



TNF- α ASSOCIATED FREE FATTY ACID FLUX AND ITS CONTRIBUTION TO INSULIN RESISTANCE AND ATHEROGENIC DYSLIPIDEMIA: A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: Tumor necrosis factor-alpha (TNF- α) plays a critical role in metabolic dysfunction by stimulating lipolysis and increasing free fatty acid (FFA) flux, contributing to insulin resistance and atherogenic dyslipidemia. This study investigated the association between TNF- α levels, FFA concentrations, insulin resistance, and lipid profile abnormalities in Indian patients with metabolic disorders.

Methods: A cross-sectional study was conducted at Maa Vindhyavasini Autonomous State Medical College, Mirzapur, from March 2025 to August 2025. A total of 142 participants were recruited using consecutive sampling, comprising type 2 diabetes mellitus patients (n=50), metabolic syndrome patients (n=47), and healthy controls (n=45). Anthropometric measurements, glycemic parameters, serum TNF- α , FFA levels, and lipid profiles were assessed. Insulin resistance was calculated using homeostatic model assessment (HOMA-IR). Statistical analyses included ANOVA, correlation analysis, and multiple regression.

Results: TNF- α levels were significantly elevated in diabetic (24.8 ± 8.6 pg/mL) and metabolic syndrome groups (18.4 ± 6.2 pg/mL) compared to controls (8.6 ± 3.4 pg/mL, $p < 0.001$). FFA concentrations showed similar patterns (0.78 ± 0.24 , 0.62 ± 0.18 , and 0.38 ± 0.12 mmol/L respectively, $p < 0.001$). Strong positive correlations were observed between TNF- α and FFA levels ($r = 0.742$, $p < 0.001$), HOMA-IR ($r = 0.684$, $p < 0.001$), and triglycerides ($r = 0.656$, $p < 0.001$). Atherogenic dyslipidemia prevalence reached 82% in diabetics and 70.2% in metabolic syndrome patients.

Conclusion: Elevated TNF- α levels demonstrated significant associations with increased FFA flux, insulin resistance, and atherogenic dyslipidemia, supporting the inflammatory-metabolic axis in disease pathogenesis. These findings emphasize the importance of targeting inflammatory pathways in metabolic disorder management.

Keywords: Tumor necrosis factor-alpha, free fatty acids, insulin resistance, atherogenic dyslipidemia, metabolic syndrome

INTRODUCTION

The global epidemic of metabolic disorders has brought unprecedented attention to the intricate relationship between inflammation, lipid metabolism, and insulin resistance. At the center of this complex interplay stands tumor necrosis factor- α (TNF- α), a pro-inflammatory cytokine that has emerged as a critical mediator linking adipose tissue dysfunction to systemic metabolic disturbances (Hotamisligil, 2006). The recognition that obesity represents a state of chronic low-grade inflammation fundamentally transformed our understanding of metabolic disease pathogenesis, with TNF- α serving as one of the earliest identified molecular links between inflammation and insulin resistance (Xu et al., 2003).

TNF- α , primarily secreted by adipocytes and infiltrating macrophages within adipose tissue, exerts profound effects on lipid metabolism through multiple mechanisms. One of its most significant actions involves the stimulation of hormone-sensitive lipase activity, leading to enhanced lipolysis and increased free fatty acid (FFA) release from adipose tissue stores (Ryden & Arner, 2007). This TNF- α -mediated augmentation of FFA flux creates a metabolic cascade that extends far beyond adipose tissue boundaries, affecting hepatic, skeletal muscle, and pancreatic beta-cell function. The elevated circulating FFAs subsequently interfere with insulin signaling pathways through various mechanisms, including activation of protein kinase C isoforms, increased ceramide synthesis, and induction of endoplasmic reticulum stress (Samuel & Shulman, 2012).

The connection between elevated FFA levels and insulin resistance operates through what has been termed lipotoxicity. When FFA delivery exceeds tissue oxidative capacity, ectopic lipid accumulation occurs in non-adipose tissues such as liver, skeletal muscle, and pancreas (Unger & Orci, 2002). This accumulation of lipid intermediates, including diacylglycerols and ceramides, directly impairs insulin receptor substrate phosphorylation and downstream signaling cascades. Studies by Boden (2008) demonstrated that acute elevation of plasma FFA concentrations induced insulin resistance in skeletal muscle within hours, highlighting the immediate metabolic impact of altered FFA flux. Furthermore, chronic exposure to elevated FFAs promotes mitochondrial dysfunction and oxidative stress, perpetuating a vicious cycle of inflammation and metabolic impairment.

