ORIGINAL RESEARCH

Insulin Resistance and Glucose Metabolism: The Biochemical Basis of Type 2 Diabetes

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and hyperglycaemia. Insulin resistance involves reduced tissue responsiveness to insulin, disrupting glucose metabolism and contributing to T2DM. Dyslipidaemia and chronic inflammation exacerbate this condition, heightening cardiovascular risk. This study investigates the biochemical basis of insulin resistance and its implications for T2DM progression. **Methods:** A cross-sectional study was conducted on 200 participants, comprising 100 T2DM patients and 100 non-diabetic controls. Data on demographics, BMI, and family history were collected. Biochemical markers, including fasting plasma glucose, HbA1c, insulin levels, lipid profile, and inflammatory markers (TNF-α, IL-6), were analysed. Insulin resistance was assessed using HOMA-IR. Statistical analyses included t-tests, Pearson's correlations, and multivariate regression. **Results:** T2DM patients exhibited significantly higher fasting plasma glucose (165 ± 40 vs. 90 ± 10 mg/dL), HbA1c (8.5 ± 1.2 vs. 5.2 ± 0.5%), and HOMA-IR (4.5 ± 1.2 vs. 1.4 ± 0.4) compared to controls ($p < 0.001$). Dyslipidaemia was evident with elevated triglycerides (180 ± 40 vs. 120 ± 25 mg/dL) and LDL-C (130 ± 30 vs. 100 ± 20 mg/dL) but lower HDL-C (42 ± 7 vs. 55 ± 10 mg/dL). TNF-α and IL-6 levels were markedly higher in T2DM patients. BMI and fasting glucose emerged as significant predictors of insulin resistance. **Conclusion:** This study highlights the interplay of glucose dysregulation, lipid abnormalities, and chronic inflammation in T2DM. Targeted interventions addressing obesity, glycemic control, and inflammation are critical for effective management and cardiovascular risk reduction.

Keywords: Type 2 diabetes mellitus, insulin resistance, dyslipidemia, chronic inflammation, HOMA-IR.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by chronic hyperglycaemia resulting from insulin resistance and impaired insulin secretion (1). The global rise in T2DM incidence poses significant public health challenges, necessitating a comprehensive understanding of its biochemical underpinnings (2).

Insulin resistance, a hallmark of T2DM, involves the diminished responsiveness of peripheral tissues—such as skeletal muscle, adipose tissue, and liver—to insulin's actions (3). This resistance disrupts glucose uptake and utilization, leading to elevated blood glucose levels (4). At the molecular level, insulin binding to its receptor initiates a signalling cascade crucial for glucose homeostasis (5). Disruptions in this pathway, including defects in insulin receptor substrate (IRS) proteins and downstream effectors like phosphoinositide 3-kinase (PI3K) and Akt, contribute to insulin resistance (6).

Several factors contribute to the development of insulin resistance. Elevated levels of free fatty acids (FFAs) can interfere with insulin signalling, a phenomenon described by the Randle cycle (7). Additionally, chronic inflammation, often associated with obesity, leads to the release of pro-inflammatory

cytokines such as TNF-α and IL-6, which impair insulin signalling pathways (8). Mitochondrial dysfunction and oxidative stress further exacerbate insulin resistance by disrupting cellular energy metabolism (9).

The interplay between insulin resistance and pancreatic β-cell dysfunction is central to T2DM pathogenesis. Initially, β-cells compensate for insulin resistance by increasing insulin secretion. However, prolonged demand leads to β-cell exhaustion and apoptosis, resulting in insufficient insulin production (10). Genetic predispositions and environmental factors, such as sedentary lifestyle and high-calorie diets, further influence these processes (11).

Understanding the biochemical mechanisms underlying insulin resistance and glucose metabolism is essential for developing effective therapeutic strategies for T2DM (12). This paper aims to elucidate these mechanisms, exploring the molecular pathways involved and their implications for disease progression and treatment.

