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Role of Serum Netrin As Potential Biomarker in Diagnosis and Treatment of Type-2 Diabetes Mellitus : A Review Article

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HIGHLIGHTS

1. Serum Netrin: Emerging diabetes diagnosis marker.
2. Netrin aids in early diabetes detection.
3. Potential therapeutic target for diabetes management.
4. Biomarker improves Type-2 diabetes prognosis.
5. Enhances treatment strategies for diabetes patients.

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ABSTRACT

Diabetes is a complex metabolic syndrome prevalent worldwide, posing significant long-term health challenges. It is intricately linked to various microvascular and macrovascular complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and stroke. These complications significantly impact quality of life, longevity, and economic well-being on a global scale. The widespread nature of diabetes and its associated health issues underscores the need for effective management strategies to mitigate its impact. Addressing the progression of diabetes and its associated complications has become a paramount objective for scientific endeavors. Despite various diagnostic tools, reliable markers to predict and monitor diabetic complications' onset and advancement remain scarce. Recently, attention has turned toward Netrin as a promising biomarker for diabetes and its enduring complications. This review explores the multifaceted role of Netrin as a potential biomarker and therapeutic target in diabetes and its diverse microvascular and macrovascular complications. Additionally, it seeks to unravel the underlying mechanisms through which Netrin exerts its pharmacological effects, shedding light on the intricate pathways involved in developing and progressing diabetes and its complications. Understanding Netrin's role could pave the way for early interventions at the subclinical stage, enabling proactive measures and the assessment of responses to preventative or therapeutic interventions. Moreover, it holds the potential to drive the exploration of novel therapeutic avenues for diabetes and its complications by modulating endogenous Netrin levels and serving as surrogate endpoints for intervention studies. By focusing on Netrin, researchers hope to enhance predictive accuracy, improve patient outcomes, and ultimately reduce the global burden of diabetes and its associated health issues. This comprehensive examination of Netrin's potential could lead to significant advancements in diabetes management and treatment strategies, offering hope for better clinical outcomes.

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INTRODUCTION

Diabetes mellitus (DM) is a prevalent and long-standing metabolic disorder characterized by the continual rise in blood sugar levels. It encompasses various classifications including type 1, type 2, gestational diabetes, and other specific types arising from different causes, with type 2 diabetes being the most widespread form. The pathogenesis of diabetes is intricate, involving either inadequate insulin secretion or the emergence of insulin resistance in target tissues, often accompanied by extensive damage to pancreatic β-cells. This multifaceted nature underscores the complexity of managing and understanding the condition[1].

Origins and Prevalence of Diabetes and Associated Complications

The insensitivity to insulin and damage to pancreatic β-cells result in the failure of insulin to effectively regulate metabolic processes associated with diet. Furthermore, alterations in β-cell function trigger a series of cellular signaling events. For example, dysfunction of β-cells initiates the activation of pathways involving advanced glycation end products, diacylglycerol kinase, oxidative stress, metabolic stress, and inflammation. These alterations collectively impair β-cell function, leading to sustained elevation of blood glucose levels[2]. Once chronic hyperglycemia sets in, individuals with diabetes become highly prone to various short- and long-term complications. Short-term complications commonly encountered include ketoacidosis, hyperosmolar hyperglycemic state, and coma. In contrast, long-term complications encompass both macrovascular and microvascular issues, such as cardiovascular diseases, nephropathy, retinopathy, stroke, foot ulcers, and neuropathy. These complications contribute significantly to morbidity and mortality associated with diabetes. The increased risk of morbidity and mortality observed in diabetic patients is exacerbated by the condition's insidious onset and delayed recognition, particularly in resource-constrained regions like Africa[3].

The global incidence of diabetes is on a rapid upward trajectory, driven by factors such as an aging population, urbanization, and pervasive lifestyle changes. It was estimated that approximately 451 million individuals aged 18 to 99 worldwide were living with diabetes, a figure projected to surge to 693 million by 2045, with 90% of cases attributed to type 2 diabetes mellitus (T2DM). By 2035, the number of individuals affected by diabetes is expected to reach 592 million, with 7.7% of this population belonging to the economically productive age groups globally[4].

Individuals with diabetes mellitus (DM) face a significantly elevated risk of mortality, approximately double that of their counterparts without diabetes at the same age. Globally, diabetes ranks as the seventh leading cause of death, with a multitude of complications exacerbating its impact. These complications include lower limb amputations, visual impairment, end-stage renal disease (ESRD), birth complications, sexual dysfunction, heart disease, and stroke. (AKI) on a global scale is estimated to be as high as 30% among adults, further complicating the health outlook for individuals with diabetes. Diabetic retinopathy (DR), a condition affecting the eyes, afflicts approximately 80% of individuals diagnosed with DM[5,6].

While several studies suggest that the onset and progression of diabetes can potentially be delayed or prevented through early implementation of current treatment strategies, accurately predicting and identifying diabetic complications remains a formidable challenge. For instance, diabetic retinopathy, a common complication, lacks definitive diagnostic methods[7]. Furthermore, for complications with available diagnostic tools, their sensitivity and/or specificity often fall short. Enhancing the efficacy of diabetic management to slow the progression of diabetes requires interventions to be initiated early in the disease process, particularly targeting individuals who stand to benefit the most from therapeutic intervention[8]. To address this imperative, there is a pressing need to identify new biomarkers capable of predicting individuals at high risk of developing diabetes and its associated complications. This priority stems from the recognition that timely preventive measures can significantly mitigate the impact of diabetes on both patients and their caregivers. Given the global burden of diabetes and its complications, there is a critical demand for innovative approaches to facilitate early diagnosis and develop safe and effective treatment options. Consequently, this review aims to explore the potential role of Netrin as a novel biomarker for the early detection of diabetic complications or as a predictor of diabetic risk. Additionally, it considers the feasibility of targeting Netrin as a therapeutic target to propose new antidiabetic agents that are both safe and efficacious[9,10].

Netrin and Netrin Receptors

Netrin represents a group of extracellular proteins that share structural similarities with laminins. This family includes Netrin-1, Netrin-3, and Netrin-4, alongside dual glycosylphosphatidylinositol-attached membrane peptides known as Netrin G1 and G2, all identified in humans. Among these, Netrin-1 was among the first to be discovered and extensively characterized. Its structure consists of approximately six hundred amino acid residues, featuring an amino-terminal domain VI, followed by three laminin-type epidermal growth factor repeats (V-1, V-2, and V-3), and a carboxy-terminal domain, as depicted in **Figure 1** [11].

