

# Neuregulin-4 (Nrg-4) as a Metabolic Regulator: A Comprehensive Review of Its Association with Dyslipidemia and Liver Function Abnormalities in Newly Diagnosed Type 2 Diabetes Mellitus

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## ABSTRACT

Neuregulin-4 (Nrg-4), a brown adipose tissue-derived adipokine, has emerged as a critical endocrine regulator linking adipose tissue function with metabolic homeostasis. Growing evidence suggests that reduced Nrg-4 levels are associated with insulin resistance, dyslipidemia, hepatic steatosis, and the early pathophysiology of type 2 diabetes mellitus (T2DM). This review explores in depth the correlation between circulating Nrg-4 levels, lipid parameters, and liver function markers among newly diagnosed T2DM patients, highlighting its potential as a diagnostic or prognostic biomarker. “Research consistently indicates that individuals with diabetes exhibit markedly reduced Nrg-4 levels, which show inverse associations with triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) whereas Nrg-4 demonstrates a positive correlation with high-density lipoprotein cholesterol (HDL-C)”. Mechanistic studies support a protective role of Nrg-4 against hepatic lipogenesis, oxidative stress, and systemic inflammation. The findings collectively indicate that Nrg-4 is detrimental in metabolic regulation and could act as promising biomarker for early metabolic derangements in diabetes. Nevertheless, heterogeneity in study design, limited sample sizes, and assay variability highlight the need for standardized large-scale cohort studies.

**KEYWORDS:** Neuregulin-4 (Nrg-4), Metabolic Regulator, Dyslipidemia, Liver Function Abnormalities, Newly Diagnosed, Type-2 Diabetes Mellitus.

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## INTRODUCTION

Diabetes mellitus (DM) is a complex, multifactorial metabolic disorder marked by persistent hyperglycaemia arising from impaired insulin secretion, defective insulin action, or a combination of both the agents (1). The global prevalence of diabetes mellitus (DM) has escalated to epidemic levels, with type 2 diabetes mellitus (T2DM) comprising over ninety percent of all diagnosed cases (2-6). As per International Diabetes Federation, an estimated five hundred thirty seven million adults were living with diabetes in 2021, and this figure is expected to rise to approximately six hundred forty three million by 2030. T2DM is not only a disorder of glucose metabolism but also a complex metabolic condition involving dyslipidemia, altered adipokine signaling, systemic inflammation, and hepatic dysfunction (7).

Over the past two decades, adipose tissue has been redefined from a mere energy storage depot to a highly active endocrine organ that secretes numerous bioactive molecules collectively termed adipokines (8-12). These adipokines—including adiponectin, leptin, resistin, visfatin, chemerin, vaspin, omentin, and the more recently discovered Neuregulin-4 (Nrg-4)—play essential roles in regulating insulin sensitivity, inflammation, lipid metabolism, and liver function.

Neuregulins belong to the epidermal growth factor (EGF) family and exert their effects through ErbB receptor tyrosine kinases. Nrg-4, discovered as a brown adipose tissue (BAT)-derived adipokine, has drawn significant attention due to its role in metabolic regulation (13-17). Unlike white adipose tissue (WAT), brown adipose tissue is metabolically active and is involved in thermogenesis and energy expenditure. Nrg-4 is primarily expressed in BAT and acts through ErbB3 and ErbB4 receptors to regulate systemic glucose and lipid homeostasis.

Experimental evidence demonstrates that Nrg-4 enhances insulin sensitivity by suppressing hepatic gluconeogenesis and promoting assimilation of glucose while decreasing lipotoxicity. In animal models, genetic deletion of Nrg-4 leads to accelerated obesity, hepatic steatosis, and insulin resistance, indicating its protective metabolic effects (18,19, 20).

## The Interrelationship Between Diabetes, Dyslipidemia, and Liver Dysfunction

T2DM is frequently accompanied by a characteristic pattern of dyslipidemia:

- Elevated triglycerides (TG)
- Increased very low-density lipoproteins (VLDL)
- Raised low-density lipoprotein cholesterol (LDL-C)
- Reduced high-density lipoprotein cholesterol (HDL-C)

In parallel, liver dysfunction, commonly manifested as non-alcoholic fatty liver disease is commonly observed among newly diagnosed diabetics. Elevated liver enzymes such as ALT and AST reflect underlying hepatic inflammation or steatosis (21).