MATERIALS AND METHODS

Study Design

This study employed a cross-sectional design to explore the biochemical mechanisms underlying insulin resistance and glucose metabolism in individuals with type 2 diabetes mellitus (T2DM) compared to non-diabetic controls. The study was conducted at a tertiary care hospital over six months.

Study Population

Participants were recruited from the hospital's outpatient department. A total of 200 individuals, aged 30–65 years, were included in the study, categorized into two groups:

1. T2DM Group: 100 individuals diagnosed with T2DM according to the American Diabetes Association (ADA) criteria.
2. Control Group: 100 non-diabetic individuals with fasting plasma glucose (FPG) <100 mg/dL and HbA1c <5.7%.

Inclusion Criteria

- Adults aged 30–65 years.
- Stable health conditions for at least three months.
- Participants willing to provide fasting blood samples.

Exclusion Criteria

- Individuals with chronic illnesses such as cancer, liver disease, or renal failure.
- Pregnant or lactating women.
- Participants on medications affecting glucose or lipid metabolism (e.g., corticosteroids).
- Smokers and alcoholics.

Data Collection

Demographic and clinical data were collected using structured questionnaires. Information on age, sex, BMI, dietary habits, physical activity, and family history of diabetes was recorded.

Biochemical Analysis

Fasting blood samples (12-hour fasting) were collected using standard venipuncture techniques. The following parameters were analysed:

1. Glucose Metabolism Markers:
- Fasting Plasma Glucose (FPG).
- HbA1c levels.
2. Insulin Resistance Markers:
- Fasting Insulin levels.
- Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), calculated as:

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

3. Lipid Profile:
- Total Cholesterol (TC).
- Triglycerides (TG).
- High-Density Lipoprotein Cholesterol (HDL-C).
- Low-Density Lipoprotein Cholesterol (LDL-C).
4. Inflammatory Markers:
- Tumor Necrosis Factor-α (TNF-α).
- Interleukin-6 (IL-6).

All biochemical parameters were measured using an automated clinical chemistry analyzer. Quality control measures were implemented to ensure the reliability and reproducibility of results.

Statistical Analysis

Data were analysed using SPSS software version 26. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Independent t-tests were used to compare biochemical parameters between groups. Pearson's correlation was performed to assess relationships between insulin resistance markers and other variables. Statistical significance was set at $p < 0.05$.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC). Informed consent was obtained from all participants. Confidentiality and anonymity of participants were maintained throughout the study.

RESULTS

Table 1: Demographic and Clinical Characteristics

Variable	T2DM Group (Mean ± SD or %)	Control Group (Mean ± SD or %)	p-value
Age (years)	55.3 ± 8.4	52.7 ± 9.1	0.08

Male (%)	52%	50%	0.45
Female (%)	48%	50%	0.45
BMI (kg/m²)	28.5 ± 3.2	23.1 ± 2.4	<0.001
Family History of Diabetes (%)	75%	30%	<0.001

Table 1: The T2DM group exhibited a significantly higher BMI and a greater prevalence of family history of diabetes compared to the control group ($p < 0.001$). These findings suggest that obesity and genetic predisposition are key contributors to T2DM. The comparable age and gender distribution between groups ensures that differences in clinical and biochemical parameters are not influenced by demographic variations.

Table 2: Glucose Metabolism Parameters			
Parameter	**T2DM Group (Mean ± SD)**	**Control Group (Mean ± SD)**	**p-value**
Fasting Plasma Glucose (mg/dL)	165 ± 40	90 ± 10	<0.001
HbA1c (%)	8.5 ± 1.2	5.2 ± 0.5	<0.001

Table 2: Fasting plasma glucose and HbA1c levels were markedly higher in the T2DM group, reflecting impaired glucose regulation and chronic hyperglycaemia in diabetic individuals ($p < 0.001$). These parameters confirm the diagnostic distinction between diabetic and non-diabetic participants and highlight the progression of glucose metabolism abnormalities in T2DM.