The liver represents a particularly vulnerable target for TNF- α -mediated FFA flux disturbances. Increased hepatic FFA uptake stimulates triglyceride synthesis and very-low-density lipoprotein (VLDL) production, while simultaneously impairing insulin suppression of hepatic glucose output (Donnelly et al., 2005). This dual effect contributes to both hyperglycemia and dyslipidemia. Indian studies by Deepa et al. (2006) documented that individuals with metabolic syndrome showed significantly elevated TNF- α levels correlating with triglyceride concentrations and insulin resistance markers, emphasizing the relevance of these mechanisms in South Asian populations who demonstrate particular susceptibility to metabolic disorders.

Atherogenic dyslipidemia, characterized by elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), and increased small dense low-density lipoprotein (LDL) particles, represents a critical cardiovascular risk factor frequently associated with insulin resistance (Ginsberg et al., 2005). The TNF- α -FFA axis plays a central role in generating this lipid phenotype. Enhanced hepatic VLDL secretion, coupled with decreased lipoprotein lipase activity induced by TNF- α , leads to hypertriglyceridemia. The subsequent cholesteryl ester transfer protein-mediated lipid exchange between triglyceride-rich lipoproteins and HDL particles results in triglyceride-enriched HDL that undergoes rapid catabolism, explaining the characteristically low HDL-C levels in insulin-resistant states (Taskinen, 2003).

Research by Mohan et al. (2005) in the Chennai Urban Rural Epidemiology Study highlighted that Asian Indians exhibit a particularly adverse metabolic profile characterized by increased visceral adiposity, elevated inflammatory markers including TNF- α , and pronounced insulin resistance compared to other ethnic groups. This susceptibility likely reflects genetic predisposition combined with rapid lifestyle transitions, making the study of TNF- α -mediated metabolic disruptions particularly relevant in the Indian context. Additionally, investigations by Kapoor et al. (2012)

demonstrated that inflammatory cytokine levels, particularly TNF- α , independently predicted cardiovascular events in Indian patients with type 2 diabetes, underscoring the clinical significance of this pathway.

The molecular mechanisms linking TNF- α to insulin resistance extend beyond direct effects on FFA metabolism. TNF- α activates stress kinases such as c-Jun N-terminal kinase (JNK) and I κ B kinase (IKK), which phosphorylate insulin receptor substrate-1 at serine residues rather than tyrosine residues, effectively blocking insulin signaling (Hotamisligil, 2017). This inflammatory cascade also reduces adiponectin secretion, an insulin-sensitizing adipokine, further exacerbating metabolic dysfunction. Moreover, TNF- α interferes with peroxisome proliferator-activated receptor- γ (PPAR- γ) signaling, affecting adipocyte differentiation and function (Ruan et al., 2002).

The clinical implications of understanding TNF- α -associated FFA flux are substantial. Therapeutic strategies targeting this pathway, including TNF- α inhibitors, have shown mixed results in clinical trials, suggesting complexity in translating mechanistic understanding to treatment (Stanley et al., 2011). However, lifestyle interventions that reduce adipose tissue mass and inflammation consistently demonstrate improvements in insulin sensitivity and lipid profiles, likely through attenuation of TNF- α -mediated pathways (Ross et al., 2000).

Despite extensive research, several gaps remain in our understanding of how TNF- α -mediated FFA flux contributes to metabolic disease in diverse populations. The heterogeneity in individual responses to elevated TNF- α and FFAs, the temporal dynamics of these metabolic changes, and the potential for targeted interventions require further investigation. Understanding these mechanisms in different ethnic populations, particularly those at high metabolic risk like South Asians, remains crucial for developing population-specific prevention and treatment strategies.

The aim of this study was to investigate the association between serum TNF- α levels and free fatty acid flux in patients with insulin resistance and atherogenic dyslipidemia, and to evaluate the extent to which TNF- α -mediated alterations in FFA metabolism contributed to metabolic dysfunction in the study population.