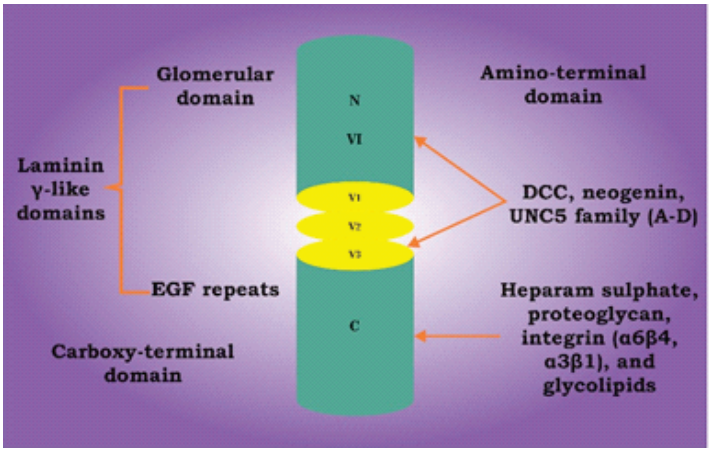

Figure 1: The principal focus is on the expression of Netrin proteins and their primary receptors, with EGF representing epidermal growth factor, UNC5 referring to uncoordinated 5, and DCC representing deleted in colorectal cancer[12]. adult pancreatic duct.

The biological functions of Netrin are predominantly mediated through two primary receptor families: deleted in colorectal cancer (DCC) receptors and uncoordinated 5 (UNC5) receptors. However, other receptors such as CD146, also known as melanoma cell adhesion molecule and Down syndrome cell adhesion molecule, may also play a role. These receptors collectively participate in diverse cellular processes regulated by Netrin, contributing to its functional versatility[12].

The DCC subfamily encompasses DCC and neogenin, which serve as key mediators of axon attraction facilitated by Netrin-1. DCC's ectodomain comprises four immunoglobulin-like (Ig-like) domains and six fibronectin type III (FNIII) domains. Specifically, the FNIII repeats of DCC facilitate interactions with Netrin-1 through its LN-LE 1–3 region. Remarkably, when this region is introduced as an Fc-fusion protein, it effectively mimics the axon outgrowth activity elicited by full-length Netrin-1. Intracellularly, DCC lacks any discernible catalytic domain but features three highly conserved motifs known as the P1–3 motifs. DCC serves as a conduit for chemotaxis in response to Netrin-1–4 and contributes to chemorepellent signaling pathways as well[13].

Neogenin, a member of the DCC family, shares approximately 50% amino acid sequence identity with DCC. Neogenin interacts with both Netrin-1 and -3 and also binds to a structurally distinct ligand called repulsive guidance molecule (RGM), which does not belong to the subset of Netrins. Although studies in zebrafish have supported the role of neogenin in mediating axonal attraction to Netrin, this function has yet to be conclusively established in mammals. In mammalian systems, neogenin has predominantly been investigated as an adhesive factor and a potential guidance receptor for RGM. In addition to their involvement in guiding axonal development, both DCC and neogenin play roles in cell-cell adhesion and tissue organization through interactions with secreted Netrins[14].

Another receptor family, UNC5, primarily facilitates axon repulsion and comprises the UNC5 A–D receptor receptors, complex. Among these receptors, UNC5B holds particular significance, especially during early blood vessel formation, where it is involved in Netrin-1-mediated angiogenesis. The extracellular domain of UNC5 consists of two immunoglobulin (Ig) domains followed by two thrombospondin type I segments. Its intracellular region includes a ZU5 domain of uncertain function, a DCC-interacting region, and a death domain associated with apoptotic signaling.UNC5 family members, alongside DCC, are referred to as dependence receptors because cell survival relies on the presence of the Netrin-1 ligand. The absence of these receptors can induce apoptosis, and the interaction between Netrin-1 and DCC significantly suppresses tumorigenesis and angiogenesis[15]. Consequently, Netrin-1 plays a pivotal role in regulating various cellular processes during embryonic development, including cell migration, cell-cell interactions, and cell-extracellular matrix adhesion in numerous tissues such as the nervous system, vasculature, pulmonary, pancreatic, and muscular systems, as well as the mammary gland. There is substantial evidence implicating Netrin in various pathological conditions, including cancer, cardiovascular disorders, and neurological diseases. Therefore, this review focuses on the role of Netrin in diabetes, particularly its involvement in micro- and macrovascular complications[16].

Netrin and its Association with Diabetes Mellitus

Netrin has traditionally been acknowledged as a guidance cue for neural development, but its influence extends beyond the nervous system to various tissues, including pancreas development. Numerous studies have highlighted Netrin's roles in tissue regeneration, angiogenesis, and suppression of inflammation. Given these diverse properties, there is growing interest in understanding Netrin's effects on β-cell function within the islets and its impact on glucose homeostasis. This review explores findings from both preclinical and clinical studies to elucidate the effects of Netrin on β-cell function and its implications for glucose regulation[17,18].

Research investigating the expression and role of Netrin-1 in regulating neuronal cell migration has utilized both fetal and adult pancreatic rats. Studies have shown transient expression of Netrin-1 mRNA in the fetal pancreas and post-ligation in the adult pancreatic duct. Interestingly, Netrin-1 expression was observed in both endocrine and exocrine cells, indicating its involvement in pancreatic morphogenesis, tissue remodeling,

and the migration and rejuvenation of islet cells. Neogenin, one of the well-known Netrin receptors, was found to be highly expressed in the pancreas, further supporting the role of Netrin-1 in these processes[19].

Additionally, investigations using human embryonic pancreatic cells demonstrated significant expression of Netrin-4 in pancreatic ductal cells and vascular endothelium. This interaction between epithelial cells, integrins α2β1 and α3β1, and Netrin-4 was associated with increased genetic expression of insulin and glucagon. Moreover, fetal pancreatic cells linked to Netrin-4 exhibited a notable downregulation of cyclins and upregulation of negative regulators of the cell cycle, suggesting a potential differentiation signal for pancreatic cells[20].

Further evaluations focused on the effects of Netrin-1 and Netrin-4 and their receptors on β-cell function, apoptosis, and proliferation. Exogenous administration of Netrin-1 and Netrin-4 in hyperglycemic states led to a downregulation of caspase-3, which was associated with decreased expression of neogenin and UNC5-A receptors. Interestingly, neogenin and UNC5 receptors promoted apoptosis in the absence of Netrin but prevented apoptosis upon interaction with Netrin, highlighting the prosurvival role of Netrin in β-cells.In a separate study comparing adipose tissue gene expression in mice fed a regular diet versus a high-fat diet (HFD), a significant increase in the expression of Netrin-1 and UNC5B was observed in HFD-fed obese mice. This heightened expression of Netrin-1 was associated with impaired adipose tissue migration and retention, exacerbating chronic inflammation, insulin resistance, and metabolic dysfunction[21].

Moreover, in diabetic mice induced by an HFD and streptozotocin (STZ), continuous administration of Netrin-1 for thirty days resulted in a stimulatory effect on insulin release from β-cells. This effect was attributed to the promotion of calcium influx and the cAMP signaling pathway, similar to neuronal axon growth and guidance cone response. Additionally, a hypoglycemic effect of Netrin-1 was observed, potentially due to enhanced β-cell function, as evidenced by increased levels of insulin and pre-proinsulin mRNA expression. Moreover, intensified islet vascularization and reduced islet macrophage infiltration were detected[22].