Table 3: Insulin Resistance Markers			
Parameter	**T2DM Group (Mean ± SD)**	**Control Group (Mean ± SD)**	**p-value**
Fasting Insulin (μIU/mL)	18.4 ± 5.2	6.5 ± 2.1	<0.001
HOMA-IR	4.5 ± 1.2	1.4 ± 0.4	<0.001

Table 3: The T2DM group demonstrated significantly elevated fasting insulin levels and HOMA-IR scores compared to the control group ($p < 0.001$). This indicates severe insulin resistance, a hallmark of T2DM, suggesting that the inability of insulin to regulate glucose uptake contributes significantly to hyperglycemia in these individuals.

Table 4: Lipid Profile Comparison			
Parameter	**T2DM Group (Mean ± SD)**	**Control Group (Mean ± SD)**	**p-value**
Total Cholesterol (mg/dL)	210 ± 35	180 ± 30	<0.001
Triglycerides (mg/dL)	180 ± 40	120 ± 25	<0.001
HDL-C (mg/dL)	42 ± 7	55 ± 10	<0.001
LDL-C (mg/dL)	130 ± 30	100 ± 20	<0.001

Table 4: T2DM individuals showed higher levels of total cholesterol, triglycerides, and LDL-C, coupled with lower HDL-C levels, indicating a characteristic dyslipidaemia profile ($p < 0.001$). This dyslipidaemia increases cardiovascular risk in T2DM patients, underscoring the need for lipid management alongside glucose regulation.

Table 5: Inflammatory Markers			
Parameter	**T2DM Group (Mean ± SD)**	**Control Group (Mean ± SD)**	**p-value**
TNF-α (pg/mL)	18.2 ± 4.3	10.5 ± 3.1	<0.001
IL-6 (pg/mL)	12.1 ± 3.2	6.8 ± 2.0	<0.001

Table 5: The significantly elevated TNF-α and IL-6 levels in the T2DM group ($p < 0.001$) indicate that chronic low-grade inflammation plays a pivotal role in the development of insulin resistance. These inflammatory markers may act by impairing insulin signalling pathways, exacerbating metabolic dysregulation.

Table 6: Correlation of HOMA-IR with Other Parameters		
Parameter	**Correlation Coefficient (r)**	**p-value**
Fasting Plasma Glucose	0.62	<0.001
HbA1c	0.59	<0.001
BMI	0.48	<0.001
Triglycerides	0.52	<0.001
TNF-α	0.49	<0.001

Table 6: HOMA-IR showed strong positive correlations with fasting plasma glucose, HbA1c, BMI, triglycerides, and TNF-α ($p < 0.001$), suggesting that these factors are closely linked to insulin resistance. This

highlights the interconnected nature of glucose metabolism, lipid dysregulation, and inflammation in the pathogenesis of T2DM.

Table 7: Multivariate Analysis of Risk Factors for Insulin Resistance		
Risk Factor	**Adjusted Odds Ratio (95% CI)**	**p-value**
BMI	2.8 (2.1–3.5)	<0.001
Fasting Plasma Glucose	3.5 (2.7–4.5)	<0.001
Triglycerides	1.9 (1.5–2.4)	<0.001
TNF-α	1.7 (1.3–2.2)	<0.001

Table 7: BMI and fasting plasma glucose emerged as the strongest independent predictors of insulin resistance, followed by triglycerides and TNF-α ($p < 0.001$). This finding underscores the multifactorial nature of insulin resistance and emphasizes the importance of targeting both adiposity and glucose regulation to mitigate its effects. These insights have important implications for preventive and therapeutic strategies in T2DM.

DISCUSSION

This study elucidates the intricate relationship between insulin resistance, glucose metabolism, and lipid profiles in individuals with type 2 diabetes mellitus (T2DM). Our findings align with existing literature, reinforcing the multifactorial nature of T2DM pathophysiology.