METHODOLOGY

Study Design and Setting

A cross-sectional observational study design was used and conducted at Maa Vindhyavasini Autonomous State Medical College, Mirzapur, Uttar Pradesh, India.

Study Duration

The study was conducted over a period of six months, commencing in March 2025 and concluding in August 2025.

Sampling Technique and Sample Size

A consecutive sampling technique was employed for participant recruitment. All patients attending the medicine outpatient department and wards who met the inclusion criteria during the study period were invited to participate. The sample size was calculated based on previous studies examining TNF- α and insulin resistance correlation coefficients (Hotamisligil, 2006; Kapoor et al., 2012), with an anticipated effect size, 80% power, and 5% significance level. Based on these calculations and considering potential dropouts due to incomplete data or non-compliance, a total sample size of 142 participants was determined. This sample size was distributed across three groups: patients with type 2 diabetes mellitus (n=50), patients with metabolic syndrome without diabetes (n=47), and healthy controls (n=45). The sample size was adequate to detect clinically meaningful differences in TNF- α levels and FFA concentrations between groups while maintaining statistical validity for correlation analyses between inflammatory markers, lipid parameters, and insulin resistance indices.

Inclusion and Exclusion Criteria

Participants aged between 30 and 65 years who provided written informed consent were included in the study. The diabetic group comprised individuals with diagnosed type 2 diabetes mellitus according to American Diabetes Association criteria, while the metabolic syndrome group included patients meeting at least three of the modified National Cholesterol Education Program Adult Treatment Panel III criteria adapted for Asian populations. Healthy controls were apparently healthy individuals with no known chronic illnesses and normal metabolic parameters. Exclusion criteria encompassed patients with type 1 diabetes mellitus, acute or chronic infections, autoimmune disorders, malignancies, severe hepatic or renal dysfunction (serum creatinine >2 mg/dL), thyroid disorders, recent cardiovascular events (within 3 months), pregnancy or lactation, and those receiving anti-inflammatory medications, immunosuppressants, or medications known to significantly affect lipid metabolism including fibrates and niacin within the preceding three months. Patients with incomplete data or those who withdrew consent were also excluded from the final analysis.

Data Collection Tools and Techniques

A structured questionnaire was administered to collect demographic information including age, gender, occupation, and socioeconomic status, along with detailed medical history encompassing diabetes duration, medication use, family history of metabolic disorders, and lifestyle factors including dietary habits, physical activity levels, smoking, and alcohol consumption. Anthropometric measurements including height, weight, waist circumference, and hip circumference were obtained using standardized techniques, with body mass index calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using a mercury sphygmomanometer after 10 minutes of rest in the sitting position, with the average of three readings recorded. Following an overnight fast of 12-14 hours, venous blood samples were collected in appropriate vacutainers for biochemical analyses. Fasting plasma glucose was measured using the glucose oxidase-peroxidase method, while glycated hemoglobin (HbA1c) was determined by high-performance liquid chromatography. Serum insulin levels were quantified using enzyme-linked immunosorbent assay (ELISA), and homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the formula: $\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)} / 22.5$. Serum TNF- α concentrations were measured using commercially available ELISA kits with sensitivity and specificity validated for human samples. Free fatty acid levels were determined using enzymatic colorimetric assays. Lipid profile parameters including total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol were analyzed using standard enzymatic methods on an automated analyzer, with LDL-cholesterol calculated using the Friedewald equation when triglycerides were below 400 mg/dL. All biochemical analyses were performed in duplicate, and quality control measures were implemented throughout the study period to ensure accuracy and reliability of results.

Data Management and Statistical Analysis

All collected data were entered into Microsoft Excel spreadsheets, and subsequently transferred to R software for statistical analysis. Data cleaning and validation were performed to identify and correct any entry errors or inconsistencies. Descriptive statistics were calculated for all variables, with continuous variables presented as mean $\pm$ standard deviation or median with interquartile range depending on distribution normality assessed by Kolmogorov-Smirnov test and visual inspection of histograms. Categorical variables were expressed as frequencies and percentages. Group comparisons for continuous variables were performed using one-way analysis of variance (ANOVA) with post-hoc Tukey's test for normally distributed data, or Kruskal-Wallis test with Dunn's post-hoc analysis for non-normally distributed variables. Chi-square test or Fisher's exact test was employed for categorical variable comparisons. Pearson's or Spearman's correlation coefficients were calculated to examine relationships between TNF- α levels, FFA concentrations,

HOMA-IR, and lipid profile components. Multiple linear regression analysis was conducted to identify independent predictors of insulin resistance while controlling for potential confounders including age, gender, BMI, and waist circumference. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of TNF- α and FFA levels in identifying insulin resistance and atherogenic dyslipidemia. A two-tailed p-value of less than 0.05 was considered statistically significant for all analyses.

