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Adipose Tissue-derived TNF-alpha as a Mediator of Insulin Resistance in Obese and Non-obese Type 2 Diabetes Mellitus

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ABSTRACT

Background: Tumor Necrosis Factor-alpha (TNF-α), a pro-inflammatory cytokine secreted predominantly by adipose tissue, has been implicated in the pathogenesis of insulin resistance, a hallmark of Type 2 Diabetes Mellitus (T2DM). This study examines the relationship between TNF-α levels, obesity status, and insulin resistance in individuals with type 2 diabetes mellitus (T2DM).

Methods: A case-control study was conducted involving 108 participants: 54 obese T2DM patients (BMI≥25 kg/m²) and 54 non-obese T2DM patients (BMI<25 kg/m²). Anthropometric data, fasting blood sugar (FBS), HbA1c, lipid profile, fasting insulin, and serum TNF-α levels were measured. Insulin resistance was evaluated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Statistical comparisons and correlation analysis were performed.

Results: Obese T2DM patients had significantly higher TNF-α levels, HOMA-IR, fasting insulin, and triglycerides compared to non-obese patients ($p<0.001$). A positive correlation was observed between TNF-α and HOMA-IR in obese T2DM individuals, indicating a link between inflammation and insulin resistance.

Conclusion: Elevated TNF-α in obese T2DM patients suggests that adipose tissue–driven inflammation contributes to insulin resistance. These findings highlight the importance of addressing inflammatory pathways in managing metabolic complications. TNF-α may serve as a useful biomarker and potential therapeutic target in obese individuals with type 2 diabetes mellitus.

Key-words: TNF-α, Insulin Resistance, Obesity, Type 2 Diabetes, HOMA-IR

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by insulin resistance and impaired glucose metabolism. Obesity, particularly visceral adiposity, is a well-recognised contributor to insulin resistance, which is largely mediated by pro-inflammatory adipokines secreted from adipose tissue [1]. TNF-α has emerged as a key link between inflammation and metabolic dysfunction.

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TNF-α, produced by macrophages and adipocytes in adipose tissue, interferes with insulin signalling by downregulating insulin receptor substrates and impairing glucose transporter-4 (GLUT-4) activity [2]. This results in decreased peripheral glucose uptake and enhanced hepatic gluconeogenesis. The chronic low-grade inflammation observed in obese individuals thus contributes to the development of insulin resistance and subsequent T2DM [2].

Recent studies indicate that individuals with both type 1 and type 2 diabetes have elevated TNF-α levels, which are linked to insulin resistance [3-5]. Specifically, a cross-sectional study revealed significantly higher TNF-α in type 2 diabetic patients, especially those who are also obese. This suggests TNF-α could be a useful marker for managing T2DM and obesity, given its correlation with glycated haemoglobin (HbA1c) and insulin resistance [3-5].

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However, the exact role of TNF-α in obesity and diabetes is still being investigated due to conflicting findings and a lack of studies focusing strictly on obese individuals. While TNF-α's connection to obesity and metabolic syndrome is recognized, there's limited data directly comparing its levels in obese versus non-obese T2DM patients. This research aims to explore the relationship between TNF-α and insulin resistance in these subgroups, potentially clarifying the role of adipose tissue inflammation in the development of T2DM.

MATERIALS AND METHODS

Research Design- This case-control study was conducted at S.C.B. Medical College and Hospital, Cuttack. A total of 108 participants were enrolled and categorized into two groups based on body mass index (BMI): obese (BMI≥25 kg/m²) and non-obese (BMI <25 kg/m²), according to WHO guidelines. The study aimed to investigate the association between serum TNF-α levels and insulin resistance in patients with type 2 diabetes mellitus (T2DM). Participants were recruited over a defined period following predefined inclusion and exclusion criteria.

Methodology- A total of 108 patients aged between 35 and 55 years were recruited, including 54 obese and 54 non-obese patients diagnosed with T2DM attending the General Medicine Outpatient Department (OPD). The sample size was calculated based on an expected moderate effect size in TNF-α levels between obese and non-obese T2DM patients, with 80% power and a 5% significance level [6].

Inclusion criteria- Diagnosis was based on patient history, clinical examination, and biochemical investigations, by the WHO diagnostic criteria (fasting plasma glucose ≥126 mg/dL or 2-hour postprandial plasma glucose ≥200 mg/dL) [7].

