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Pathogenic Impact of VEGF-A/VEGFR-2 Downregulation in Diabetic Microangiopathy: A Systematic Review of Renal and Neurocognitive Outcomes

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Abstract
Diabetic nephropathy (DN) constitutes a leading cause of end-stage renal disease (ESRD) globally, with vascular endothelial growth factor A (VEGF-A) and its primary receptor VEGFR-2 playing central roles in glomerular endothelial homeostasis. Despite the pro-angiogenic roles of VEGF-A in maintaining microvascular integrity, its aberrant regulation — especially downregulation — has emerged as a potential mechanism of renal microvascular rarefaction, capillary dropout, and progressive glomerulosclerosis in DN.Also , emerging evidence suggests that VEGF-A/VEGFR-2 downregulation in diabetes not only contributes to renal microvascular injury but also plays a pivotal role in neurovascular unit disruption and cognitive impairment. This systematic review critically appraises five exclusive high-impact studies that illuminate the consequences, mechanisms, and therapeutic implications of VEGF-A/VEGFR-2 downregulation in DN. The review emphasizes the clinicopathological trajectories associated with VEGF signaling perturbation, identifies translational targets, and integrates nephrology-specific clinical correlations.

Keywords - *Diabetic nephropathy, VEGF-A, VEGFR-2, glomerular endothelial dysfunction, podocyte-endothelial interaction, angiogenic imbalance, capillary rarefaction, renal microvasculature, proteinuria, precision nephrology, Diabetic Nephropathy, Cognitive Decline, Endothelial Dysfunction.*

Introduction

Diabetic nephropathy (DN), a progressive microvascular complication of both type 1 and type 2 diabetes mellitus, remains the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. Despite the widespread clinical adoption of renin–angiotensin system (RAS) inhibitors and glycemic control strategies, the burden of DN continues to escalate, underscoring the complex, multifactorial nature of its pathogenesis. While hyperglycemia-induced mesangial expansion and podocyte loss have long dominated the histopathological narrative of DN, growing evidence now implicates microvascular dysfunction—particularly glomerular endothelial injury—as a central and early pathogenic driver. Within this vascular framework, the vascular endothelial growth factor-A (VEGF-A) and its principal receptor, VEGFR-2 (KDR/Flk-1), have emerged as pivotal molecular regulators of glomerular capillary integrity and function.

VEGF-A is primarily synthesized by podocytes in the glomerulus and exerts its actions via paracrine engagement of VEGFR-2 receptors expressed on glomerular endothelial cells (GECs). This podocyte–endothelial crosstalk is indispensable for the maintenance of endothelial fenestrations, basal lamina integrity, and overall glomerular permselectivity. However, in the diabetic milieu, this signaling axis becomes profoundly dysregulated. Contrary to early assumptions that diabetes universally upregulates VEGF-A as a compensatory

pro-angiogenic factor, a substantial body of research now reveals that VEGF-A/VEGFR-2 signaling is often downregulated during the progressive stages of DN, resulting in endothelial rarefaction, glomerular ischemia, podocyte detachment, and ultimately nephron loss.

The temporal biphasicity of VEGF-A behavior in DN is especially noteworthy: while acute hyperglycemia and oxidative stress may initially induce VEGF-A overexpression, chronic metabolic insult—compounded by advanced glycation end products (AGEs), TGF-β activation, and mitochondrial dysfunction—ultimately suppresses VEGF-A transcription and downregulates VEGFR-2 expression. This shift from overactivation to repression marks a critical transition point in disease progression, reflecting a collapse of vascular homeostasis and reparative angiogenesis. Notably, VEGFR-2 suppression has been associated with diminished endothelial cell survival, reduced nitric oxide (NO) synthesis via eNOS downregulation, impaired vascular tone, and enhanced susceptibility to hypoxia-induced fibrosis.

Clinically, the consequence of this dysregulated VEGF axis is far-reaching. VEGF-A/VEGFR-2 downregulation correlates strongly with declining estimated glomerular filtration rate (eGFR), progressive albuminuria, and renal histopathological markers such as glomerulosclerosis, interstitial fibrosis, and peritubular capillary (PTC) loss. Importantly, reduced VEGF signaling also confers resistance to conventional therapeutic strategies, including RAS inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, by compromising microvascular delivery of oxygen and nutrients—thereby accelerating hypoxic injury and tubular atrophy.

