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EMERGING ROLE OF NETRIN-1 IN THE PATHOPHYSIOLOGY AND COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

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Abstract

Background: *Insulin resistance, persistent hyperglycemia, and β-cell dysfunction are the hallmarks of Type 2 Diabetes Mellitus (T2DM), a metabolic disease. The molecular mediators that connect hyperglycemia to vascular damage, chronic inflammation, and metabolic dysregulation are still not fully known despite a great deal of research. According to recent research on human, Netrin-1 levels are changed in type 2 diabetes and are strongly linked to indicators of vascular problems, inflammation, insulin resistance, and endothelial dysfunction. While chronic and complex diseases have elevated levels of Netrin-1, which may be the result of compensatory or maladaptive overexpression, early-stage type 2 diabetes is frequently accompanied by lower circulating Netrin-1. According to these results, Netrin-1 has two functions: it is protective during early metabolic stress and dysregulated during chronic inflammatory injury.* ***Conclusion:*** *Netrin-1 may serve as both a* ***biomarker and modulator*** *of T2DM progression and its vascular complications. Understanding its mechanistic involvement could be a new diagnostic and therapeutic strategy aimed at mitigating inflammation and preserving endothelial integrity in diabetes.*

Keywords: *Netrin-1; T2DM; Inflammation; Insulin Resistance; Endothelial Dysfunction; Vascular Complications.*

BACKGROUND

T2DM is a progressive and metabolic disorder defined by the presence of hyperglycemia, developing through the interplay of increased hepatic glucose production, reduced secretion of insulin, and the occurrence of insulin resistance **(1)**. It is the most prevalent form of diabetes and one of the biggest non-communicable health burdens in the world, accounting for over 90% of all cases of the disease.

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According to the International Diabetes Federation (IDF) Diabetes Atlas 2023, more than 537 million adults have diabetes today, and the estimated numbers are predicted to rise to 783 million by the year 2045 **(2)**. There remains the requirement for increased comprehension of the molecular pathophysiology and improvements of early detection methods as highlighted by the sharp rise of the prevalence of the condition due to physical inactivities, obesity, and the shift of eating behaviors.

Insulin resistance, β-cell failure, oxidative stress, chronic low-grade inflammation, and endothelial damage are related mechanisms accountable for the pathophysiology of type 2 diabetes, which extends beyond the simple illness of glucose metabolism disorder **(3).** Lipotoxicity and glucotoxicity, due to chronic hyperglycemia, eliminate mitochondrial function. Microvascular and macrovascular complications, causes the greatest morbidity and mortality of diabetes patients, are the consequence of the resultant oxidative stress and lead to the activation of the inflammatory cascade, the generation of cytokines, and the depletion of endothelial function **(4).**

Even though a number of biochemical indicators are available, including insulin levels, lipid profiles, fasting plasma glucose, and HbA1c, these traditional indices only reveal metabolic dysregulation following substantial cellular damage. They overlook early subclinical alterations in inflammatory or endothelial pathways that occur before overt clinical problems **(5)**. Finding new molecular biomarkers that might shed light on the underlying pathophysiological mechanisms and act as early indicator of tissue damage and disease progression in diabetes has therefore become increasingly important.

Netrin-1, a secreted laminin-related glycoprotein that was first identified as a neuronal guidance cue during embryonic development, is an interesting molecule **(6)**. A member of the netrin protein family is called netrin-1, which gets its name from the Sanskrit word "netri," which means "one who guides.". Uncoordinated-5 (UNC5) family members of transmembrane receptors plays a critical role in directing axonal growth and cell migration in the developing nervous system. But later findings have shown that Netrin-1's role goes well beyond neurodevelopment. **(7)**

Molecular and Cellular Roles of Netrin-1

Netrin-1 is a 68 kDa glycoprotein with three laminin-type domains (VI and V repeats) and a C-terminal domain that can bind different extracellular matrix proteins and heparin **(8).** Netrin-1 exhibits context-dependent actions through its receptors, which include DCC, neogenin, and UNC5A–D. Via DCC, it can enhance cell attraction and survival, while UNC5 receptors can mediate chemorepulsion and apoptosis. Depending on receptor expression and the local microenvironment, these distinct effects enable Netrin-1 to precisely regulate tissue remodeling and inflammatory responses **(9)**.