Exclusion criteria- Individuals with any history of chronic inflammatory disorders, thyroid or endocrine diseases, or diabetes-related complications were excluded from the study. Written informed consent was obtained from all participants, and data were collected using a standardized proforma.

Clinical and Biochemical Assessment- The study recorded demographic characteristics, including name, age, sex, and risk factors such as smoking, family history, medications, and alcohol intake. Anthropometric measurements, including height, weight, and Body Mass Index (BMI), were recorded, with participants classified into two groups: normal/underweight (BMI <25) and overweight/obese (BMI≥25), based on WHO guidelines. Blood pressure was measured manually using a sphygmomanometer. Venous blood samples were collected after 8 hours of fasting and 2 hours after a heavy breakfast to measure various biochemical parameters such as plasma glucose, total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL), and very low-density lipoprotein (VLDL), triglycerides, urea, creatinine, and insulin. Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) method, and serum TNF-α levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit according to the manufacturer's protocol, with the assay demonstrating an inter-assay coefficient of variation of <10% and an intra-assay coefficient of variation of <12%. All biochemical analyses were conducted using automated clinical analyzers.

Statistical Analysis- Data were analysed using SPSS v25. Results were expressed as mean±SD. Group comparisons used Student's t-test. Pearson correlation was used to assess the relationships between TNF-α and metabolic variables.

Ethical Approval- Institutional Ethics Committee (IEC) approval (Regd No. ECR/84/Inst/OR/2013) was obtained before the commencement of the study. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

RESULTS

This study compared various biochemical parameters between obese and non-obese type 2 diabetic patients. Statistically significant differences were observed in several metabolic markers.

Obese diabetics exhibited significantly higher BMI (30.73±2.58 vs 22.88±2.04; p<0.001), total cholesterol (232.89±31.67 vs 189.33±17.11; p<0.001), triglycerides (297.3±80.51 vs 158±28.52; p<0.001), LDL (131.96±32.45 vs 115.81±17.44; p=0.026), VLDL (59.29±16.03 vs 31.59±5.87; p<0.001), fasting insulin (16.09±3.5 vs

9.55±3.13 µIU/ml; *p*<0.001), and HOMA-IR (8.18±0.18 vs 4.95±0.65; *p*<0.001) compared to non-obese diabetics. TNF-α levels were significantly elevated in the obese group (1181.6±93.71 vs 956.44±75.34 pg/ml; *p*<0.001). However, no significant differences were noted in urea, creatinine, HDL, fasting, and postprandial glucose levels between the two groups (Table 1).

Table 1: Comparison of Biochemical Parameters Between Obese and Non-Obese Diabetic Patients

Parameters	Obese Diabetics (n=54) (Mean±SD)	Non-Obese Diabetics (n=54) (Mean±SD)	p-value
BMI	30.73±2.58	22.88±2.04	<0.001**
Urea (mg/dl)	28.96±7.18	26.14±4.66	0.09
Creatinine (mg/dl)	0.88±0.17	0.85±0.17	0.51
Total Cholesterol (mg/dl)	232.89±31.67	189.33±17.11	<0.001**
Triglycerides (mg/dl)	297.3±80.51	158±28.52	<0.001**
HDL Cholesterol (mg/dl)	37.92±5.43	39.37±4.64	0.29
LDL Cholesterol (mg/dl)	131.96±32.45	115.81±17.44	0.02*
VLDL Cholesterol (mg/dl)	59.29±16.03	31.59±5.87	<0.001**
Fasting Blood Sugar (mg/dl)	217.67±60.3	233.63±83.39	0.42
Postprandial Blood Sugar (mg/dl)	359.07±85.76	347.67±97.93	0.65
Fasting Plasma Insulin (µIU/ml)	16.09±3.5	9.55±3.13	<0.001**
HOMA-IR	8.18±0.18	4.95±0.65	<0.001**
TNF-alpha (pg/ml)	1181.6±93.71	956.44±75.34	<0.001**

Significance: p<0.05; p<0.001***

Correlation analysis revealed that in obese diabetics, TNF-α was positively and significantly correlated with triglycerides (*r*=0.495, *p*<0.001) and VLDL (*r*=0.487, *p*<0.001). No significant correlation was observed between TNF-α and fasting insulin or other lipid parameters in either group (Table 2).