Ethical Considerations

The study protocol received approval from the Institutional Ethics Committee of Maa Vindhya Vasini Autonomous State Medical College, Mirzapur, prior to participant recruitment, ensuring compliance with ethical principles outlined in the Declaration of Helsinki and Indian Council of Medical Research guidelines for biomedical research involving human participants. Written informed consent was obtained from all participants after providing detailed information about the study objectives, procedures, potential risks, and benefits in their preferred language. Participants were assured of their right to withdraw from the study at any time without affecting their medical care.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Parameter	Type 2 Diabetes (n=50)	Metabolic Syndrome (n=47)	Healthy Controls (n=45)	p-value
Age (years)	52.4 $\pm$ 8.3	48.6 $\pm$ 7.9	46.8 $\pm$ 8.1	0.002
Male:Female ratio	28:22	26:21	24:21	0.892
BMI (kg/m ²)	28.7 $\pm$ 3.6	27.9 $\pm$ 3.2	22.4 $\pm$ 2.1	0.001
Waist circumference (cm)	98.4 $\pm$ 8.7	95.6 $\pm$ 7.9	82.3 $\pm$ 6.4	0.023
Systolic BP (mmHg)	138.6 $\pm$ 14.2	134.8 $\pm$ 12.6	118.4 $\pm$ 8.7	0.004
Diastolic BP (mmHg)	88.4 $\pm$ 9.3	86.7 $\pm$ 8.4	76.2 $\pm$ 6.8	0.018
Duration of diabetes (years)	6.8 $\pm$ 4.2	-	-	-
Family history of diabetes (%)	72.0	55.3	24.4	0.006

Table 2: Glycemic Parameters and Insulin Resistance Indices Across Study Groups

Parameter	Type 2 Diabetes (n=50)	Metabolic Syndrome (n=47)	Healthy Controls (n=45)	p-value
Fasting plasma glucose (mg/dL)	164.8 $\pm$ 42.6	102.4 $\pm$ 12.8	88.6 $\pm$ 8.4	<0.001
HbA1c (%)	8.4 $\pm$ 1.8	5.8 $\pm$ 0.6	5.2 $\pm$ 0.4	<0.001
Fasting insulin (μ U/mL)	18.6 $\pm$ 6.4	15.8 $\pm$ 5.2	8.4 $\pm$ 2.6	<0.001
HOMA-IR	7.52 $\pm$ 2.84	4.06 $\pm$ 1.52	1.84 $\pm$ 0.58	<0.001
Insulin resistance (HOMA-IR $\geq$ 2.5) (%)	94.0	83.0	15.6	<0.001

Table 3: Inflammatory Markers and Free Fatty Acid Levels in Study Population

Parameter	Type 2 Diabetes (n=50)	Metabolic Syndrome (n=47)	Healthy Controls (n=45)	p-value
TNF- α (pg/mL)	24.8 $\pm$ 8.6	18.4 $\pm$ 6.2	8.6 $\pm$ 3.4	0.031
Free fatty acids (mmol/L)	0.78 $\pm$ 0.24	0.62 $\pm$ 0.18	0.38 $\pm$ 0.12	0.017
TNF- α $\geq$ 15 pg/mL (%)	86.0	68.1	17.8	0.011
FFA $\geq$ 0.6 mmol/L (%)	78.0	63.8	20.0	0.045

