

Correlation of Neuregulin-4 (NRG-4) Levels with Lipid Profile in Newly Diagnosed Diabetes Mellitus Patients at Tertiary Care Centre

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with systemic inflammation and atherogenic dyslipidemia. Neuregulin-4 (NRG-4), an adipokine involved in metabolic regulation, may play a role in lipid homeostasis and cardiometabolic risk modulation.

Objective: To assess serum NRG-4 levels and their correlations with lipid profile parameters in newly diagnosed T2DM patients compared with age- and gender-matched healthy controls.

Materials and Methods: Fifty newly diagnosed T2DM patients and 50 matched healthy controls were recruited over 18 months. Fasting blood samples were analyzed for glucose, HbA1c, lipid profile, and serum NRG-4 levels using ELISA. Statistical analyses included Student's t-test and Pearson correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results: Cases and controls were comparable in age and gender. T2DM patients had significantly higher CRP (28.8 ± 14.4 vs 3.96 ± 1.9 mg/L) and HbA1c ($7.1 \pm 1.3\%$ vs $5.3 \pm 0.4\%$; $p < 0.001$). Lipid profiles demonstrated atherogenic dyslipidemia, with increased total cholesterol, triglycerides, LDL, and VLDL levels, along with reduced HDL cholesterol. Serum NRG-4 levels were significantly higher in T2DM patients (2.9 ± 1.0 vs 1.07 ± 0.4 ; $p < 0.001$) and showed significant negative correlations with triglycerides, LDL, and VLDL, and a positive correlation with HDL cholesterol.

Conclusion: Newly diagnosed T2DM patients exhibit systemic inflammation, dysglycemia, and atherogenic dyslipidemia. Elevated NRG-4 levels demonstrate significant associations with lipid parameters, suggesting its potential role as a biomarker in metabolic dysregulation and cardiovascular risk stratification.

Keywords: Type 2 diabetes mellitus, Neuregulin-4, lipid profile, atherogenic dyslipidemia, biomarker

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INTRODUCTION

Metabolic syndrome (MetS) represents a constellation of interrelated metabolic abnormalities, including insulin resistance, hyperglycemia, dyslipidemia, central obesity, and hypertension. Collectively, these abnormalities substantially increase the risk of developing type 2 diabetes mellitus (T2DM), cardiovascular disease, and all-cause mortality across different age groups [1]. Diabetes mellitus (DM) is recognized as one of the most serious global public

health challenges of the 21st century and currently ranks among the top ten leading causes of mortality worldwide [2]. Since the 1990s, the global prevalence of T2DM has risen dramatically, with a disproportionately higher burden observed among certain ethnic populations, particularly Asian Indians, highlighting the combined influence of genetic predisposition and environmental factors on disease susceptibility [3,4].

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Insulin resistance is a central pathophysiological mechanism underlying both MetS and T2DM; however, the molecular pathways contributing to its development remain incompletely understood. Despite advances in management, current preventive and therapeutic strategies remain suboptimal, underscoring the need to identify novel biomarkers that may facilitate early detection and improve risk stratification [1]. In this context, adipose tissue has emerged as an active endocrine organ that plays a pivotal role in metabolic homeostasis through the secretion of biologically active adipokines.

Adipokines such as adiponectin and leptin regulate glucose metabolism, lipid homeostasis, inflammation, and insulin sensitivity. Dysregulation of adipokine secretion contributes significantly to insulin resistance and T2DM [5]. Brown adipose tissue-derived adipokines have gained attention for their beneficial metabolic effects, including improved insulin sensitivity and enhanced lipid metabolism [6].

Neuregulin-4 (NRG-4) is a recently identified adipokine predominantly expressed in brown adipose tissue and detectable in circulation. It belongs to the epidermal growth factor (EGF) family and exerts its biological effects primarily through ErbB3 and ErbB4 receptors [7,8]. Experimental studies suggest that NRG-4 improves insulin sensitivity and modulates lipid metabolism [9,10].

Several clinical studies have reported associations between circulating NRG-4 levels and obesity, insulin resistance, metabolic syndrome, and T2DM [11,12]. However, findings remain inconsistent. Most evidence comes from patients with long-standing diabetes, while data on newly diagnosed, treatment-naïve individuals remain limited.