Table 2: Correlation of TNF-α with Lipid Profile and Fasting Insulin in Obese and Non-Obese Diabetic Patients (n=54)

Parameters	Obese Diabetics (n=54)		Non-Obese Diabetics(n=54)	
	r value	p-value	r value	p-value
Total Cholesterol (mg/dl)	0.04	0.74	–0.15	0.27
Triglycerides (mg/dl)	0.49	0.00**	0.00	0.97
HDL (mg/dl)	0.15	0.25	–0.10	0.47
LDL (mg/dl)	–0.00	0.98	–0.08	0.52
VLDL (mg/dl)	0.48	0.00**	–0.01	0.92
Fasting Insulin (µIU/ml)	0.05	0.70	0.09	0.47

The relationship between TNF-α levels and insulin resistance (as measured by HOMA-IR) was analysed using linear regression in both obese and non-obese type 2 diabetic patients. In obese type 2 diabetic patients, there was a positive correlation between TNF-α and HOMA-IR, though the association was weak and statistically non-significant, with an R^2 value of 0.02, indicating that only 2.7% of the variation in HOMA-IR can be explained by TNF-α levels (Fig. 1).

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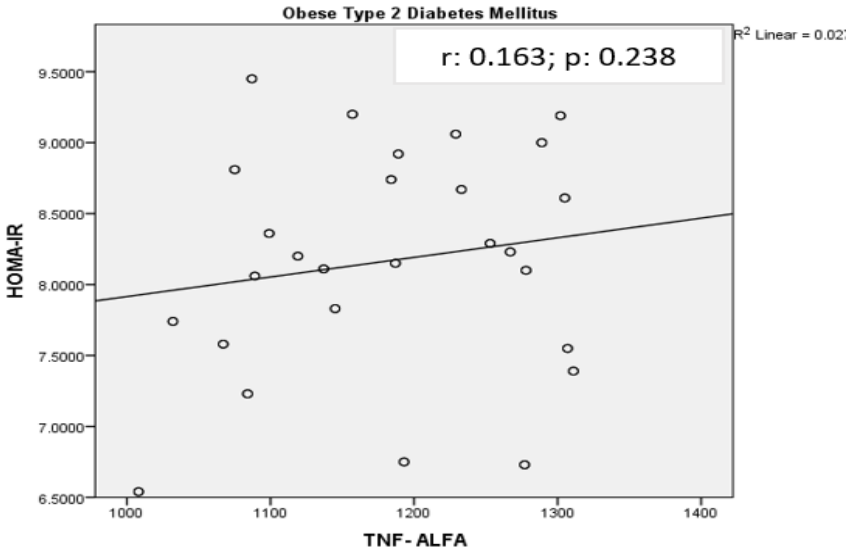

Fig. 1: Scatter plot with line of best fit showing correlation of TNF-α levels and insulin resistance in obese Type 2 Diabetes Mellitus

In contrast, non-obese type 2 diabetic patients showed a weak and non-significant negative correlation between TNF-α and HOMA-IR, with an R^2 value of 0.044, suggesting that 4.4% of the variation in insulin resistance was inversely related to TNF-α levels (Fig. 2).

These findings suggest a marginal trend in opposite directions between the two groups, indicating that TNF-α may have a more pro-inflammatory and insulin-desensitising role in obese individuals with diabetes. At the same time, its association appears less pronounced or even inverse in non-obese individuals with diabetes. However, due to the low R^2 values, the data imply that factors beyond TNF-α are likely contributing significantly to insulin resistance in both groups.