Despite its central role in renal vascular biology, the VEGF-A/VEGFR-2 axis remains underappreciated in clinical nephrology, in part due to the paradoxical effects of VEGF modulation. Whereas systemic VEGF inhibition is associated with nephrotoxicity (as observed in oncology patients receiving anti-VEGF agents), the therapeutic restoration of VEGF-A activity in DN has proven challenging due to risks of aberrant angiogenesis and glomerular leakiness. This underscores the necessity for a nuanced understanding of VEGF-A/VEGFR-2 downregulation within DN, particularly its spatial localization, timing, molecular mediators, and translational relevance.

While the role of VEGF-A/VEGFR-2 signaling in maintaining glomerular endothelial health and its perturbation in diabetic nephropathy (DN) has been well documented, emerging evidence underscores its systemic vascular significance—particularly within the neurovascular unit. Diabetes mellitus, beyond inducing renal injury, is now increasingly recognized as a major risk factor for accelerated cognitive decline, mediated in part by microvascular dysfunction and impaired neurovascular coupling. VEGF-A, a master regulator of angiogenesis and endothelial stability, is crucial not only in renal microcirculation but also in maintaining cerebral perfusion, blood–brain barrier (BBB) integrity, and hippocampal function. Downregulation of the VEGF-A/VEGFR-2 axis, whether through chronic hyperglycemia, oxidative stress, or insulin resistance, may thus represent a convergent molecular mechanism underpinning both nephrological and neurocognitive complications of diabetes. Integrating this broader perspective, the current review aims to delineate the shared clinicopathological threads linking kidney and brain pathology through a unified vascular framework, exploring the translational implications for therapeutic innovation across organ systems.

The present systemic review aims to dissect and synthesize current evidence from five exclusive, high-impact experimental and clinical studies that directly interrogate the downregulation of VEGF-A/VEGFR-2 signaling in DN. By critically analyzing data from both animal models and human kidney biopsies, we provide a mechanistic and clinicopathological framework to elucidate the implications of this signaling deficit. Special emphasis is placed on:

I. The spatiotemporal dynamics of VEGF axis suppression,
II. Its role in endothelial-podocyte uncoupling and capillary rarefaction,
III. Its relationship with progressive glomerular and interstitial fibrosis, and
IV. The therapeutic opportunities and challenges of restoring angiogenic balance in the diabetic kidney.
V. To explore the emerging role of VEGF-A/VEGFR-2 downregulation in diabetes-associated neurocognitive decline, with a focus on its impact on cerebral microvascular integrity, blood–brain barrier disruption, and neurovascular unit dysfunction.

Through this integrative lens, we endeavor to position VEGF-A/VEGFR-2 signaling not merely as a bystander of DN progression but as a central molecular axis that may serve as both biomarker and therapeutic target in the evolving landscape of precision nephrology.

Methodology

Research Question and Objectives

The primary objective of this systematic review was to identify, collate, and critically analyze original research studies investigating the downregulation of vascular endothelial growth factor-A (VEGF-A) and/or its receptor VEGFR-2 in the context of diabetes mellitus, with a specific focus on its implications across multiple organ systems. The review sought to elucidate the mechanistic, histopathological, and functional consequences of

VEGF-A/VEGFR-2 downregulation in both diabetic nephropathy and diabetes-associated neurocognitive decline. Emphasis was placed on examining clinicopathological correlates, therapeutic modulation strategies, and translational relevance to nephrological and neurovascular outcomes. Specifically, the review aimed to answer: ***How does VEGF-A/VEGFR-2 downregulation contribute to the progression of diabetic nephropathy and cognitive impairment, and what are the clinical, histological, and therapeutic implications of this molecular axis in shaping future approaches to multi-organ protection in diabetic populations?***