A recent clinical investigation led by Jung et al. suggests that Netrin-1 might serve as a novel biomarker for the early detection of impaired fasting glucose (IFG) or type 2 diabetes mellitus (T2DM). In their study, they observed a significant elevation in serum Netrin-1 levels among subjects with IFG or T2DM compared to the control group. Moreover, the study found that serum Netrin-1 levels exhibited significant positive correlations with markers of glycemic control such as fasting glucose, HbA1c, and homeostasis model assessment of insulin resistance (HOMA-IR), as well as with markers of liver function including aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[23]. Conversely, an inverse correlation was noted between serum Netrin-1 levels and high-density lipoprotein (HDL) cholesterol levels and estimated glomerular filtration rate (eGFR). Furthermore, serum Netrin-1 was identified as an independent predictor of the presence of IFG or T2DM. In contrast, a separate clinical investigation conducted by Liu et al. involved 56 human subjects, where 30 individuals newly diagnosed with type 2 diabetes were allocated to the treatment group, while the remaining served as controls. Their findings presented a different perspective, showing a significant reduction in Netrin-1 levels among diabetic patients compared to healthy controls. Additionally, the study revealed an inverse relationship between Netrin-1 levels and markers of insulin resistance (such as HOMA-IR) and glycemic control (fasting and post-meal plasma glucose, fasting insulin, triglycerides, and HbA1c levels) [24,25].

These two clinical studies present contradictory findings regarding the association between Netrin-1 levels and diabetes mellitus. This discrepancy underscores the need for further investigation to elucidate the precise nature of the relationship between Netrin-1 and diabetes, considering factors such as disease progression, patient characteristics, and potential confounding variables. Additional research in this area is crucial for better understanding the diagnostic and therapeutic implications of Netrin-1 in diabetes management[26].

Netrin and Retinopathy

Diabetic retinopathy (DR) stands out as one of the most prevalent microvascular complications observed in individuals with hyperglycemia, occurring when the delicate blood vessels within the retina undergo impairment. These vessels may become swollen and leaky or may become occluded, preventing the passage of blood. DR is characterized by the specific loss of pericytes, which contributes to increased blood vessel permeability and the development of new blood vessels, a process known as retinal neovascularization. This condition is a significant cause of visual impairment, primarily through macular edema and vitreous hemorrhage. The accumulation of plasma glucose in diabetic individuals damages the microvasculature and elevates the levels of inflammatory mediators, such as prostaglandin E2, by activating the NFκB factor in the retina. These changes culminate in vision loss and potentially permanent blindness in diabetic patients if prompt interventions are not undertaken[27].

A decrease in oxygen supply and ischemia are the underlying factors driving pathological neovascularization. Prolonged hyperglycemia in diabetic individuals can lead to inadequate blood supply, resulting in breakdown of the blood-retina barrier, heightened vascular permeability, and avascularity. Consequently, numerous angiogenic cytokines, including hypoxia-inducible factors (HIFs), vascular endothelial growth factor (VEGF), and erythropoietin, are overexpressed to increase blood flow to ischemic tissue, enhance vascular permeability, and maintain tissue perfusion pressure. Retinal neovascularization may also manifest in various ocular conditions other than diabetic retinopathy, such as retinopathy of prematurity and secondary neovascular glaucoma[28].

Despite being a prominent complication of diabetes and a leading cause of blindness in diabetic patients, there is currently no known biomarker that can reliably indicate the onset or sever-

-ity of retinopathy in individuals with diabetes mellitus (DM). However, emerging evidence suggests that neural guidance and their receptors, such as ephrins, Netrin, and semaphorins, play crucial roles as angiogenic regulators. Studies have shown that Netrin-1, in particular, can induce a proangiogenic phenotype in endothelial cells and promote developmental and therapeutic neovascularization. Additionally, Netrin-1 is involved in guiding retinal ganglion cell axons out of the eye and into the optic nerve, closing the
optic fissure during embryonic eye development, and attracting dorsal commissural interneurons when interacting with the DCC receptor[29].

Furthermore, in diabetic mice, a single subconjunctival administration of Netrin-1 has been shown to significantly accelerate the rate of corneal epithelial wound healing compared to diabetic controls. Fortunately, recent experimental and human trials have shed light on the potential role of Netrin in diabetes-induced retinopathy as both an innovative marker and a promising therapeutic target. According to the findings of these studies, alterations in the body's Netrin levels may serve as a future biomarker for detecting retinopathy at its earliest stages and assessing its severity, thereby aiding in the discovery of new drugs for this challenging disease condition[30].

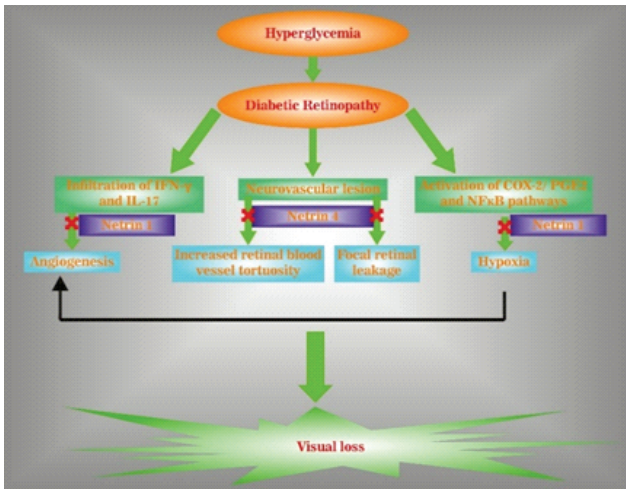

Figure 2 : The association between Netrin-1 and -4 and diabetic retinopathy[31].

Netrin and Nephropathy

Diabetic nephropathy, characterized by tubular abnormalities primarily due to changes in tubular epithelial cells, plays a pivotal role in the progression of kidney diseases, whether acute or chronic. Inflammatory responses originating from tubular epithelial cells can impact various components of the kidney, including vasculature and glomerular mesangial cells, through the release of inflammatory mediators such as cytokines, chemokines, and prostanoid metabolites[32].

These mediators contribute to hyperfiltration, matrix expansion, apoptosis, and vasodilation, further amplifying cellular damage.Acute kidney injury (AKI) represents a common manifestation of nephropathy, characterized by a rap-

-id decline in renal function within 48 hours, resulting in the inability to maintain electrolyte, acid-base, and fluid balance. Diabetes emerges as a leading cause of nephropathy, and both animal and human studies suggest that inflammation plays a crucial role in the pathogenesis of both acute and chronic kidney diseases (CKD). Cells activate defensive mechanisms, including anti-inflammatory cytokines, neuronal guidance cues like Netrins, adenosine, and hemeoxygenase, alongside the inflammatory response to mitigate the detrimental effects of innate immune cells. However, inadequate responses or downregulation of these counteracting pathways can exacerbate inflammation and tissue injury[33].