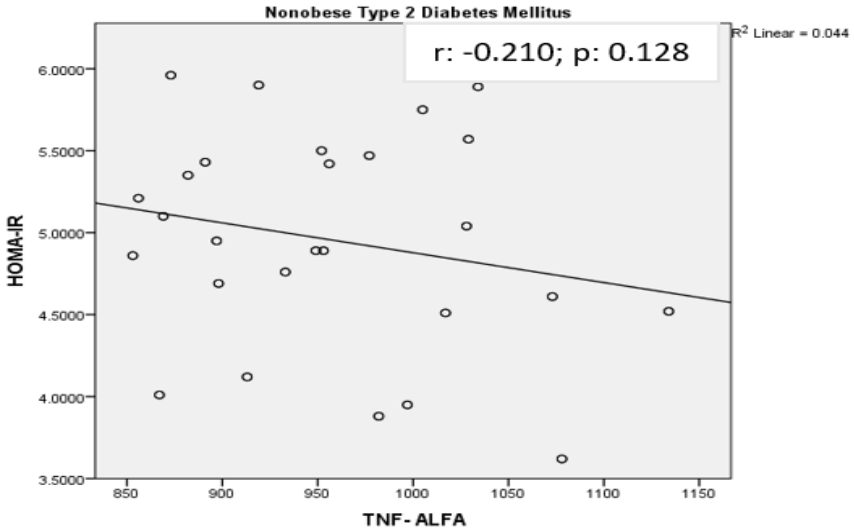

Fig. 2: Scatter plot with line of best fit showing correlation of TNF-α levels and insulin resistance in non-obese Type 2 Diabetes Mellitus

DISCUSSION

In this comparative study of obese and non-obese type 2 diabetic patients, significant differences were observed in metabolic parameters, particularly those related to insulin resistance and lipid metabolism. The obese group demonstrated higher BMI, HOMA-IR, and fasting insulin levels, indicating more pronounced insulin resistance. These findings are consistent with existing literature, which suggests that obesity, particularly visceral adiposity, is a central driver of insulin resistance in T2DM due to its role in adipokine secretion and chronic low-grade inflammation [8-10].

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In obesity, the infiltration of immune cells into adipose tissue, liver, muscle, and pancreas shifts these organs to a pro-inflammatory state, leading to the production of cytokines that disrupt insulin signalling in peripheral tissues and impair β-cell function, thereby increasing the risk of type 2 diabetes and its macrovascular complications [9].

While both groups had comparable fasting and postprandial glucose levels, the obese diabetics had significantly elevated levels of triglycerides, VLDL, LDL, and total cholesterol, consistent with the dyslipidemic profile often observed in metabolic syndrome [11]. These abnormalities increase cardiovascular risk, even in patients with controlled glycemia.

The lipid abnormalities seen in the obese diabetic cohort likely reflect the interplay between insulin resistance and hepatic lipid metabolism. Ectopic lipid accumulation in the liver and skeletal muscle impairs insulin signalling, initially reducing muscle glucose uptake and hepatic glycogen synthesis. This muscle insulin resistance then redirects glucose to the liver, fuelling hepatic *de novo* lipogenesis and hyperlipidaemia. Subsequently, macrophage infiltration into white adipose tissue increases lipolysis, delivering more fatty acids to the liver, which in turn boosts hepatic triglyceride synthesis and gluconeogenesis, thereby driving fasting and postprandial hyperglycaemia largely independently of hepatic insulin signalling [11]. This contributes to hypertriglyceridemia and increased VLDL, both observed in the current study. Elevated LDL cholesterol and low HDL levels—although HDL was not significantly different here—also typify the pro-atherogenic lipid profile associated with obesity-related insulin resistance [11].

A central focus of this study was TNF-α, a key inflammatory cytokine known to interfere with insulin signalling. We found that TNF-α levels were significantly higher in obese diabetics, supporting its established role in obesity-associated inflammation and insulin resistance. TNF-α, secreted predominantly by adipose tissue macrophages and hypertrophied adipocytes, disrupts insulin signaling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby impairing downstream insulin action [12]. Additionally, TNF-α has been shown to reduce the expression of GLUT4 in adipocytes and skeletal muscle, leading to decreased glucose uptake and hyperglycaemia [13].

TNF-α levels are markedly increased in individuals who are overweight or obese, as evidenced by multiple studies, including meta-analyses and cross-sectional research. This elevation often shows a positive correlation with body mass index (BMI), waist-to-hip ratio, and metabolic indicators such as glucose, cholesterol, and triglycerides [14,15]. The extent of adiposity and insulin resistance is frequently associated with this increase [14].

Adipose tissue is a primary contributor to TNF-α production, particularly in dysfunctional and expanded white adipose tissue (WAT) associated with obesity. Within the adipose microenvironment, hypertrophic adipocytes and infiltrating immune cells, particularly M1-polarized macrophages, are significant producers of this pro-inflammatory cytokine [16].