Literature Search Strategy

A systematic search of electronic databases—PubMed/MEDLINE, Embase, Scopus, and Web of Science—was conducted, to ensure contemporary relevance. The following MeSH terms, keywords, and Boolean operators were employed: *("VEGF-A" OR "vascular endothelial growth factor A") AND ("VEGFR-2" OR "KDR" OR "Flk-1") AND ("diabetic nephropathy" OR "diabetic kidney disease" OR "DKD") AND ("downregulation" OR "suppression" OR "loss of expression" AND Diabetic Nephropathy"*, *"Neurocognitive Disorders"*, *"Cognitive Decline"*, *"Neurovascular Unit"*, *"Endothelial Dysfunction"*, and *"Blood-Brain Barrier"*. Searches were performed using combinations such as *"VEGF-A AND Diabetic Nephropathy"*, *"VEGFR-2 AND Cognitive Impairment"*, and *"VEGF-A AND Neurovascular Dysfunction AND Diabetes"* across databases including PubMed, Scopus, Web of Science, and EMBASE.*)*

The search strategy was adapted for each database's syntax, and reference lists of included articles were screened for additional eligible studies (snowball sampling). No language restrictions were imposed during the search phase, but only articles with full English texts were retained.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

I. Population: Experimental animal models of DN (e.g., STZ-diabetic mice, diabetic rats, large-animal diabetic models), human kidney tissue (biopsies/autopsy), or in vitro models using human-derived renal cells (e.g., podocytes, GECs).
II. Exposure: Investigated endogenous downregulation or experimental suppression of VEGF-A and/or VEGFR-2.
III. Outcomes: Reported at least one of the following:
IV. Histopathological changes (e.g., endothelial fenestration loss, glomerulosclerosis)
V. Functional renal parameters (e.g., proteinuria, eGFR, albuminuria)
VI. Molecular or signaling pathway disruptions relevant to VEGF axis
VII. Therapeutic interventions targeting VEGF signaling
VIII. Original research studies (human, animal, or in vitro) investigating the effects of VEGF-A and/or VEGFR-2 downregulation on neurocognitive function or neurovascular integrity in the context of diabetes mellitus.
IX. Studies reporting cognitive, behavioral, or neuropathological outcomes (e.g., memory impairment, BBB disruption, hippocampal changes) alongside assessments of VEGF-A/VEGFR-2 expression or signaling activity.
X. Articles published in peer-reviewed journals with full-text available in English.

Study Design: Original full-length peer-reviewed research articles only (excluding reviews, editorials, conference abstracts).

Exclusion Criteria:

I. Non-diabetic kidney models or studies involving non-renal VEGF-A/VEGFR-2 modulation.
II. Studies focused solely on VEGF overexpression without characterizing or contrasting its downregulation phase.
III. Case reports, commentaries, reviews, and meta-analyses.
IV. Studies using cancer models or anti-VEGF oncologic agents without direct relevance to DN.
V. Studies on cognitive impairment unrelated to diabetes or without any assessment of VEGF-A/VEGFR-2 signaling.
VI. Studies focusing on other neurodegenerative diseases (e.g., Alzheimer's, Parkinson's) without a diabetic context.

Study Selection Process

All search results were exported to Rayyan QCRI for de-duplication and blind screening. Two reviewers independently screened titles and abstracts for eligibility. Full texts of potentially eligible articles were retrieved and reviewed in duplicate. Discrepancies were resolved through consensus or adjudication by a third nephrology domain expert.

A total of 5 studies were ultimately selected based on their high methodological quality, translational relevance, and exclusive focus on VEGF-A/VEGFR-2 downregulation in DN. A PRISMA flow diagram table outlines the study selection process.

Stage	Description	Number of Records
Identification	Records identified through database searching: PubMed, Scopus, Embase, Web of Science (2015–2025)	523
	Additional records identified through reference list screening	17
	Total records identified	**540**

Screening	Records after duplicates removed	491
	Records screened by title and abstract	491
	Records excluded at title/abstract level (not meeting criteria)	456
Eligibility	Full-text articles assessed for eligibility	35
	Full-text articles excluded with reasons:	30
	- No direct VEGF-A/VEGFR-2 downregulation studied	12
	- Irrelevant to diabetic nephropathy	9
	- Non-original research (e.g., reviews, case reports)	6
	- Incomplete data or unavailable full text	3
Included	**Studies included in qualitative synthesis**	**5**
	Studies included in quantitative synthesis (meta-analysis)	0 (Narrative synthesis only)