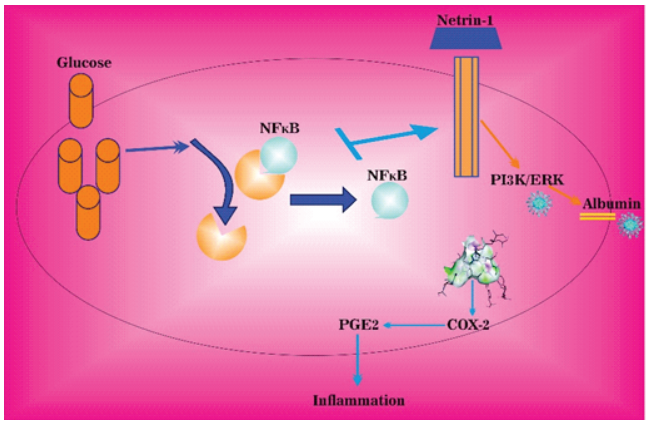

Figure 3: Netrin-1 plays a crucial role in regulating inflammation and enhancing albumin uptake in proximal tubular epithelial cells within the diabetic kidney. In conditions of hyperglycemia and oxidative stress, NF-KB is activated through the degradation of IKB.

Upon binding to the UNC5B receptor, Netrin-1 initiates downstream signaling pathways such as PI3K, ERK, and other unidentified pathways. Activation of PI3K and ERK pathways leads to increased albumin uptake by tubular epithelial cells, consequently reducing albuminuria. Additionally, Netrin-1 inhibits IKB degradation through an unidentified pathway, potentially increasing IKB expression, which in turn suppresses the release and translocation of NF-kB into the nucleus. This suppression of NF-kB activity inhibits COX-2 gene transcription, subsequently reducing the production of prostaglandin E2 (PGE2) and PGE2-mediated inflammation. By suppressing inflammation, Netrin-1 protects the kidney from damage and helps prevent the development of nephropathy[34]. Presently, the diagnosis of renal dysfunction relies on a reduction in glomerular filtration rate (GFR) and an increase in serum creatinine (Scr), often accompanied by oliguria. Diagnostic criteria such as the Acute Kidney Injury Network (AKIN) and RIFLE (Risk, Injury, Failure, Loss, and End-stage) criteria of kidney disease are utilized to classify nephropathy. Although these methods are considered reliable predictors, they lack sensitivity and specificity, especially in the early detection of AKI. Moreover, alterations in Scr and blood urea nitrogen (BUN) concentrations mainly reflect functional changes in filtration capacity rather than actual injury markers[35]. To overcome these challenges, novel biomarkers, particularly Netrin protein, are gaining attention as promising markers for detecting AKI and CKD with improved specificity and sensitivity. Netrin-1, an axon-guidance molecule, has emerged as a subject of investigation for its potential to modulate inflammation, apoptosis, and other pathological alterations in renal tubular epithelial cells. For instance, Netrin-1 exerts anti-inflammatory effects by suppressing diabetes-induced COX-2 expression and PGE2 production. This suppressive action on COX-2 is achieved through the inhibition of NFκB activation. These anti-inflammatory properties of Netrin-1 are believed not only to impact diabetic nephropathy but also to influence the progression of various microvascular diabetic complications[36].

Moreover, the reduction in albuminuria mediated by Netrin-1 involves an augmentation in albumin uptake by proximal tubular epithelial cells, facilitated through the activation of PI3k and ERK pathways. Numerous animal and human studies have consistently demonstrated a notable increase in Netrin-1 secretion in both acute and chronic kidney diseases. Notably, in line with decreased serum levels of Netrin-1, diminished expression of UNC5B mRNA and Netrin-1 has been observed in diabetic kidneys. Conversely, mice with genetically deleted UNC5B/Netrin-1 in the kidney displayed exacerbated albuminuria/proteinuria, whereas administration of recombinan t Netrin-1 significantly ameliorated diabetes-induced albuminuria and suppressed interstitial and glomerular injuries[37]. In microalbuminuric diabetic patients, serum concentrations of Netrin-1 were significantly elevated compared to both normoalbuminuric diabetic patients and the control group. The increase in plasma Netrin-1 levels correlated positively with albuminuria and negatively with estimated glomerular filtration rate (eGFR), indicating potential glomerular damage. Extensive research has been conducted to investigate the role of Netrin in various animal models of nephropathy as well as in human trials. Consistently, alterations in plasma and/or urinary levels of Netrin-1 have been observed, exhibiting an inverse relationship with albuminuria and eGFR in both animal and human studies. These findings provide valuable insights into the contribution of Netrin-1 to glomerular damage in diabetic/chemically induced nephropathy and suggest its potential as a therapeutic target for the development of novel agents aimed at mitigating acute kidney injury (AKI), chronic kidney disease (CKD), and renal fibrosis[38].

Diabetic Neuropathy and Netrin

Diabetic neuropathy (DN) stands as one of the most prevalent microvascular complications associated with diabetes mellitus (DM). Population-based studies have indicated that more than half of patients diagnosed with either type 1 or type 2 diabetes develop DN, with approximately 30% of cases being painful. Neuropathic complications may manifest as autonomic or sensory dysfunctions, affecting various systems such as the peripheral, gastrointestinal, and genitourinary systems. Sensory complications often present as numbness, paresthesia, and tingling sensations in the extremities, which can exacerbate serious foot ulceration in diabetic individuals and may ultimately lead to amputation. Autonomic complications, on the other hand, can include postural hypotension, sexual dysfunction, bladder dysfunction, and gastrointestinal disturbances[39].

The elevation of blood sugar levels plays a pivotal role in the progression and development of diabetic neuropathy, with one of its mechanisms involving neural degeneration through increased oxidative stress. Metabolic abnormalities and oxidative stress disrupt the normal functioning of glial cells, contributing to neuropathic symptoms. Mechanical allodynia, a condition characterized by pain from normally non-painful stimuli, may arise due to abnormal development of myelinated afferent fibers in the spinal dorsal horn, which can be associated with postherpetic neuralgia and peripheral nerve damage. Additionally, spinal cord injury can induce central sprouting of Aβ afferents and neuropathic hyperalgesia[40].

Early intensive glucose control has been demonstrated to reduce the risk of neuropathic complications, emphasizing the importance of early metabolic regulation. Novel biomarkers, such as ephrins, slits, semaphorins, and netrins, have shown promising effects on clinical outcomes by aiding in earlier identification and management of neuropathy. Among these axonal guidance proteins, Netrin-1 stands out for its enduring chemoattractive capacity, particularly in enriching axonal extension, and its heightened expression in the adult nervous system following nerve damage[41].

Studies by Dun and Parkinson have elucidated the pivotal role of Netrin-1 in promoting Schwann cell proliferation, peripheral nenerves and functional recovery[18]. Further investigations by Lee et al. have demonstrated that UNC5B, a receptor for Netrin--1 is crucial for Netrin-1-induced proliferation of Schwann cells,

highlighting the potential of Netrin-1 as an endogenous trophic factor for Schwann cells in injured peripheral nerves[42]. Similarly, Wu et al. explored the functional role of Netrin-1 in mechanical allodynia and the sprouting of myelinated afferent fibers in postherpetic neuralgia (PHN) and neuropathic pain induced by resiniferatoxin (RTX). Their findings revealed increased Netrin-1 expression follow-ing spinal cord injury and RTX treatment, with RTX significantly amplifying Netrin-1 expression in the spinal dorsal horn. Notably, this effect was antagonized by a transient receptor potential vanilloid 1 (TRPV1) antagonist, suggesting the involvement of TRPV1 in regulating Netrin-1 expression in neuropathic pain conditions [43].