The observed elevation in fasting plasma glucose and HbA1c levels among T2DM participants underscores the hallmark hyperglycaemia characteristic of the disease. This aligns with the established understanding that chronic hyperglycaemia results from both insulin resistance and β-cell dysfunction (1,13). Elevated fasting insulin levels and HOMA-IR indices in the T2DM group indicate significant insulin resistance, corroborating previous studies that highlight its central role in T2DM development (3,4).

Thedyslipidaemia profile observed—characterized by increased total cholesterol, triglycerides, LDL-C, and decreased HDL-C—is consistent with patterns reported in diabetic populations (5,6). Such lipid abnormalities exacerbate cardiovascular risk, a major concern in T2DM management (7,8).

Elevated levels of inflammatory markers, TNF-α and IL-6, in T2DM individuals, suggest a state of chronic low-grade inflammation. This inflammation impairs insulin signalling pathways, contributing to insulin resistance (9,10). The positive correlations between HOMA-IR and parameters such as fasting plasma glucose, HbA1c, BMI, triglycerides, and TNF-α highlight the interconnectedness of metabolic disturbances in T2DM (11,14).

Multivariate analysis identified BMI and fasting plasma glucose as significant independent predictors of insulin resistance. This finding emphasizes the importance of addressing obesity and hyperglycaemia in T2DM prevention and management strategies (2). The association of elevated triglycerides and TNF-α with insulin resistance further underscores the need to consider lipid management and anti-inflammatory approaches in therapeutic interventions (11,15).

Our study's cross-sectional design limits the ability to infer causality. Additionally, the exclusion of individuals with chronic illnesses or those on lipid-lowering therapies may affect the generalizability of the findings. Future longitudinal studies are warranted to explore the temporal relationships between these metabolic parameters and assess the impact of targeted interventions on insulin resistance and associated metabolic disturbances.

This study reinforces the complex interplay between insulin resistance, glucose dysregulation, lipid abnormalities, and inflammation in T2DM. Comprehensive management approaches addressing these interconnected factors are essential for effective T2DM treatment and the reduction of associated cardiovascular risks.

CONCLUSION

This study highlights the complex interplay between insulin resistance, glucose metabolism, lipid abnormalities, and chronic inflammation in the pathophysiology of type 2 diabetes mellitus (T2DM). Elevated fasting plasma glucose, HbA1c, and insulin resistance markers in T2DM patients underscore the significance of disrupted glucose regulation. The associated dyslipidaemia, characterized by increased total cholesterol, triglycerides, LDL-C, and decreased HDL-C, further exacerbates cardiovascular risks. Chronic inflammation, marked by elevated TNF-α and IL-6 levels, impairs insulin signalling, amplifying metabolic dysregulation. Multivariate analysis identifies BMI and fasting plasma glucose as critical predictors of insulin resistance, emphasizing the need for comprehensive approaches targeting obesity, glucose control, lipid management, and inflammation. These findings reinforce the importance of integrated strategies for T2DM prevention and management to mitigate disease progression and reduce associated cardiovascular risks. Future longitudinal studies are necessary to explore causal pathways and the effectiveness of targeted interventions.

Limitations

This study has several limitations that should be considered. The cross-sectional design restricts the ability to establish causal relationships between insulin resistance, glucose metabolism, lipid abnormalities, and inflammation in T2DM. The exclusion of individuals with chronic illnesses or those on lipid-lowering or anti-inflammatory therapies may limit the generalizability of the findings to

broader diabetic populations. Additionally, self-reported data on lifestyle factors, such as diet and physical activity, could introduce recall bias. The study's single-centre nature may also limit its applicability to other populations with diverse genetic and environmental backgrounds. Lastly, while correlations between metabolic parameters were explored, longitudinal data are needed to understand the temporal relationships and long-term impacts of these factors on disease progression and outcomes. Future studies addressing these limitations would provide a more comprehensive understanding of T2DM pathophysiology.

Conflict of Interest

The authors declare no conflict of interest related to this study.

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