Importantly, in our study, TNF-α showed a significant positive correlation with triglycerides and VLDL levels among obese diabetics, suggesting a mechanistic link between inflammation and dyslipidaemia. TNF-α downregulates lipoprotein lipase, an enzyme crucial for triglyceride clearance, and stimulates hepatic lipogenesis, thereby promoting hypertriglyceridemia [17]. This correlation was not observed in the non-obese diabetic group, emphasizing the unique pathophysiological environment in obesity, where inflammatory mediators such as TNF-α play a dominant role.

In obese T2DM patients, a positive but weak and statistically non-significant correlation was observed between TNF-α levels and HOMA-IR (r^2=0.02). This suggests that TNF-α accounts for a very minor portion of the variability in insulin resistance within this cohort. This result, although weak, aligns broadly with the established understanding of TNF-α as a pro-inflammatory cytokine implicated in obesity-induced insulin resistance [14,15]. Adipose tissue, particularly in states of obesity, is a major source of TNF-α, and its elevated presence is often linked to the extent of adiposity and cellular mechanisms impairing insulin signalling, such as the activation of NF-κB and JNK pathways [13,16]. However, the weak correlation in our study might indicate that in the context of established obesity and T2DM, other factors or more downstream inflammatory mediators could play a more dominant role in driving the severity of insulin resistance. It is also plausible that the cross-sectional nature of this analysis

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might not fully capture the dynamic interplay of these factors.

Conversely, in non-obese T2DM patients, a negative but similarly weak and statistically non-significant correlation was found between TNF-α levels and HOMA-IR (r^2=0.04). This inverse relationship is particularly intriguing and warrants further exploration. While the literature predominantly points towards TNF-α's pro-inflammatory and insulin-desensitizing effects, some studies suggest complex roles or compensatory mechanisms in certain contexts. For instance, in conditions of metabolic stress, TNF-α might be transiently elevated as part of an acute immune response, which could have differential effects depending on the individual's metabolic profile and the underlying causes of their non-obese diabetes [18]. In normal-weight individuals with type 2 diabetes, the disease might develop differently than in obese individuals. For instance, their pancreas might not produce enough insulin, or they might have specific genes that make them more susceptible. It is essential to note that the non-significant nature of both correlations in our study suggests that TNF-α alone is not a primary driver of HOMA-IR variation in either group within this specific patient population.

HOMA-IR is influenced by a myriad of genetic, environmental, and lifestyle factors, as well as the intricate interplay of various adipokines, cytokines, and hormonal signals [19,20]. The weak correlations suggest that while TNF-α is undoubtedly part of the inflammatory milieu associated with T2DM, its direct linear relationship with HOMA-IR may be overshadowed by the combined influence of these other contributing factors.

Longitudinal studies would be necessary to understand the temporal dynamics of TNF-α levels and their impact on the progression or remission of insulin resistance. Future research could benefit from more detailed assessments of insulin sensitivity, characterization of specific TNF-α receptor expression, and investigation into other inflammatory markers and their interactions with TNF-α in obese and non-obese diabetics.

Traditional antidiabetic drugs such as metformin and thiazolidinediones (e.g., pioglitazone) indirectly reduce TNF-α levels through their insulin-sensitizing effects and modulation of adipose tissue inflammation [21]. However, the development of specific TNF-α inhibitors offers a novel therapeutic avenue. Biological agents, such as etanercept, infliximab, and adalimumab—initially developed for autoimmune diseases—have been evaluated in small clinical trials for metabolic disorders. For instance, infliximab has been shown to improve insulin sensitivity in obese patients with rheumatoid arthritis, suggesting a potential role beyond immunomodulation [22]. In another study, TNF-α blockade improved endothelial function and reduced systemic inflammation in patients with metabolic syndrome [23]. Despite these promising findings, the routine use of TNF-α inhibitors in diabetes management remains experimental, primarily due to concerns about long-term safety, cost, and the risk of immunosuppression.

CONCLUSIONS

In conclusion, our findings underscore the role of TNF-α as a key mediator linking obesity, inflammation, insulin resistance, and dyslipidaemia in type 2 DM. Obese diabetics exhibit not only a worsened metabolic profile but also an enhanced inflammatory burden, particularly elevated TNF-α levels, which correlate strongly with atherogenic lipids. Targeting inflammation, especially TNF-α may offer therapeutic benefits in managing obesity-associated diabetes, incorporating weight reduction, insulin sensitization, lipid management, and anti-inflammatory strategies.

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