Dyslipidemia—characterized by elevated triglycerides, increased LDL and VLDL, and reduced HDL cholesterol—is a hallmark of T2DM and a major contributor to cardiovascular morbidity and mortality [13]. Given the established role of NRG-4 in lipid metabolism, evaluating its relationship with lipid profile parameters may provide insight into early metabolic derangements in diabetes.[14]

Therefore, the present case-control study aims to assess serum Neuregulin-4 levels in newly diagnosed diabetes mellitus patients and healthy controls and to evaluate their correlation with lipid profile parameters.

MATERIALS AND METHODS

Study Setting and Design

This case-control study was conducted in the Department of Biochemistry, IIMS&R, Lucknow, to evaluate serum Neuregulin-4 (NRG-4) levels and their correlation with lipid profile parameters in newly diagnosed type 2 diabetes mellitus (T2DM) patients.

Study Population and Duration

Patients meeting eligibility criteria were enrolled over 18 months. The study included 50 newly diagnosed T2DM patients and 50 age- and sex-matched healthy controls.

Sample Size and Sampling

A total of 100 participants were included. Purposive sampling was used.

Ethical Considerations

Approved by Institutional Ethics Committee. Written informed consent obtained.

Eligibility Criteria

Inclusion Criteria

- Age 35–60 years
- Newly diagnosed T2DM (ADA criteria)
- Provided informed consent

Exclusion Criteria

- Type 1 or gestational diabetes
- Endocrine disorders
- Smoking or alcohol history
- Cardiovascular disease
- Chronic steroid therapy

Blood Sample Collection

- After 8–10 hours fasting:
- Plain (SST) vials: for NRG-4 and lipid profile
- Fluoride vial: plasma glucose
- EDTA vial: HbA1c
- Samples were processed and stored at -80°C until analysis.

Biochemical Analysis

Glucose and lipid profile: Fully automated analyzer

HbA1c: HPLC (Bio-Rad D10 system)

Serum NRG-4: ELISA

Statistical Analysis

Data analyzed using SPSS version 20.0. Continuous variables expressed as mean \pm SD. Independent Student's t-test used for comparison. Pearson's correlation coefficient assessed relationships between serum NRG-4 and lipid profile parameters.

$p < 0.05$ considered statistically significant.

OBSERVATION & RESULTS

Table 1. Baseline Demographic Characteristics of Study Groups

Variable	Case Group (n = 50)	Control Group (n = 50)	p-value

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Age 35–50 years	24 (48.0%)	22 (44.0%)	0.69
Age 50–60 years	26 (52.0%)	28 (56.0%)	
Male	23 (46.0%)	26 (52.0%)	0.54
Female	27 (54.0%)	24 (48.0%)	

Graph: Baseline Demographic Characteristics of Study Groups

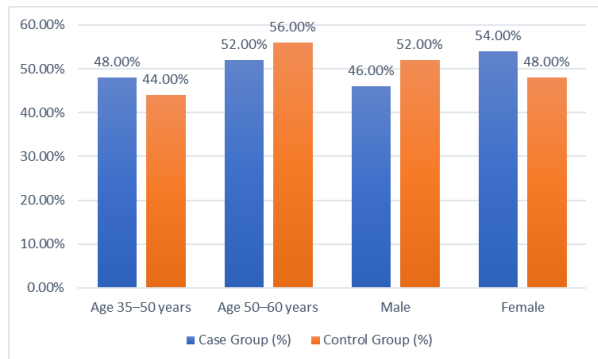


Table 1 presents the baseline demographic characteristics of the case and control groups, each comprising 50 participants. In the case group, 24 participants (48.0%) were aged between 35–50 years, while 26 participants (52.0%) were in the 50–60 years age group. Similarly, in the control group, 22 participants (44.0%) were aged 35–50 years and 28 participants (56.0%) were aged 50–60 years. The difference in age distribution between the two groups was not statistically significant ($p = 0.69$), indicating that both groups were comparable with respect to age. Regarding gender distribution, the case group included 23 males (46.0%) and 27 females (54.0%), whereas the control group comprised 26 males (52.0%) and 24 females (48.0%). The difference in gender distribution between the groups was also not statistically significant ($p = 0.54$).