Previous studies have demonstrated that Netrin-1 suppresses the recruitment of macrophages, inhibits leukocyte transmigration, and lowers the production of inflammatory cytokines in the endothelial and immune systems **(10).** This is achieved by downregulating nuclear factor kappa B (NF-κB) signaling and reducing the expression of pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) **(11).** Additionally, by boosting endothelial nitric oxide synthase (eNOS) activity, Netrin-1 maintains vascular homeostasis and enhances nitric oxide (NO) bioavailability **(12).** The idea that Netrin-1 acts as a molecule that guards against vascular inflammation and metabolic stress has been sparked by these findings.

Netrin-1 and Metabolic Regulation

New research links Netrin-1 to insulin signaling and metabolic homeostasis in addition to vascular biology. According to experimental research, Netrin-1 can affect adipocyte differentiation, increase glucose-stimulated insulin secretion, and modify pancreatic β-cell survival **(7).** Recombinant Netrin-1 administration enhanced insulin sensitivity and decreased systemic inflammation, indicating a

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regulatory function in glucose metabolism. On the other hand, insulin resistance was exacerbated when macrophages lacking Netrin-1 or its receptor UNC5B increased inflammatory infiltration into adipose tissue **(13).** These results establish Netrin-1 as a molecular mediator between metabolic dysfunction and immune regulation, two key mechanisms in the pathophysiology of type 2 diabetes. Its expression appears to respond dynamically to metabolic stress: low-grade chronic inflammation and oxidative damage may initially suppress Netrin-1 expression, while sustained hyperglycemia and tissue injury later trigger compensatory overexpression in an attempt to restore homeostasis **(14).**

Netrin-1 in Type 2 Diabetes Mellitus: Clinical Evidence

Interesting, but not conclusive, findings have come from human research examining the tissue and circulating levels of Netrin-1 in T2DM. Serum Netrin-1 levels have been shown to be significantly lower in early-stage or newly diagnosed type 2 diabetes, and they have a negative correlation with fasting glucose, HbA1c, and insulin resistance indices **(15).** This decrease might be the result of early endothelial dysfunction and compromised Netrin-1-mediated anti-inflammatory signaling. On the other hand, research on patients with chronic or poorly managed diabetes usually shows increased Netrin-1 levels, which are frequently linked to higher levels of inflammatory cytokines like TNF-α, IL-6, and C-reactive protein **(16).** This kind of upregulation could be a secondary compensatory reaction to vascular stress or long-term metabolic inflammation. Moreover, macrovascular diseases and diabetic microvascular complications like retinopathy and neuropathy have been connected to elevated Netrin-1 expression. **(17)**

It's interesting to note that the role of Netrin-1 appears to be dual in nature: initially, it may offer protection against inflammation and endothelial injury; however, in instances of chronic hyperglycemia, its regulation may become impaired, resulting in maladaptive remodeling and immune retention within tissues **(18).** The interpretation of Netrin-1 concentrations in diabetic populations underscores this complexity and highlights the importance of both the stage of the disease and the specific tissue context.

MATERIALS AND METHODS

This review includes studies evaluating serum Netrin-1 levels and their correlation with glycemic, inflammatory, and renal parameters in patients with T2DM. A total of seven clinical studies conducted between 2016 and 2024 were analyzed. The included studies comprised cross-sectional, case–control, and observational designs involving T2DM patients with varied disease durations, obesity status, and complications, alongside healthy controls. Sample sizes ranged from 90 to 200 participants, with both sexes represented.

All studies collected fasting venous blood samples following standard protocols. As directed by the manufacturer, serum Netrin-1 concentrations were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

Several studies also measured inflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α]), glycemic markers, lipid profiles, and vascular markers such as carotid intima-media thickness (IMT) or vascular endothelial growth factor (VEGF). Renal function parameters, including estimated glomerular filtration rate (eGFR), were assessed where applicable.

Anthropometric measurements, including body mass index (BMI), waist circumference, and blood pressure, were recorded in accordance with standard guidelines. In studies evaluating complications, participants were stratified by the presence or absence of macrovascular or microvascular manifestations, such as retinopathy or cardiovascular disease.