Nrg-4 appears to be a key adipokine linking BAT function with hepatic metabolism and systemic lipid regulation. Existing literature indicates that lower Nrg-4 levels are associated with:

Increased hepatic lipogenesis

- Higher TG and LDL-C levels
- Lower HDL-C
- Elevated liver enzymes
- Worsened insulin resistance

These findings suggest that Nrg-4 deficiency may represent a novel metabolic abnormality in early diabetes (22-26).

Despite rapid advances in research on Nrg-4, evidence remains scattered, limited by small sample sizes, and varied methodologies. A consolidated, updated review is essential to understand the correlations among Nrg-4, lipid profile, and liver function tests (LFTs) in newly diagnosed diabetes .

This review synthesizes the available clinical, biochemical, and mechanistic evidence to highlight the relevance of Nrg-4 as a metabolic biomarker in diabetes.

## MATERIALS AND METHODS

This review was undertaken using a structured narrative methodology. A comprehensive search of various databases available online identifying studies that are published from 2005 to 2025 from sources: PubMed, Scopus, Web of Science, and Google Scholar. Keywords included:

“Neuregulin-4”, “Nrg-4”, “diabetes mellitus”, “insulin resistance”, “lipid profile”, “liver function tests”, “adipokines”, “metabolic syndrome”, “NAFLD”.

### Inclusion criteria:

1. Human studies evaluating circulating Nrg-4 levels
2. Studies on newly diagnosed or untreated T2DM
3. Correlation analyses with lipid profile and/or liver enzymes
4. Published in English

### Exclusion criteria:

1. Animal-only studies
2. Studies without clear Nrg-4 quantification
3. Case reports, editorials, and non-scientific reviews

Data were extracted for study population, Nrg-4 levels, lipid profile, LFTs, and correlation strength.

## RESULTS

### 1. Nrg-4 Levels in Newly Diagnosed Diabetes

Most studies report significantly lower circulating Nrg-4 levels in newly diagnosed diabetics compared with healthy controls.

### 2. Correlation with Lipid Profile

- Negative correlation: TG, TC, LDL-C
- Positive correlation: HDL-C
- Strongest correlation observed with triglycerides.

### 3. Correlation with Liver Function Tests

- Lower Nrg-4 levels were associated with:
- Higher ALT
- Higher AST
- Moderately elevated ALP

### 4. Nrg-4 and Insulin Resistance

Most studies show an inverse correlation with HOMA-IR, suggesting Nrg-4 plays a direct role in insulin sensitivity.

### 5. Association with NAFLD

Nrg-4 deficiency strongly predicts hepatic steatosis in diabetics, indicating its hepatoprotective role.

## DISCUSSION

Neuregulin-4 (Nrg-4) has recently emerged as a potent endocrine factor predominantly derived from brown adipose tissue (BAT), with far-reaching implications in metabolic homeostasis, insulin sensitivity, lipid regulation, and hepatic health (27). The present review synthesizes evidence from clinical, experimental, and translational studies to examine its relationship with dyslipidemia and liver function abnormalities in recent onset of T2DM. The collective data strongly indicate that Nrg-4 plays a protective metabolic role, and its deficiency is closely associated with the early pathophysiological disturbances that characterize T2DM, particularly dyslipidemia and non-alcoholic fatty liver disease.

### **Nrg-4 and Metabolic Dysfunction in T2DM**

Several clinical studies indicate that circulating Nrg-4 levels are significantly lower among individuals with impaired glucose tolerance, insulin resistance, and overt T2DM.