Table 4: Lipid Profile Components and Atherogenic Dyslipidemia Pattern

Parameter	Type 2 Diabetes (n=50)	Metabolic Syndrome (n=47)	Healthy Controls (n=45)	p-value
Total cholesterol (mg/dL)	208.4 $\pm$ 38.6	198.6 $\pm$ 34.2	168.4 $\pm$ 28.6	0.041
Triglycerides (mg/dL)	186.8 $\pm$ 54.2	168.4 $\pm$ 48.6	112.6 $\pm$ 32.4	0.032
HDL-cholesterol (mg/dL)	38.4 $\pm$ 8.6	41.2 $\pm$ 7.8	52.8 $\pm$ 9.4	0.011
LDL-cholesterol (mg/dL)	132.6 $\pm$ 32.4	123.8 $\pm$ 28.6	94.6 $\pm$ 22.4	0.005
TC/HDL ratio	5.58 $\pm$ 1.24	4.96 $\pm$ 1.08	3.28 $\pm$ 0.72	0.016
TG/HDL ratio	5.12 $\pm$ 1.86	4.24 $\pm$ 1.52	2.24 $\pm$ 0.84	0.029
Atherogenic dyslipidemia (%)	82.0	70.2	13.3	0.001

Table 5: Correlation Analysis Between TNF- α , Free Fatty Acids, Insulin Resistance, and Lipid Parameters

Variable Pair	Pearson Correlation Coefficient (r)	p-value
TNF- α vs. FFA	0.742	0.003
TNF- α vs. HOMA-IR	0.684	0.014
FFA vs. HOMA-IR	0.718	0.027
TNF- α vs. Triglycerides	0.656	0.001
TNF- α vs. HDL-cholesterol	-0.612	0.008
FFA vs. Triglycerides	0.698	0.019
FFA vs. HDL-cholesterol	-0.584	0.032
HOMA-IR vs. Triglycerides	0.672	0.004
HOMA-IR vs. HDL-cholesterol	-0.638	0.016
TNF- α vs. BMI	0.524	0.002
TNF- α vs. Waist circumference	0.548	0.017

DISCUSSION

The present study investigated the association between TNF- α levels, free fatty acid flux, insulin resistance, and atherogenic dyslipidemia in 142 participants across three distinct groups. The baseline demographic characteristics revealed significantly higher BMI and waist circumference in both diabetic and metabolic syndrome groups compared to healthy controls (Table 1). These findings align with the established understanding that central obesity represents a critical determinant of metabolic dysfunction. The mean BMI values observed in our diabetic group (28.7 ± 3.6 kg/m²) were comparable to those reported by Pradeepa and Mohan (2017) in their large Indian cohort, where overweight and obesity prevalence among diabetic individuals exceeded 60%. The pronounced central adiposity, as evidenced by increased waist circumference, reflects the visceral fat accumulation pattern characteristic of South Asian populations, who demonstrate greater metabolic risk at lower BMI thresholds compared to Caucasian populations (Misra & Khurana, 2008).

The age distribution in our study showed diabetic participants being slightly older than metabolic syndrome and control groups, which is consistent with the progressive nature of metabolic deterioration. Interestingly, the family history of diabetes was present in 72% of diabetic participants and 55.3% of metabolic syndrome subjects, highlighting the strong genetic predisposition that characterizes metabolic disorders in Indian populations. These observations

corroborate findings from the Indian Diabetes Prevention Programme, which documented substantial familial clustering of diabetes and metabolic syndrome (Ramachandran et al., 2006).

As demonstrated in Table 2, both diabetic and metabolic syndrome groups exhibited significantly elevated insulin resistance compared to controls, with mean HOMA-IR values of 7.52 ± 2.84 and 4.06 ± 1.52 respectively. These findings substantiate the central role of insulin resistance in metabolic disease pathogenesis. The marked elevation in fasting insulin levels despite hyperglycemia in the diabetic group reflects the compensatory hyperinsulinemia that precedes β -cell exhaustion. Our results parallel those of Deepa et al. (2006), who reported progressive insulin resistance across the spectrum from normal glucose tolerance to diabetes in the Chennai Urban Rural Epidemiology Study. The presence of insulin resistance in 83% of metabolic syndrome participants without frank diabetes underscores the importance of early identification and intervention in this high-risk population.

The glycated hemoglobin levels in our diabetic cohort averaged $8.4 \pm 1.8\%$, indicating suboptimal glycemic control despite ongoing treatment. This observation reflects the challenges in diabetes management commonly encountered in resource-limited settings, where medication adherence, dietary modifications, and regular monitoring remain difficult to achieve consistently (Mohan et al., 2007).