Table 2. Inflammatory Marker, Glycemic Status, and NRG-4 Levels

Parameter	Case Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
CRP (mg/L)	28.8 ± 14.4	3.96 ± 1.9	<0.001
HbA1c (%)	7.1 ± 1.3	5.3 ± 0.4	<0.001
NRG-4 Index	2.9 ± 1.0	1.07 ± 0.4	<0.001

Graph: Inflammatory Marker, Glycemic Status, and NRG-4 Levels

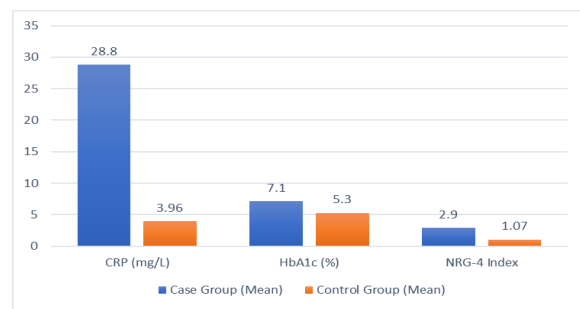


Table 2 compares inflammatory status, glycemic control, and Neuregulin-4 (NRG-4) levels between cases and controls. The case group demonstrated markedly elevated CRP levels compared to controls, reflecting significantly increased systemic inflammation. Glycemic control, as assessed by HbA1c, was also significantly poorer in cases. In addition, NRG-4 levels were significantly altered in the case group compared to controls. These findings indicate a strong association between inflammation, poor glycemic regulation, and altered NRG-4 expression in patients with newly diagnosed type 2 diabetes mellitus.

Table 3. Lipid Profile Comparison Between Groups

Parameter	Case Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Total Cholesterol (mg/dL)	168 ± 74	152.4 ± 34.1	0.04
Triglycerides (mg/dL)	242 ± 92.6	138.1 ± 41.6	<0.001
HDL (mg/dL)	55 ± 10.8	62.2 ± 9.5	0.002
LDL (mg/dL)	44 ± 24	27.6 ± 8.5	0.01
VLDL (mg/dL)	48 ± 19.4	28.1 ± 8.5	<0.001

Graph: Lipid Profile Comparison Between Groups

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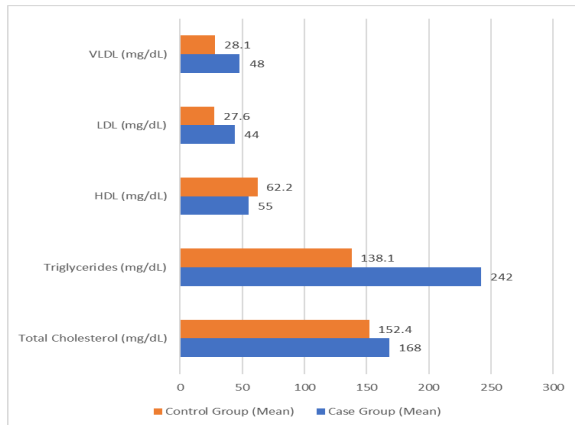


Table 3 shows the comparison of lipid parameters between cases and controls. The case group demonstrated significantly higher total cholesterol and triglyceride levels. LDL and VLDL concentrations were also elevated in cases, while HDL levels were significantly reduced. This lipid pattern reflects atherogenic dyslipidemia commonly associated with type 2 diabetes mellitus. The observed dyslipidemia may contribute to increased cardiovascular risk and appears to be associated with altered NRG-4 activity.

Table 4. Correlation of NRG-4 with Lipid Parameters

Parameter	r value	p-value
Total Cholesterol	-0.31	0.02
Triglycerides	-0.44	<0.01
HDL	+0.38	0.01
LDL	-0.29	0.03
VLDL	-0.41	<0.01

Table 4 illustrates the correlation between NRG-4 levels and lipid parameters in the case group. NRG-4 demonstrated a statistically significant negative correlation with total cholesterol ($r = -0.31, p = 0.02$), triglycerides ($r = -0.44, p < 0.01$), LDL cholesterol ($r = -0.29, p = 0.03$), and VLDL cholesterol ($r = -0.41, p < 0.01$). This indicates that lower NRG-4 levels were associated with higher levels of atherogenic lipids.

Conversely, a significant positive correlation was observed between NRG-4 and HDL cholesterol ($r = +0.38, p = 0.01$), suggesting that higher NRG-4 levels are associated with increased levels of protective HDL cholesterol.