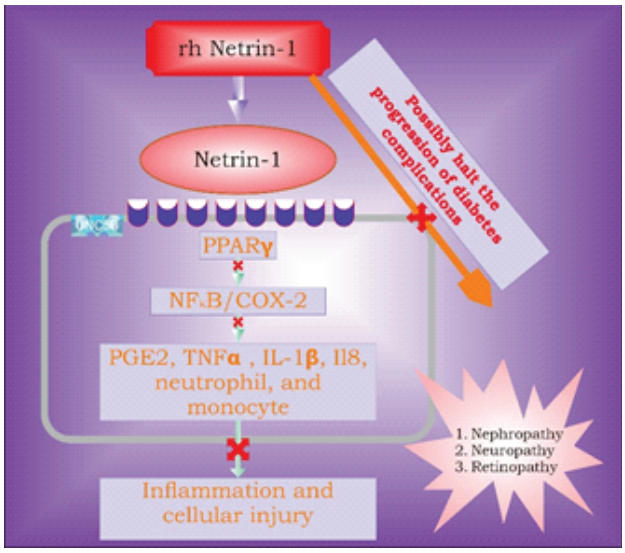

Figure 4: The diagram presents a conceptual framework outlining the potential molecular pathway through which recombinant human Netrin-1 (rhNetrin-1) exerts its anti-inflammatory effects, primarily mediated via UNC5B receptor engagement.

This mechanism intersects with several well-known inflammatory signaling pathways, indicating a multifaceted approach to inflammation regulation. Notably, rhNetrin-1 appears to modulate the activity of common inflammatory mediators such as prostaglandin E2 (PGE2) and tumor necrosis factor (TNF), suggesting its ability to intervene in key processes underlying inflammation. Furthermore, rhNetrin-1 may influence cyclooxygenase (COX) activity, thereby impacting prostaglandin synthesis, and may also interact with peroxisome proliferator-activated receptors (PPARs), known regulators of inflammation. These interactions collectively highlight the potential of rhNetrin-1 to mitigate inflammatory responses, offering insights into its prospective role in attenuating the progression of diabetic microvascular complications[12,43,44].

Netrin and Cardiovascular Diseases

Among the macrovascular complications associated with diabetes, cardiovascular disorders stand out as the most significant sequelae. It's observed that a considerable number of diabetic patients succumb to various cardiovascular diseases (CVDs), including coronary artery disease (CAD), cerebrovascular disorders, peripheral vascular illnesses, and stroke. Among these CVDs, the majority of mortality cases are attributed to CAD, primarily stemming from atherosclerosis.In recent years, Netrin-1 has garnered attention for its potential role in atherosclerosis, ischemia/reperfusion injury, and angiogenesis, wherein it may act as a cardioprotective peptide[45]. However, its precise role in these disorders, whether protective or deleterious, remains a subject of debate.

The identification of DCC and UNC5-binding sites on cell types beyond neurons has led to the proposition that Netrin-1 might have additional functions outside the central nervous system (CNS). Over the past decade, it has become increasingly evident that Netrin-1 participates in various biological processes, ranging from angiogenesis to inflammatory responses, thereby emerging as a promising novel pharmacologic target for CVDs'[46]. In recent years, numerous studies, both animal and human-based, have been conducted to elucidate the role of Netrin in various CVDs, exploring its potential as an investigative biomarker and therapeutic target by modulating associated pathophysiological mechanisms. Based on the findings of these studies, Netrin holds promise as a potential biomarker for the early detection of diabetes-related CVDs and associated conditions[47,48].

Role of Netrin-1 in Angiogenesis

Angiogenesis, the physiological process of generating new blood vessels from pre-existing ones, is primarily observed during embryonic development but also occurs in adults during processes such as the ovarian cycle and normal tissue repair.Intriguingly, blood vessels and nerves often share similar pathways, suggesting the possibility of utilizing common signals to induce both vascularization and innervation. The vascular endothelium plays a crucial role in regulating vascular smooth muscle tone by increasing the production of nitric oxide, an endogenous vasodilator[49]. Dysfunction of the vascular endothelium (VED)) is a significant factor in the development of vascular complications associated with diabetes. Decreased availability of L-arginine due to increased arginase activity in

diabetes can lead to uncoupling of nitric oxide synthase (NOS), excessive generation of reactive oxygen species (ROS), decreased nitric oxide levels, and VED[50]. Studies have shown that Netrin-1 enhances proliferation, promotes cell migration, and facilitates the connection between endothelial cells and vascular smooth muscle cells, exhibiting effects similar to those of vascular endothelial and platelet-derived growth factors. The mechanism by which Netrin-1 promotes angiogenesis has also been elucidated: Netrin-1-mediated angiogenesis is facilitated by nitric oxide (NO), and NO induction involves extracellular signal-regulated kinase (ERK) 1/2 and the DCC receptor. Activation of DCC receptors in endothelial cells initiates this process. Conversely, the introduction of NO scavengers or antibodies to DCC inhibits Netrin-1-induced angiogenesis in endothelial cells[51].

Expression of Netrin-1 in Atherosclerosis

Atherosclerosis is a pathological condition characterized by the accumulation of fatty substances within the arterial walls, eventually leading to artery blockage. It involves a progressive inflammatory process, lipid deposition, and fibrosis. The inflammatory response in arteries begins with the retention of plasma LDL (low-density lipoprotein) beneath the endothelium, which becomes oxidatively modified and attracts monocytes. Unlike other inflammatory conditions, inflammati on in atherosclerosis tends to persist, leading to the presence of cholesterol-laden macrophages within the arterial wall. These macrophages, also known as foam cells, play a key role in plaque formation by recruiting additional leukocytes and vascular smooth muscle cells, thereby contributing to plaque instability[52].

Several studies have investigated the role of Netrin protein in inhibiting the migration of monocytes, neutrophils, and lymphocytes through the UNC5B receptor. Netrin-1 is predominantly produced by macrophage foam cells, as observed in both in vitro and in vivo models, as well as in atherosclerotic lesions. These studies have demonstrated that Netrin-1 expression by foam cells regulates the cellular composition of atherosclerotic plaques. Specifically, Netrin-1 inhibits macrophage migration and promotes the chemotaxis of coronary artery smooth muscle cells. Additionally, Netrin-1 significantly reduces the recruitment of leukocytes into the vascular wall during atherosclerosis. Conversely, the absence or inhibition of Netrin-1 by proatherogenic factors has been shown to increase leukocyte adhesion to the endothelium[53].

Role of Netrin-1 in Hypertension and Ischemic Heart Disease

Hypertension (HTN) is a prevalent cardiovascular disorder disorder characterized by persistently elevated arterial blood pressure. Poorly controlled diabetes can lead to structural and functional abnormalities in the kidneys, including hyperfiltration with glomerular hypertension, renal hypertrophy, thickening of the glomerular basement membrane, tubular atrophy, and interstitial fibrosis. These changes contribute to the development of proteinuria and exacerbate systemic hypertension. Despite current therapies ai--med at blocking the renin-angiotensin system, protection against the progression of these conditions remains limited. The presence of hypertension as a comorbidity in diabetic patients also increases the risk of various microvascular complications such as diabetic nephropathy and macrovascular complications like stroke. Several endogenous molecules are being investigated for their potential role in early detection and treatment of these conditions, with particular emphasis on the involvement of Netrin in hypertension[54].