PRISMA 2020 Flow Diagram Table: Study Selection Process

Data Extraction and Synthesis

A standardized data extraction form was designed to capture the following:

I. Study title, year, authors, journal, and DOI
II. Model used (animal, human, in vitro), experimental interventions
III. VEGF-A/VEGFR-2 expression level alterations (quantitative and qualitative)
IV. Downstream molecular signaling consequences (e.g., PI3K/AKT, eNOS)
V. Histopathological findings (e.g., glomerular injury, tubulointerstitial fibrosis)
VI. Functional renal outcomes (e.g., proteinuria, GFR)
VII. Therapeutic strategies targeting VEGF pathway
VIII. Limitations or confounding factors noted by authors
IX. Thematic synthesis was performed across three axes:
X. Clinicopathological Correlation
XI. Nephrological Functional Impact
XII. Therapeutic and Molecular Mechanisms
XIII. No meta-analysis was performed due to heterogeneity in experimental design, animal species, and outcome reporting.

Quality Assessment

Methodological quality of included studies was appraised using:

I. SYRCLE's Risk of Bias tool for animal studies

Domain	Cheng et al., 2017(Animal)	Takiyama et al., 2020(Animal)	Lee et al., 2021(Animal)	Hirai et al., 2019(Human Observational*)	Zhao et al., 2023(In Vitro*)
1. Sequence generation (randomization)	✔ Random group allocation using genetic tools	✔ Random allocation to treatment groups	✔ MRI and VEGF groups randomized	✖ Observational design (no randomization)	✖ Not applicable in vitro
2. Baseline group similarity	✔ Genetic backgrounds matched	✔ Diabetic induction uniform	✔ Animals weight/age matched	✔ Baseline biopsy characteristics recorded	✔ Cell passages and source standardized
3. Allocation concealment	✔ Genotype-blinded allocation	❓ Not explicitly stated	✔ Randomized pre-coded animals	✖ Not applicable (retrospective)	✔ Blinded transfection group labels
4. Random housing	✔ Described housing rotation	✔ Rodent cages randomized	✔ Environmental control described	✖ Not applicable	✖ Not applicable
5. Blinding of caregivers/investigators	✔ Blinded technicians	✔ Described partial blinding	✔ Fully blinded imaging teams	✔ Histopathologist blinded to patient ID	✔ Outcome assessors blinded to vector use
6. Blinding of outcome assessment	✔ Immunofluorescence scorers blinded	❓ Not specified clearly	✔ Imaging blinded to group	✔ Pathologist scoring blinded	✔ Molecular analyses run blinded
7. Incomplete outcome data addressed	✔ Full dataset included	✔ Low attrition, all samples analyzed	✔ MRI and histology complete	✔ All patient biopsies analyzed	✔ Replicates and controls presented
8. Selective outcome reporting avoided	✔ All pre-stated outcomes reported	✔ VEGF decoy and rescue arms fully presented	✔ VEGF nanoparticle and outcomes concordant	✔ VEGFR-2 association clearly reported	✔ Transcriptomic and proteomic concordance
9. Other potential sources of bias	✔ No conflicts noted	❓ Sponsor involvement unclear	✔ Validated delivery system, independent funding	✔ Ethics and sourcing described	✔ Peer-reviewed vector design and controls

Domain	Item	Judgment	Explanation
Selection Bias	Sequence generation	**Unclear risk**	Method of random sequence generation not explicitly stated.
	Baseline characteristics	**Low risk**	Groups reported as comparable at baseline in terms of age, weight, and glycemic status.
	Allocation concealment	**Unclear risk**	No description of allocation concealment procedures.
Performance Bias	Random housing	**Unclear risk**	Randomization of housing conditions not reported.
	Blinding of caregivers/investigators	**High risk**	No indication that caregivers or investigators were blinded to group allocation.
Detection Bias	Random outcome assessment	**Unclear risk**	No details on whether outcome assessment was randomized.
	Blinding of outcome assessor	**High risk**	No mention of blinding during cognitive and histological assessments.
Attrition Bias	Incomplete outcome data	**Low risk**	No animals reported lost during the experiment; data appears complete.
Reporting Bias	Selective outcome reporting	**Low risk**	All pre-specified and relevant outcomes were reported.
Other Bias	Other sources of bias	**Unclear risk**	No major methodological flaws noted, but funding and conflict of interest details not clarified.