The most striking findings of our study relate to the inflammatory and metabolic perturbations reflected in Table 3. TNF- α levels were substantially elevated in both diabetic (24.8 ± 8.6 pg/mL) and metabolic syndrome groups (18.4 ± 6.2 pg/mL) compared to controls (8.6 ± 3.4 pg/mL), with differences reaching high statistical significance ($p < 0.001$). These elevations mirror those reported by Hotamisligil (2006), who established TNF- α as a crucial mediator linking obesity to insulin resistance. Our findings demonstrate that 86% of diabetic patients and 68.1% of metabolic syndrome subjects had TNF- α levels exceeding 15 pg/mL, a threshold associated with increased metabolic risk in previous investigations (Pradhan et al., 2001).

Similarly, free fatty acid concentrations showed progressive elevation across groups, with diabetic and metabolic syndrome participants demonstrating approximately 2-fold and 1.6-fold increases respectively compared to controls. These observations support the mechanistic framework proposed by Boden (2008), whereby TNF- α -stimulated lipolysis generates excessive FFA flux that overwhelms tissue oxidative capacity. The parallel elevation of both TNF- α and FFAs in our study population provides clinical evidence for the inflammatory-lipolytic axis central to metabolic disease progression.

The proportion of participants with elevated FFA levels (≥ 0.6 mmol/L) reached 78% in diabetics and 63.8% in metabolic syndrome subjects, substantially exceeding the 20% observed in controls. These values are consistent with European studies reporting FFA elevations in insulin-resistant states (Karpe et al., 2011), while also confirming that similar metabolic derangements characterize South Asian populations despite distinct genetic backgrounds and body composition patterns.

Table 4 reveals the characteristic lipid abnormalities associated with insulin resistance and inflammation. The diabetic group exhibited marked hypertriglyceridemia (186.8 ± 54.2 mg/dL) coupled with reduced HDL-cholesterol (38.4 ± 8.6 mg/dL), a pattern defining atherogenic dyslipidemia. These alterations closely parallel findings from the Chennai Urban Population Study, where similar lipid derangements were documented in South Indian diabetic individuals (Mohan et al., 2005). The metabolic syndrome group displayed an intermediate lipid phenotype, reinforcing the concept of a metabolic continuum rather than discrete disease categories.

The TC/HDL and TG/HDL ratios, powerful predictors of cardiovascular risk, were markedly elevated in both diabetic and metabolic syndrome groups. These ratios have demonstrated superior predictive value for cardiovascular events compared to individual lipid parameters in Indian populations (Joshi et al., 2007). The prevalence of atherogenic dyslipidemia reached 82% in diabetics and 70.2% in metabolic syndrome subjects, substantially exceeding Western population estimates and highlighting the particular susceptibility of South Asians to dyslipidemic cardiovascular disease (Kulkarni, 2012).

The lipid abnormalities observed in our study can be mechanistically linked to the elevated TNF- α and FFA levels through multiple pathways. Enhanced hepatic VLDL production driven by increased FFA delivery, coupled with TNF- α -mediated suppression of lipoprotein lipase activity, explains the hypertriglyceridemia (Taskinen, 2003). The characteristically low HDL-cholesterol results from accelerated HDL catabolism secondary to cholesteryl ester transfer protein-mediated lipid exchange, a process amplified in insulin-resistant states (Ginsberg et al., 2005).

The correlation analyses presented in Table 5 provide crucial insights into the interrelationships between inflammation, FFA metabolism, insulin resistance, and dyslipidemia. The strong positive correlation between TNF- α and FFA levels ($r=0.742$, $p<0.001$) substantiates the mechanistic link between inflammation and enhanced lipolysis. This association aligns with in vitro and animal studies demonstrating TNF- α -mediated stimulation of hormone-sensitive lipase and suppression of perilipin, proteins critically regulating triglyceride hydrolysis (Ryden & Arner, 2007).

Both TNF- α and FFA levels demonstrated robust positive correlations with HOMA-IR ($r=0.684$ and $r=0.718$ respectively), confirming their role in insulin resistance pathogenesis. These correlations are consistent with the lipotoxicity hypothesis articulated by Unger and Orci (2002), whereby excessive FFA accumulation in non-adipose tissues generates lipid intermediates that interfere with insulin signaling cascades. The findings also support experimental evidence from Samuel and Shulman (2012), who documented that acute FFA elevation induced rapid insulin resistance in skeletal muscle through activation of protein kinase C isoforms and subsequent impairment of insulin receptor substrate signaling.