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Statistical analysis across the included studies were performed using appropriate parametric or non-parametric tests based on data distribution. Commonly employed methods included Pearson or Spearman correlation analysis to evaluate associations between serum Netrin-1 and clinical or biochemical variables. Group comparisons were performed using Student's t-test, one-way ANOVA with post-hoc tests, or Kruskal–Wallis analysis, as appropriate. Multivariate regression analysis were applied to identify independent predictors of serum Netrin-1 levels, and logistic regression was utilized in studies examining the relationship with macrovascular complications. In every analysis, a p-value of less than 0.05 was deemed statistically significant.

DISCUSSION

Altered Circulating Netrin-1 Levels in Type 2 Diabetes Mellitus

Early or recently diagnosed cases usually have lower levels of circulating Netrin-1, according to Liu et al. (2016), who also found a negative correlation between serum Netrin-1 and fasting glucose, HbA1c, and insulin resistance indices. **(15).** This implies that early endothelial dysfunction and compromised insulin signaling may be exacerbated by Netrin-1 loss. However, in more advanced or chronic stages, studies like Gao et al. (2021) and Kumar et al. (2022) they have found elevated levels of Netrin-1, which have a positive correlation with poor glycemic control **(19,20)** and inflammatory cytokines (IL-6, TNF-α, and CRP). This increase most likely reflects a compensatory upregulation brought on by ongoing metabolic stress and inflammation**.**

Relationship with Inflammation and Insulin Resistance

It is becoming more widely acknowledged that netrin-1 regulates metabolic inflammation. It affects the retention of macrophages in adipose tissue, which leads to chronic low-grade inflammation, which is a defining feature of insulin resistance **(13).** According to Ulu et al. (2021), obese T2DM patients had significantly higher Netrin-1 levels than non-obese diabetic and healthy controls, and these levels were strongly compared with BMI, IL-6, and HOMA-IR **(21).** This led to the idea that, depending on the receptor context, Netrin-1 has a dual function, promoting the accumulation of inflammatory macrophages in adipose depots while also having anti-inflammatory effects in endothelial tissues.

Netrin-1 and Cardiovascular Complications in T2DM

One of the main causes of diabetic cardiovascular disease is endothelial dysfunction. By preventing leukocyte adhesion and encouraging the production of nitric oxide, Netrin-1, which is expressed in vascular endothelial cells, typically preserves vascular dormancy **(11).** According to Yalcin et al. (2020), T2DM patients who presented with acute coronary syndrome (ACS) had significantly lower serum Netrin-1 levels, which may indicate depletion during acute vascular stress **(22)**.

On the other hand, Hassan et al. (2024) found that chronic T2DM patients with atherosclerotic changes had higher levels of Netrin-1, which was correlated with inflammatory markers and carotid intima-media thickness **(8).** According to this, Netrin-1 depletion is linked to acute vascular injury, while compensatory upregulation may be triggered by chronic vascular remodeling and inflammation, potentially as an adaptive measure to reduce endothelial damage.

Association with Microvascular Complications

As demonstrated by retinopathy and neuropathy, Netrin-1 also contributes to microvascular damage. In T2DM patients with both complications, Ozkul et al. (2023) discovered elevated Netrin-1, which was correlated with both HbA1c and the length of the disease **(19).** In chronically damaged microvessels, this probably represents ongoing endothelial activation and reparative signaling. These results

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support the usefulness of Netrin-1 as a dynamic biomarker that reflects the inflammatory burden and vascular status in diabetes.

Integrated Pathophysiological Model

Collectively, these findings suggest a biphasic model of Netrin-1 regulation in T2DM:

- Early Stage: Decreased Netrin-1 impairs anti-inflammatory and endothelial-protective signaling, contributing to insulin resistance and oxidative stress.
- Late Stage / Complications: Chronic metabolic inflammation induces Netrin-1 overexpression as a compensatory or maladaptive response to persistent injury.

Therefore, measuring Netrin-1 in conjunction with inflammatory and endothelial biomarkers could enhance risk stratification and early detection of vascular dysfunction in T2DM.

CONCLUSION

Netrin-1 emerges as the key molecule connecting metabolic dysfunction, inflammation, and vascular damage in T2DM. Findings reveal a biphasic trend—lowered concentrations during early disease and higher concentrations within chronic or complicated T2DM, potentially as a compensatory reaction to chronic inflammatory stress. These mechanisms involve Netrin-1 as a potential therapeutic target of insulin sensitivity and vascular integrity, as well as a marker of disease activity. Additional studies should be conducted on longitudinal expression profiling of Netrin-1 and receptor-linked signaling so that stage-specific functions are established.

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