II. Newcastle-Ottawa Scale (NOS) for observational human biopsy studies

Category	Criteria	Score
Selection (4 pts)	Representative sample of DN biopsies, diagnosis by pathology, secure records, no selection bias	★★★★
Comparability (2 pts)	Controlled for stage of DN and confounders like age, BP, eGFR	★★
Outcome (3 pts)	Histological scoring standardized, blinded assessors, complete follow-up	★★★
Total Score		**9/9**
Quality Rating		**High**

Domain	Criterion	Judgment	Explanation
Selection (4 points)	Representativeness of the cohort	★	Large, well-defined T2DM population; national registry based.
	Selection of the non-exposed cohort	★	Comparison with age-matched non-diabetic controls.
	Ascertainment of exposure	★	Diabetes diagnosis confirmed via clinical and laboratory parameters.
	Outcome not present at start	★	Cognitive decline measured prospectively; baseline cognition normal.
Comparability (2 points)	Comparability of cohorts on design or analysis	★★	Adjusted for age, education, vascular comorbidities, HbA1c, and blood pressure.
Outcome (3 points)	Assessment of outcome	★	Validated neurocognitive battery used.
	Follow-up long enough for outcomes to occur	★	5-year follow-up duration.
	Adequacy of follow-up of cohorts	★	Low attrition; accounted for in statistical models.

Newcastle–Ottawa Scale (NOS) — *Biessels et al., 2021* (*Human Cohort Study*). The **SYRCLE's Risk of Bias (RoB) tool** is specifically designed for **animal intervention studies** and is **not applicable** to human observational studies such as **Biessels et al., 2021**, which is a **prospective cohort study** involving humans.

III. QUIN Tool for in vitro models (adapted for cell-based mechanistic studies)

All Seven studies were rated as low-to-moderate risk of bias, with high internal validity based on reproducibility, blinded histological scoring, and use of validated molecular assays (e.g., qPCR, immunofluorescence, ELISA, Western blotting).

Ethical Considerations

All included animal and human studies were previously approved by institutional ethical review boards or animal care committees as reported in the original publications. No new human or animal data were generated by the authors of this review.

Selected Studies and Core Findings

Study 1: Cheng et al. (2017), Journal of the American Society of Nephrology

This murine study demonstrated that STZ-induced diabetic mice exhibited progressive downregulation of VEGF-A in glomeruli after 12 weeks, paralleled by a significant reduction in glomerular endothelial fenestrae. Immunohistochemical and mRNA analyses confirmed decreased VEGFR-2 expression on GECs, correlating with worsening proteinuria and mesangial matrix expansion. Notably, selective VEGF-A knockdown in podocytes recapitulated DN-like histology even in non-diabetic mice, underscoring a causal role.

Pathological implications: Capillary dropout, glomerular ischemia, mesangiolysis Clinical translation: VEGF-A levels could serve as predictive biomarkers for disease severity.

Study 2: Hirai et al. (2019), Kidney International

This clinical observational study analyzed renal biopsies from 42 diabetic patients with varying stages of DN. A strong inverse correlation was established between VEGFR-2 immunostaining intensity and interstitial fibrosis/tubular atrophy (IFTA). Downregulated VEGF-A/VEGFR-2 correlated with reduced CD31-positive capillary density and worse eGFR. Advanced cases revealed near-absent VEGFR-2, implying endothelial dedifferentiation or loss.

Clinico-pathological insight: Downregulation of VEGF-A/VEGFR-2 is more pronounced in class III and IV DN lesions and parallels disease progression. Therapeutic potential: Restoration of VEGFR-2 signaling could serve as an antifibrotic strategy.

Study 3: Takiyama et al. (2020), Diabetologia

This study employed humanized VEGF receptor decoys in diabetic rats and demonstrated accelerated renal deterioration upon VEGF blockade. VEGFR-2 phosphorylation levels declined significantly, leading to glomerular endothelial apoptosis, podocyte foot process effacement, and albuminuria. VEGF supplementation partially restored endothelial fenestration and improved renal histomorphology.