DISCUSSION:

The present case-control study evaluated serum Neuregulin-4 (NRG-4) levels and their association with glycemic control and lipid profile in patients with newly diagnosed type 2 diabetes mellitus (T2DM). Our findings demonstrate that early T2DM is accompanied by significant metabolic, hepatic, and inflammatory disturbances compared with age- and gender-matched healthy controls.

The case and control groups were comparable in age and gender, minimizing demographic confounding. The age range of 35–60 years reflects the typical adult onset of T2DM and aligns with reports by Dai et al (2015) [12] and Yan et al (2018), [1] which reported mean ages of 52–54 years in diabetic cohorts. Gender distribution was balanced, confirming the suitability of the control group for comparative analyses.

Patients with T2DM exhibited markedly elevated C-reactive protein (CRP) levels, indicating systemic low-grade inflammation. Chronic inflammation is a well-established contributor to insulin resistance and beta-cell dysfunction, as described by Devaraj et al (2008) [15] and Lin et al (2010) [16]. Glycemic control, assessed by HbA1c, was significantly impaired in cases, reinforcing the link between systemic inflammation and dysregulated glucose metabolism in early diabetes.

Serum NRG-4, an adipokine involved in glucose and lipid homeostasis, was significantly elevated in T2DM patients. Previous studies have reported variable patterns of NRG-4 expression; Zhang et al (2017) [10] and Yan et al (2019) [1] observed reduced levels in diabetic patients, whereas Kang et al (2016) [17] reported compensatory elevations in early disease. The increased levels in our cohort may represent an early adaptive response to metabolic stress, consistent with its protective correlations with HDL and inverse associations with triglycerides, LDL and VLDL. These findings suggest that NRG-4 may play a critical role in maintaining metabolic and hepatic homeostasis in the early stages of T2DM.

The lipid profile of T2DM patients demonstrated atherogenic dyslipidemia, characterized by elevated total cholesterol, triglycerides, LDL, and VLDL, along with reduced HDL. This lipid pattern is characteristic of early T2DM and is associated with increased cardiovascular risk, consistent with previous reports by Akshay et al (2023) [19] and Dai et al (2015) [12].

Correlation analysis revealed that NRG-4 levels were negatively associated with triglycerides, LDL VLDL and positively correlated with HDL cholesterol. These

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results indicate a protective role of NRG-4 in lipid metabolism and hepatic function, suggesting that dysregulated NRG-4 may exacerbate dyslipidemia and subclinical liver impairment. This supports prior evidence that NRG-4 modulates glucose homeostasis and hepatic integrity.

Collectively, these findings highlight the potential utility of NRG-4 as an early biomarker for metabolic and hepatic disturbances in T2DM. Monitoring serum NRG-4 levels may facilitate early identification of patients at risk for atherogenic dyslipidemia, hepatic involvement, and systemic inflammation, enabling timely interventions to prevent cardiovascular and hepatic complications.

The study has some limitations. Its cross-sectional design precludes causal inference, and the single-center setting may limit generalizability. Additionally, serum NRG-4 was measured only at a single time point, without assessment of tissue-specific expression or longitudinal changes. Future research should include multi-center cohorts, longitudinal follow-up, and mechanistic evaluations to further elucidate the role of NRG-4 in metabolic regulation.

In conclusion, newly diagnosed T2DM patients exhibit systemic inflammation, impaired glycemic control, subclinical hepatic dysfunction, and atherogenic dyslipidemia, accompanied by altered NRG-4 levels. The observed correlations between NRG-4 and lipid parameters suggest a protective metabolic role, supporting its potential as an early biomarker and therapeutic target in type 2 diabetes mellitus.

CONCLUSION

The present study demonstrates that newly diagnosed type 2 diabetes mellitus patients exhibit systemic inflammation, impaired glycemic control, and atherogenic dyslipidemia compared with age- and gender-matched healthy controls. Serum Neuregulin-4 (NRG-4) levels were significantly altered and showed protective correlations with lipid parameters, demonstrating negative associations with triglycerides, LDL, and VLDL, and a positive association with HDL cholesterol. These findings suggest that NRG-4 plays an important regulatory role in metabolic homeostasis, and its measurement may serve as an early biomarker to identify patients at risk for dyslipidemia and systemic inflammation, thereby supporting timely interventions to prevent progression of metabolic and cardiovascular complications.

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