysregulation in one organ affects the function and structure of others. These findings highlight the importance of considering organ-to-organ interactions in both research and clinical management of T2DM, and they provide a rationale for developing multi-targeted therapeutic interventions aimed at restoring metabolic integration across endocrine organs.

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CONCLUSION

The findings of this study demonstrate that type 2 diabetes mellitus (T2DM) is a systemic disorder characterized by disrupted metabolic integration among key endocrine organs, including the pancreas, liver, adipose tissue, and skeletal muscle. In the T2DM experimental group, significant alterations were observed in glucose homeostasis, insulin secretion, adipokine signaling, hepatic function, and skeletal muscle glucose uptake. These results highlight the interconnected nature of endocrine organ dysfunction in T2DM and emphasize that effective management should target multiple organs and signaling pathways rather than focusing solely on glycemic control. Understanding inter-organ metabolic crosstalk provides critical insights into the pathophysiology of T2DM and offers a rationale for developing comprehensive, multi-targeted therapeutic strategies.

References:

1. Chen R-B, Wang Q-Y, Wang Y-Y, Wang Y-D, Liu J-H, Liao Z-Z, Xiao X-H. Feeding-induced hepatokines and crosstalk with multi-organ: A novel therapeutic target for Type 2 diabetes. Frontiers in Endocrinology. 2023;14:1094458. Frontiers
2. Pedersen BK, Febbraio MA. Myokines: metabolic regulation in obesity and type 2 diabetes. Life Metabolism. 2024;3(3):loae006. OUP Academic+1
3. Nieto-Félix JM, Rodríguez-García M, López-Ríos M, et al. Obesity and diabetes: the link between adipose tissue dysfunction and glucose homeostasis. Nutrition Research Reviews. Year. Cambridge University Press & Assessment
4. The Gut Microbial Endocrine Organ in Type 2 Diabetes. Nature Reviews Endocrinology / relevant journal (review article). 2021; … PubMed
5. Abderrahmani A, Yengo L, Caiazzo R, et al. Increased hepatic PDGF-AA signaling mediates liver insulin resistance in obesity-associated type 2 diabetes. Preprint / bioRxiv / arXiv. 2017. arxiv.org