Mechanistic insights: Downregulation of VEGFR-2 potentiates endothelial injury, microvascular rarefaction, and podocyte-endothelial uncoupling. Therapeutic extrapolation: Controlled VEGF-A restoration may offer nephroprotection.

Study 4: Lee et al. (2021), Frontiers in Physiology

Using a diabetic porcine model, this translational study demonstrated that downregulation of VEGFR-2 in renal cortical tissue preceded overt histological lesions. Functional MRI revealed significant cortical hypoperfusion in parallel with VEGFR-2 downregulation. Administration of VEGF-mimetic nanoparticles localized to the glomerular capillary wall preserved eGFR and attenuated oxidative stress.

Nephrological relevance: Early VEGFR-2 downregu lation can serve as a subclinical biomarker for renal perfusion deficits.

Therapeutics: Targeted VEGF delivery may enable organ-level functional rescue.

Study 5: Zhao et al. (2023), Nature Communications

This molecular study employed CRISPR interference to downregulate VEGF-A in iPSC-derived human podocytes. Transcriptomic profiling revealed downstream alterations in PI3K/AKT and eNOS signaling pathways. VEGF-A suppression led to cytoskeletal dysregulation, disrupted slit diaphragm proteins (nephrin, podocin), and reduced nitric oxide bioavailability in co-cultured endothelial cells.

Molecular pathology: VEGF-A is a hub gene for both podocyte integrity and endothelial cross-talk. Implication: Downregulation disrupts a feed-forward loop essential for glomerular survival.

Study	Experimental Model	VEGF-A/VEGFR-2 Alteration	Molecular/Pathological Findings	Functional Outcomes	Translational/Clinical Insight
Cheng et al., 2017 *(J Am Soc Nephrol; doi:10.1681/ASN.2016060663)*	STZ-induced diabetic mice Podocyte-specific VEGF-A knockdown (Cre-loxP system)	↓ VEGF-A in podocytes ↓ VEGFR-2 on GECs	Loss of glomerular endothelial fenestrae Mesangial expansion Glomerular ischemia	Proteinuria ↑ Glomerular sclerosis ↑	VEGF-A necessary for endothelial-podocyte survival axis; potential biomarker of glomerular injury
Hirai et al., 2019 *(Kidney Int; doi:10.1016/j.kint.2018.12.017)*	Human DN renal biopsies (n = 42) Stages I–IV DN	↓ VEGFR-2 expression (stage-dependent)	Interstitial fibrosis ↑ Tubular atrophy ↑ Peritubular capillary rarefaction ↓ CD31 microvascular density	eGFR ↓ across stages VEGFR-2 loss strongest in class III–IV DN	VEGFR-2 as inverse correlate of progression; may guide staging/prognosis in nephropathology
Takiyama et al., 2020 *(Diabetologia; doi:10.1007/s00125-019-05031-8)*	Diabetic Wistar rats Treated with VEGF-receptor decoy fusion proteins	↓ VEGF bioavailability ↓ VEGFR-2 phosphorylation	Glomerular endothelial apoptosis ↑ Podocyte foot process effacement Decreased capillary density	Albuminuria ↑ Tubular hypoxia ↑	VEGF inhibition accelerates DN; caution against anti-VEGF drugs in diabetic patients
Lee et al., 2021 *(Front Physiol; doi:10.3389/fp*	Diabetic Yorkshire pigs With/without VEGF-mimetic nanoparticles	Early ↓ VEGFR-2 VEGF	Cortical hypoperfusion ↑ Nitrotyrosine (oxidative stress	eGFR preservation with VEGF	VEGFR-2 downregulation is a **preclinical marker** Targeted VEGF therapy is

hys.2021.714859)		delivered via nanocarrier	marker) Vascular rarefaction before histologic injury	treatment Improved renal blood flow	feasible in large-animal models
Zhao et al., 2023 *(Nat Commun; doi:10.1038/s41467-023-38321-5)*	Human iPSC-derived podocytes CRISPR interference of VEGF-A	↓ VEGF-A transcription ↓ VEGFR-2 activation in GEC co-cultures	Downregulation of PI3K/AKT/eNOS signaling Slit diaphragm collapse Nephrin and podocin dysregulation ↓ NO bioavailability	Disrupted podocyte morphology Endothelial NO ↓	Confirms mechanistic role of VEGF-A in cytoskeletal & cross-cellular homeostasis; validates in vitro human model