Wang et al. reported that serum Nrg-4 levels were markedly reduced in newly diagnosed T2DM patients, and low levels independently predicted insulin resistance indices such as HOMA-IR after adjusting for age and BMI (1). Similarly, Cai et al. demonstrated a negative correlation between Nrg-4 and fasting plasma glucose, HbA1c & markers of chronic inflammation notably TNF- $\alpha$  & IL-6, reinforcing the hypothesis that Nrg-4 acts as an anti-inflammatory adipokine ameliorating metabolic stress (28).

Evidence from animal models corroborates these clinical observations. Rosell et al. found that Nrg-4 overexpression protected mice from diet-induced obesity and hepatic steatosis, primarily through attenuation of hepatic lipogenesis and improvement in insulin sensitivity (29). Conversely, Nrg-4-deficient mice experienced rapid metabolic deterioration under high-fat feeding, marked by hyperglycemia, hepatic fat accumulation, and dyslipidemia (30). Collectively, these findings suggest that Nrg-4 deficiency may represent an early biomarker of metabolic maladaptation contributing to the onset of T2DM.

### **Association Between Nrg-4 and Dyslipidemia**

Dyslipidemia represents one of the earliest metabolic derailments in T2DM, typically manifesting as elevated triglycerides, increased LDL-C, and reduced HDL-C. Multiple studies have examined how Nrg-4 influences lipid profiles and lipid metabolism. Xu et al. reported a strong inverse association between serum Nrg-4 and serum triglycerides among obese and diabetic adults, implying a lipid-lowering effect mediated by Nrg-4 (31). The mechanistic basis lies in Nrg-4's ability to inhibit hepatic de novo lipogenesis by downregulating SREBP-1c signaling, a central transcription factor promoting fat synthesis (32). Supporting this, Wang et al. observed that individuals in the lowest Nrg-4 quartile had significantly higher total cholesterol, triglycerides, and LDL-cholesterol levels, suggesting that Nrg-4 insufficiency accelerates atherogenic lipid accumulation (33).

In addition, recent data indicate that Nrg-4 enhances lipid clearance by stimulating thermogenic activity in BAT, leading to augmented fatty acid oxidation and energy expenditure. Barlaka et al. demonstrated that Nrg-4 supplementation increased UCP1 expression in brown adipocytes and enhanced lipid oxidation, thereby reducing circulating lipid burden (34). These results underscore that lower Nrg-4 levels in newly diagnosed T2DM may directly contribute to dyslipidemia by reducing thermogenic lipid disposal.

Furthermore, some population-based studies in East Asia have identified Nrg-4 as a potential biomarker for dyslipidemia risk prediction. Sun et al. observed that decreased Nrg-4 concentrations predicted hypertriglyceridemia even after controlling for BMI, age, and insulin resistance, suggesting a direct metabolic link independent of obesity (35). This is particularly relevant for Asian populations where dyslipidemia manifests early even at lower BMI values.

### **Nrg-4 and Liver Function Abnormalities in T2DM**

Liver dysfunction is common in newly diagnosed T2DM, especially as NAFLD is tightly linked to insulin resistance. Nrg-4 appears to play a critical role in hepatic protection. Zhang et al. first identified Nrg-4 as a BAT-derived cytokine that directly communicates with the liver through ErbB4 receptors, mitigating hepatic lipogenesis and inflammation (10). In this landmark study, Nrg-4-deficient mice exhibited severe hepatic steatosis, ballooning, and elevated ALT/AST levels when fed a high-fat diet, indicating susceptibility to liver injury (36).

Human studies have consistently demonstrated similar patterns. Guo et al. found significantly lower serum Nrg-4 in T2DM patients with elevated liver enzymes, particularly ALT and GGT, compared to those with normal liver profiles (37). Importantly, Nrg-4 levels negatively correlated with hepatic steatosis severity on ultrasound and MRI-based fat quantification (38). This supports the hypothesis that Nrg-4 deficiency contributes to NAFLD pathogenesis in T2DM by enabling unchecked hepatic lipid accumulation.

Mechanistic studies also highlight that Nrg-4 suppresses key lipogenic pathways in the liver. Ma et al. showed that Nrg-4 inhibits expression of FASN, ACC, and SCD1 — enzymes responsible for fatty acid synthesis — while enhancing  $\beta$ -oxidation and reducing oxidative stress markers (39). These effects have been shown to reduce hepatic inflammation, fibrosis progression, and oxidative damage in NAFLD models (40).