Ischemic heart disease (IHD) refers to a condition characterized by a reduced supply of oxygen and inadequate blood flow to the myocardium due to narrowing or obstruction of the coronary artery. This can manifest as acute coronary syndrome (ACS), encompassing unstable angina, non–ST-segment elevation or ST-segment elevation myocardial infarction (MI), chronic stable exertional angina, asymptomatic ischemia, or ischemia caused by coronary artery vasospasm. Reperfusion therapy is the primary approach for reducing infarct size and improving outcomes in patients, particularly those with ST-segment elevation myocardial infarction[55]. However, despite restoring coronary blood flow, reperfusion therapy can paradoxically lead to further myocardial injury, termed reperfusion injury. This phenomenon involves various factors, including oxidative stress, intracellular calcium accumulation, rapid normalization of pH, inflammatory response, and activation of mitochondrial permeability transition opening.Supplementation with exogenous Netrin-1 has demonstrated cardioprotective effects against ischemia/reperfusion (I/R) injury by increasing nitric oxide (NO) levels through the DCC/ERK1/NOS/DCC signaling pathway[56]. Netrin-1 has also shown to improve myocardial infarction in diabetic animal models and mitigate I/R-induced cardiac mitochondrial dysfunction by reducing NADPH oxidase activity and restoring NO levels. Additionally, Netrin-1 treatment has been found to reduce autophagy in a coronary ligation model of myocardial infarction[57,58].

Role of Netrin-1 in Ischemic Stroke

Ischemic strokes occur due to the blockage of a cerebral artery either by local clot formation or the presence of emboli. While atherosclerosis, particularly in the cerebral vasculature, is a leading cause of ischemic stroke, about 30% of cases remain cryptogenic. Emboli can originate from both intra- and extracranial arteries, including the aortic arch, or from cardiac sources, such as in conditions involving the heart. Cardiogenic embolisms are suspected in patients with concurrent atrial fibrillation, valvular heart disease, or other heart conditions predisposing to clot formation[59, 60].

Genetic variations in synaptic plasticity-associated genes have been observed, which may influence the development of stroke and the recovery of functionality post-stroke. Netrin-1, along with its receptor NGL-1, plays a crucial role in promoting neurite outgrowth, regulating synapse formation, and balancing excitatory and inhibitory responses. Specifically, Netrin-1 facilitates axonal outgrowth of thalamocortical neurons, promotes excitatory synapse formation, and contributes to subdendritic branching in cortical and hippocampal regions[61].

Moreover, studies suggest that Netrin-1 is involved in immune responses, which are believed to play a significant role in the progression of ischemic stroke. Netrin-1 may serve as a guidance cue involved in immune cell communication and trafficking and is crucial in stimulating N-methyl-D-aspartate receptors, thereby influencing neuronal loss in the brain through inflammation. Furthermore, evidence suggests that Netrin-1 may inhibit leukocyte chemotaxis in microglia, indicating its potential clinical implications in various central nervous system (CNS) disorders, warranting further comprehensive evaluation. Another study revealed that Netrin-1 and its receptors, DCC and UNC5H2, were overexpressed in the infarct/peri-infarct zone of an ischemic adult brain. UNC5H2 levels were notably elevated in neurons in the ipsilateral ventroposterior nucleus (VPN) at 8 and 14 days post-middle cerebral artery occlusion, correlating temporally and spatially with neuronal apoptosis. In contrast, DCC expression was only minimally detected. This suggests that in secondary neuronal death following primary brain ischemia, UNC5H2, rather than DCC, plays a primary role[62-64].

CONCLUSION

While diabetes mellitus and its associated complications have been addressed through various diagnostic criteria and medication classes, the incidence of morbidity and mortality related to diabetes has risen significantly. To address these challenges, early detection and treatment of diabetes mellitus and its micro- and macrovascular complications are crucial for effective management. Netrin, a laminin-related protein involved in regulating cell migration, cell-cell interactions, and cell-extracellular matrix adhesion during embryonic development across multiple tissues such as the nervous system, vasculature, lung, pancreas, muscle, and mammary gland, has emerged as a novel biomarker and therapeutic approach for the early detection of diabetes mellitus and its associated complications.Studies involving different animal models and diabetic human subjects, either induced or naturally occurring, with various micro- and/or macrovascular complications, have shown alterations in Netrin levels under different disease conditions. However, the expression of Netrin in diabetic models has shown inconsistent results across various clinical studies, necessitating further investigation. Despite this variability, overall, Netrin levels were found to be significantly elevated earlier compared to corresponding control groups in different micro- and macrovascular complications. Therefore, a comprehensive understanding of these pathological changes is imperative to harness Netrin as a novel biomarker and potential therapeutic target for the early detection and management of diabetes mellitus and its related complications. Moreover, a thorough identification of Netrin's substrates is essential for a better comprehension of its signaling cascades, which could elucidate the complex intracellular signaling networks in various scenarios. Further analysis of Netrin expression in diabetes and its associated complications will provide insights into the underlying biological mechanisms and potential therapeutic applications.

ABBREVIATIONS

Here are the rewritten, paraphrased, and elaborated definitions of the provided acronyms:

1. ACS: Acute coronary syndrome-ACS refers to a spectrum of conditions resulting from decreased blood flow to the heart muscles, including unstable angina and myocardial infarction (heart attack).
2. AKI: Acute kidney injury-AKI is a sudden loss of kidney function, typically characterized by a rapid increase in serum creatinine levels or a reduction in urine output.
3. BUN: Blood urea nitrogen - BUN is a measure of the amount of urea nitrogen found in the blood and is used to assess kidney function.
4. CABG: Coronary artery bypass grafting-CABG is a surgical procedure used to treat coronary artery disease by bypassing blocked or narrowed coronary arteries with healthy blood vessels from other parts of the body.
5. CAD: Coronary artery disease-CAD is a condition characterized by the narrowing or blockage of the coronary arteries, which supply blood to the heart muscle, often leading to chest pain (angina) or heart attack.
6. CKD: Chronic kidney disease-CKD is a long-term condition where the kidneys gradually lose function over time, often leading to end-stage renal disease (ESRD) if left untreated.
7. COX: Cyclooxygenase - COX is an enzyme involved in the production of prostaglandins, which play a role in inflammation and pain.
8. CVD: Cardiovascular disease-CVD refers to a group of conditions affecting the heart and blood vessels, including coronary artery disease, hypertension, and stroke.
9. DCC: Deleted in colorectal cancer receptors-DCC receptors are involved in cell signaling and have been implicated in various biological processes, including cancer development and neuronal guidance.
10. DM: Diabetes mellitus - DM is a chronic metabolic disorder characterized by high blood sugar levels due to either insufficient insulin production or the body's inability to respond effectively to insulin.
11. DN: Diabetic neuropathy - DN is a type of nerve damage that can occur in people with diabetes, leading to symptoms such as numbness, tingling, and pain in the extremities.
12. DR: Diabetic retinopathy-DR is a complication of diabetes that affects the eyes, causing damage to the blood vessels in the retina and potentially leading to vision loss.
13. EndoMT: Endothelial-to-mesenchymal transition-EndoMT is a biological process where endothelial cells, which line blood vessels, undergo a transformation into mesenchymal cells, contributing to tissue fibrosis and other pathological conditions.
14. ESRD: End-stage renal disease-ESRD is the final stage of chronic kidney disease when the kidneys can no longer function well enough to meet the body's needs, requiring dialysis or kidney transplantation for survival.
15. HbA1c: Hemoglobin A1c-HbA1c is a measure of long-term blood glucose control, reflecting average blood sugar levels over the past 2-3 months.