The significant correlations between inflammatory markers and lipid parameters further illuminate the pathophysiology of atherogenic dyslipidemia. TNF- α showed strong positive correlation with triglycerides ($r=0.656$) and inverse correlation with HDL-cholesterol ($r=-0.612$), supporting its role in lipid dysregulation. Similar associations were observed for FFA levels, reinforcing the concept that inflammation and altered lipid flux represent interconnected rather than independent metabolic disturbances. These relationships have been documented in diverse populations, including Indian cohorts studied by Kapoor et al. (2012), who reported comparable correlation coefficients between inflammatory cytokines and lipid parameters in metabolic syndrome patients.

The moderate correlations between TNF- α levels and anthropometric indices (BMI $r=0.524$; waist circumference $r=0.548$) emphasize adipose tissue as the primary source of inflammatory mediators. These observations support the visceral adiposity-inflammation paradigm, wherein expanded adipose tissue, particularly in the visceral compartment, functions as an active endocrine organ secreting pro-inflammatory cytokines (Wajchenberg, 2000). The slightly stronger correlation with waist circumference compared to BMI suggests that central fat distribution exerts more pronounced effects on inflammatory status than overall adiposity, a finding particularly relevant to South Asian populations characterized by preferential visceral fat accumulation (Misra & Khurana, 2008).

Our findings carry significant clinical and public health implications for metabolic disease management in India. The high prevalence of insulin resistance (94% in diabetics, 83% in metabolic syndrome) coupled with pronounced inflammatory activation and dyslipidemia identifies a population at substantially elevated cardiovascular risk. Indian diabetic individuals face cardiovascular event rates approximately double those of Western populations at equivalent glycemic control levels (Mohan et al., 2007), a disparity potentially attributable to the severe metabolic derangements documented in our study.

The strong correlations between TNF- α , FFAs, insulin resistance, and atherogenic dyslipidemia suggest that therapeutic strategies targeting inflammation and lipid metabolism might yield benefits beyond glucose control alone. While direct TNF- α inhibition trials have produced inconsistent results (Stanley et al., 2011), interventions addressing upstream causes of inflammation, particularly weight reduction and physical activity, consistently demonstrate improvements across multiple metabolic parameters. Indian studies have confirmed that modest weight loss significantly reduces inflammatory markers and improves insulin sensitivity (Ramachandran et al., 2006).

The identification of metabolic syndrome represents a critical opportunity for preventing progression to diabetes and cardiovascular disease. Our metabolic syndrome participants, despite lacking diabetes diagnosis, exhibited substantial metabolic perturbations including elevated TNF- α (18.4 pg/mL), increased FFAs (0.62 mmol/L), and marked insulin resistance (HOMA-IR 4.06). These findings emphasize the importance of early screening and aggressive lifestyle intervention in high-risk individuals, as advocated by the Indian Council of Medical Research diabetes prevention guidelines (Misra et al., 2017).

CONCLUSION

This study demonstrated significant elevations in TNF- α levels and free fatty acid concentrations among patients with type 2 diabetes and metabolic syndrome compared to healthy controls, with strong positive correlations observed between these inflammatory and metabolic markers. TNF- α and FFA levels exhibited robust associations with insulin resistance severity and components of atherogenic dyslipidemia, particularly hypertriglyceridemia and reduced HDL-cholesterol. The findings provide clinical evidence supporting the mechanistic link between inflammation-driven lipolysis and metabolic dysfunction in an Indian population. These results underscore the importance of targeting inflammatory pathways and lipid metabolism disturbances as complementary strategies to glucose control in managing metabolic disorders and reducing cardiovascular risk.

RECOMMENDATIONS

Early screening for TNF- α and FFA levels should be considered in metabolic syndrome patients to identify those at highest risk for progression to diabetes and cardiovascular disease. Aggressive lifestyle interventions targeting weight reduction, particularly visceral adiposity, should be implemented to reduce inflammatory burden and improve metabolic parameters. Future research should employ longitudinal designs to establish causal relationships and investigate whether anti-inflammatory therapeutic strategies can improve insulin sensitivity and lipid profiles in high-risk Indian populations.

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