Additionally, emerging evidence suggests that Nrg-4 may modulate hepatocyte apoptosis by suppressing JNK and NF- $\kappa$ B inflammatory signaling. Tian et al. demonstrated reduced hepatocyte apoptosis and improved liver histology in Nrg-4-treated animals with metabolic liver disease (41). Thus, the decline in Nrg-4 seen in T2DM may render the liver more vulnerable to

inflammatory injury and impaired repair responses.

### Clinical Relevance of Nrg-4 in Newly Diagnosed T2DM

The early decline of Nrg-4 in newly diagnosed T2DM implies its potential role as a biomarker for early metabolic dysfunction. Several authors emphasize the utility of Nrg-4 in predicting metabolic risk even before overt glucose abnormalities appear. Liu et al. found that reduced Nrg-4 preceded the development of metabolic syndrome, indicating its value as a screening marker (42). Furthermore, Nrg-4 holds promise for early identification of T2DM patients at higher risk of lipid abnormalities and hepatic injury. Chen et al. observed that Nrg-4 levels predicted NAFLD severity better than alanine aminotransferase and traditional lipid markers (43). This underscores the clinical importance of including Nrg-4 in metabolic risk panels to stratify patients upon diagnosis.

Several authors have also explored Nrg-4 as a therapeutic candidate. Exogenous Nrg-4 administration in animal models not only reversed hepatic steatosis but also improved systemic insulin sensitivity, reduced inflammatory markers, and normalized lipid profiles (44). Although human trials have yet to be conducted, the promising preclinical results indicate that Nrg-4 agonists or analogues may represent future therapy for metabolic syndrome and T2DM.

### Comparison With Other Authors' Findings

Our synthesis aligns with several contemporary reviews that portray Nrg-4 as a metabolic regulator with strong anti-diabetic, anti-lipogenic, and hepatoprotective effects. Li et al. emphasized the importance of Nrg-4 in BAT-liver crosstalk and proposed that low Nrg-4 serves as a bridge linking obesity, dyslipidemia, and NAFLD (45). Similarly, Alvarez et al. highlighted the role of Nrg-4 in attenuating hepatic ER stress and reducing fibrosis markers in NAFLD, suggesting broader therapeutic potential (46). A meta-analysis by Yakar et al. concluded that Nrg-4 deficiency is consistently associated with hypertriglyceridemia, low HDL-C, elevated liver enzymes, and increased risk of NAFLD across multiple populations (47).

Furthermore, a recent systematic review by Habib et al. emphasized that individuals with newly diagnosed T2DM consistently display 20–40% lower Nrg-4 levels, and this decline is directly linked to insulin resistance severity and hepatic lipid accumulation (48).

### Overall Interpretation

Taken together, the available evidence strongly supports that Nrg-4 is a protective metabolic adipokine, and its decline in newly diagnosed T2DM contributes to dyslipidemia and liver function abnormalities.

#### Its dual roles in:

- inhibiting hepatic lipogenesis,
- reducing inflammation,
- enhancing lipid oxidation,
- and improving insulin sensitivity
- make it a unique metabolic regulator bridging BAT activity with systemic metabolic health.

The consistent associations across human observational studies, animal models, and cellular experiments highlight that Nrg-4 is not merely a biomarker but may represent a central player in metabolic disease pathogenesis.

## CONCLUSION

Nrg-4 is a promising biomarker linking adipose tissue, lipid metabolism, and liver health. Lower levels of Nrg-4 in newly diagnosed diabetics are consistently associated with dyslipidemia and elevated liver enzymes. Nrg-4 plays a protective role in metabolic regulation, making it a potential target for early diagnosis and therapeutic intervention.

### LIMITATIONS OF CURRENT KNOWLEDGE

1. Lack of longitudinal studies
2. Small, heterogeneous sample sizes
3. Variations in ELISA assay sensitivity
4. Limited ethnic diversity
5. Need for standardized metabolic cutoff values

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