16. HCD: High cholesterol diet-HCD refers to a diet high in cholesterol, which can contribute to the development of cardiovascular disease by increasing levels of LDL cholesterol in the blood.
17. HIF-1α: Hypoxia-inducible factor-1α - HIF-1α is a protein that regulates cellular responses to low oxygen levels (hypoxia) and plays a key role in angiogenesis, metabolism, and cell survival.
18. I/R: Ischemia/reperfusion- I/R injury occurs when blood flow is temporarily restricted (ischemia) and then restored (reperfusion), leading to tissue damage due to oxidative stress and inflammation.
19. IHD: Ischemic heart disease-IHD is a condition characterized by reduced blood supply to the heart muscle, often due to coronary artery disease, leading to chest pain (angina) or heart attack.
20. IS: Ischemic stroke-IS occurs when blood flow to part of the brain is blocked, usually by a blood clot, leading to damage or death of brain cells.
21. KIM-1: Kidney injury molecule-1-KIM-1 is a protein that is expressed in the kidney in response to injury or stress and is used as a biomarker for acute kidney injury.
22. MI: Myocardial infarction-MI, commonly known as a heart attack, occurs when blood flow to part of the heart muscle is blocked, leading to tissue damage or cell death.
23. NGAL: Neutrophil gelatinase-associated lipocalin - NGAL is a protein that is produced by neutrophils and other cells in response to inflammation and is used as a biomarker for kidney injury.
24. NHE3: Na+/H+ exchanger isoform 3-NHE3 is a protein involved in the regulation of sodium and hydrogen ion exchange across cell membranes, playing a role in the maintenance of cellular pH and electrolyte balance.
25. NOS: Nitric oxide synthase-NOS is an enzyme that produces nitric oxide (NO), a molecule involved in various.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this review, as it does not involve any commercial or financial affiliations that could create a conflict of interest.

REFERENCES

1. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna journal of medicine. 2020;10(4):174-88.
2. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Current diabetes reviews. 2013;9(1):25-53.
3. Fayfman M, Pasquel FJ, Umpierrez GE. Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. The Medical clinics of North America. 2017;101(3):587-606.
4. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Resu-
-lts from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes research and clinical practice. 2019;157:107843.
5. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, et al. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edit ion. Diabetes research and clinical practice. 2020;162:1080 86.
6. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complication s. Physical therapy. 2008;88(11):1254-64.
7. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England journal of medicine. 1993;329(14):977-86.
8. Sugandh F, Chandio M, Raveena F, Kumar L, Karishma F, Khuwaja S, et al. Advances in the Management of Diabetes Mellitus: A Focus on Personalized Medicine. Cureus. 2023;15(8):e43697.
9. Ortiz-Martínez M, González-González M, Martagón AJ, Hlavinka V, Willson RC, Rito-Palomares M. Recent Developments in Biomarkers for Diagnosis and Screening of Type 2 Diabetes Mellitus. Current diabetes reports. 2022;22(3):95-115.
10. Dorcely B, Katz K, Jagannathan R, Chiang SS, Oluwadare B, Goldberg IJ, et al. Novel biomarkers for prediabetes, diabetes, and associated complications. Diabetes, metabolic syndrome and obesity : targets and therapy. 2017;10:345-61.
11. Rajasekharan S, Kennedy TE. The netrin protein family. Genome biology. 2009;10(9):239.
12. Yimer EM, Zewdie KA. Netrin as a Novel Biomarker and Its Therapeutic Implications in Diabetes Mellitus and Diabetes-Associated Complications. 2018;2018:8250521.
13. Finci L, Zhang Y, Meijers R, Wang JH. Signaling mechanism of the netrin-1 receptor DCC in axon guidance. Progress in biophysics and molecular biology. 2015;118(3):153-60.
14. Villanueva AA, Sanchez-Gomez P, Muñoz-Palma E. The Netrin-1-Neogenin-1 signaling axis controls neuroblastoma cell migration via integrin-β1 and focal adhesion kinase activation. 2021;15(1):58-73.
15. Larrivée B, Freitas C, Trombe M, Lv X, Delafarge B, Yuan L, et al. Activation of the UNC5B receptor by Netrin-1 inhibits sprouting angiogenesis. Genes & development. 2007;21(19):2433-47.
16. Claro V, Ferro A. Netrin-1: Focus on its role in cardiovascular physiology and atherosclerosis. 2020;9:2048004020959574.
17. Moore SW, Tessier-Lavigne M, Kennedy TE. Netrins and their receptors. Advances in experimental medicine and biology. 2007;621:17-31.
18. Dun XP, Parkinson DB. Role of Netrin-1 Signaling in Nerve Regeneration. International journal of molecular sciences. 2017;18(3).
19. De Breuck S, Lardon J, Rooman I, Bouwens L. Netrin-1 expr-

-ession in fetal and regenerating rat pancreas and its effect on the migration of human pancreatic duct and porcine islet precursor cells. Diabetologia. 2003;46(7):926-33.

20. Yebra M, Diaferia GR, Montgomery AM, Kaido T, Brunken WJ, Koch M, et al. Endothelium-derived Netrin-4 supports pancreatic epithelial cell adhesion and differentiation through integrins α2β1 and α3β1. PLoS One. 2011;6(7):e22750.
21. Zewdie KA, Ayza MA. Targeting Netrin-1 and -4 as a Novel Diagnostic Parameter and Treatment Option for Diabetic Retinopathy. 2020;14:1741-7.
22. Wu J, Yan LJ. Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity. Diabetes, metabolic syndrome and obesity : targets and therapy. 2015;8:181-8.
23. Behnoush AH, Khalaji A. Urinary and circulatory netrin-1 as biomarker in diabetes and its related complications: a systematic review and meta-analysis. 2023.
24. Nedeva I, Gateva A, Assyov Y, Karamfilova V, Velikova T, Kamenov Z. Relationship between circulating netrin-1 levels, obesity, prediabetes and newly diagnosed type 2 diabetes. Archives of physiology and biochemistry. 2022;128(6):1533-8.
25. Yim J, Kim G, Lee BW, Kang ES, Cha BS, Kim JH, et al. Relationship Between Circulating Netrin-1 Concentration, Impaired Fasting Glucose, and Newly Diagnosed Type 2 Diabetes. Frontiers in endocrinology. 2018;9:691.
26. Inderjeet K, Adole PS, Vinod KV, Pillai AA. Association between serum netrin-1, netrin-4 and risk of the acute coronary syndrome in patients with type 2 diabetes mellitus-A pilot study. Indian heart journal. 2022;74(1):72-5.
27. Wong TY, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nature reviews Disease primers. 2016;2:16012.
28. Costa PZ, Soares R. Neovascularization in diabetes and its complications. Unraveling the angiogenic paradox. Life sciences. 2013;92(22):1037-45.
29. Kropp M, Golubnitschaja O. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications-risks and mitigation. 2023;14(1):21-42.
30. Jenkins AJ, Joglekar MV, Hardikar AA, Keech AC, O'Neal DN, Januszewski AS. Biomarkers in Diabetic Retinopathy. The review of diabetic studies : RDS. 2015;12(1-2):159-95.
31. Zewdie KA, Ayza MA, Amare Tesfaye B, Yimer EM. Targeting Netrin-1 and -4 as a Novel Diagnostic Parameter and Treatment Option for Diabetic Retinopathy. Clinical Ophthalmology. 2020;14(null):1741-7.
32. Yu SM, Bonventre JV. Acute Kidney Injury and Progression of Diabetic Kidney Disease. Advances in chronic kidney disease. 2018;25(2):166-80.
33. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. The Clinical biochemist Reviews. 2016;37(2):85-98.
34. Mohamed R, Jayakumar C, Ranganathan PV, Ganapathy V, Ramesh G. Kidney proximal tubular epithelial-specific overexpression of netrin-1 suppresses inflammation and albuminuria through suppression of COX-2-mediated PGE2 production in streptozotocin-induced diabetic mice. The American journal of pathology. 2012;181(6):1991-2002.
35. Goyal A, Daneshpajouhnejad P, Hashmi MF, Bashir K. Acute Kidney Injury. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Parnaz Daneshpajouhnejad declares no relevant financial relationships with ineligible companies. Disclosure: Muhammad Hashmi declares no relevant financial relationships with ineligible companies. Disclosure: Khalid Bashir declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

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36. Bucsics T, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. Gastroenterology report. 2017;5(2):127-37.
37. Wang W, Reeves WB, Ramesh G. Netrin-1 increases proliferation and migration of renal proximal tubular epithelial cells via the UNC5B receptor. American journal of physiology Renal physiology. 2009;296(4):F723-9.
38. Ay E, Marakoğlu K, Kizmaz M, Ünlü A. Evaluation of Netrin-1 Levels and Albuminuria in Patients With Diabetes. Journal of clinical laboratory analysis. 2016;30(6):972-7.
39. Quiroz-Aldave J, Durand-Vásquez M, Gamarra-Osorio E, Suarez-Rojas J, Jantine Roseboom P, Alcalá-Mendoza R, et al. Diabetic neuropathy: Past, present, and future. Caspian journal of internal medicine. 2023;14(2):153-69.
40. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, et al. Diabetic neuropathy. Nature reviews Disease primers. 2019;5(1):42.
41. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52(11):2288-98.
42. Lee HK, Seo IA, Seo E, Seo SY, Lee HJ, Park HT. Netrin-1 induces proliferation of Schwann cells through Unc5b receptor. Biochemical and biophysical research communicati ons.2007;362(4):1057-62.
43. Wu CH, Yuan XC, Gao F, Li HP, Cao J, Liu YS, et al. Netrin-1 Contributes to Myelinated Afferent Fiber Sprouting and Neuropathic Pain. Molecular neurobiology. 2016;53(8):564 0-51.
44. Ranganathan P, Jayakumar C, Ramesh G. Proximal tubule-specific overexpression of netrin-1 suppresses acute kidney injury-induced interstitial fibrosis and glomerulosclerosis through suppression of IL-6/STAT3 signaling. American Journal of Physiology-Renal Physiology. 2013;304(8): F105 4-F65.
45. Huang D, Refaat M. Macrovascular Complications in Patients with Diabetes and Prediabetes. 2017;2017:7839101.
46. Ahn EH, Kang SS, Ye K. Netrin-1/receptors regulate the pathogenesis in Parkinson's diseases. Precis Future Med. 2021;5(2):50-61.
47. Llambi F, Causeret F, Bloch-Gallego E, Mehlen P. Netrin-1 acts as a survival factor via its receptors UNC5H and DCC.

The EMBO journal. 2001;20(11):2715-22.

48. Kruger RP, Lee J, Li W, Guan KL. Mapping netrin receptor binding reveals domains of Unc5 regulating its tyrosine phosphorylation. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2004;24(48):10826-34.
49. Tahergorabi Z, Khazaei M. A review on angiogenesis and its assays. Iranian journal of basic medical sciences. 2012;15(6):1110-26.
50. Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. International journal of vascular medicine. 2012;2012:918267.
51. Park KW, Crouse D, Lee M, Karnik SK, Sorensen LK, Murphy KJ, et al. The axonal attractant Netrin-1 is an angiogenic factor. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(46):16210-5.
52. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. International journal of preventive medicine. 2014;5(8):927-46.
53. Ziegon L, Schlegel M. Netrin-1: A Modulator of Macrophage Driven Acute and Chronic Inflammation. 2021;23(1).
54. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. Advances in chronic kidney disease. 2011;18(1):28-41.
55. Dababneh E, Goldstein S. Chronic Ischemic Heart Disease Selection of Treatment Modality. StatPearls. Treasure Island (FL) ineligible companies.
56. Araszkiewicz A, Grygier M, Lesiak M, Grajek S. The impact of ischemia-reperfusion injury on the effectiveness of primary angioplasty in ST-segment elevation myocardial infarction. Postepy w kardiologii interwencyjnej = Advances in interventional cardiology. 2013;9(3):275-81.
57. Jensen RV, Hjortbak MV, Bøtker HE. Ischemic Heart Disease: An Update. Seminars in nuclear medicine. 2020;50(3):195-207.
58. Severino P, D'Amato A, Pucci M. Ischemic Heart Disease Pathophysiology Paradigms Overview: From Plaque Activation to Microvascular Dysfunction. 2020;21(21).
59. Arboix A, Alio J. Acute cardioembolic cerebral infarction: answers to clinical questions. Current cardiology reviews. 2012;8(1):54-67.
60. Huang JC, Bhaskar SMM. Clot Morphology in Acute Ischemic Stroke Decision Making. 2022;23(20).
61. Luo Y, Liao S, Yu J. Netrin-1 in Post-stroke Neuroprotection: Beyond Axon Guidance Cue. Current neuropharmacology. 2022;20(10):1879-87.
62. Ly NP, Komatsuzaki K, Fraser IP, Tseng AA, Prodhan P, Moore KJ, et al. Netrin-1 inhibits leukocyte migration in vitro and in vivo. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(41):14729-34.
63. Yu J, Li C, Ding Q, Que J, Liu K, Wang H, et al. Netrin-1 Ameliorates Blood-Brain Barrier Impairment Secondary to Ischemic Stroke via the Activation of PI3K Pathway. Frontiers in neuroscience. 2017;11:700.
64. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death & Differentiation. 2018;25(3):486-541.