A Comparative Table: VEGF-A/VEGFR-2 Downregulation Across Five Key Studies in Diabetic Nephropathy[**GECs** = Glomerular endothelial cells ,**eGFR** = Estimated glomerular filtration rate,↓ = Decreased/Downregulated,↑ = Increased/Upregulated]

The ramifications of VEGF-A/VEGFR-2 downregulation in diabetes extend beyond renal pathology and into the neurovascular domain, particularly influencing cognitive trajectories in affected individuals. The diabetic milieu, characterized by chronic hyperglycemia, oxidative stress, and low-grade inflammation, induces microvascular impairment,a pathophysiological hallmark common to both diabetic nephropathy and cognitive dysfunction.

Study 6 : landmark prospective cohort study by **Biessels et al. (2021)** published in *Lancet Neurology* demonstrated that long-standing type 2 diabetes was significantly associated with progressive cognitive decline, particularly in executive function and processing speed. The study highlighted diminished cerebral perfusion as a key correlate—an effect hypothesized to be partially mediated by endothelial dysfunction and impaired VEGF-A–VEGFR-2 axis, mirroring the pathogenesis observed in diabetic nephropathy.

Study	**Design & Population**	**Main Findings**	**VEGF-A/VEGFR-2 Implication**	**Conclusion**
Biessels et al., 2021 (*Lancet Neurology*)	Prospective cohort; >3,500 T2DM patients; 5-year follow-up	Progressive cognitive decline in executive and processing domains	Endothelial dysfunction with microvascular hypoperfusion implicated; indirect VEGF axis attenuation suspected	Vascular compromise in diabetes contributes to neurodegeneration; overlaps with renal microangiopathy

Study 7: A mechanistic study by **Zhou et al. (2022)** in *Frontiers in Aging Neuroscience* employed diabetic murine models and reported that hippocampal neurovascular unit (NVU) integrity was markedly disrupted in hyperglycemic states, with reduced VEGFR-2 phosphorylation leading to decreased angiogenic support and heightened blood-brain barrier (BBB) permeability. Restoration of VEGF-A signaling via exogenous recombinant protein mitigated NVU damage and partially rescued cognitive deficits.

These findings consolidate the **systemic vascular compromise** in diabetes as a **unifying mechanism** linking renal and cerebral end-organ dysfunction. Given VEGF-A's essential role in maintaining microvascular stability, its downregulation plausibly contributes to the parallel evolution of diabetic nephropathy and cognitive impairment, underscoring the **need for therapeutics** that holistically preserve VEGF-A–VEGFR-2 integrity across vascular beds.

Study	**Design & Population**	**Main Findings**	**VEGF-A/VEGFR-2 Implication**	**Conclusion**
Zhou et al., 2022(*Frontiers in Aging Neuroscience*)	Mechanistic experimental study in STZ-induced diabetic mice	Diabetic mice showed hippocampal NVU disruption, blood–brain barrier leakage, and impaired memory	Reduced VEGFR-2 phosphorylation and impaired VEGF-A signaling; recombinant VEGF-A restored vascular and cognitive integrity	VEGF-A/VEGFR-2 downregulation contributes to cognitive deficits through neurovascular dysfunction, paralleling renal pathology

Pathophysiological Continuum

The intricate orchestration of vascular endothelial growth factor-A (VEGF-A) and its cognate receptor VEGFR-2 (KDR/Flk-1) constitutes a fundamental pillar in the preservation of glomerular endothelial and podocytic integrity. Within the diabetic nephropathy (DN) milieu, the pathogenesis is not merely a linear trajectory of hyperglycemia-induced insult but represents a multifactorial convergence of metabolic dysregulation, endothelial-podocyte uncoupling, oxidative derailment, and angiocrine dysfunction. The reviewed literature elucidates an

evolving paradigm shift: from a prior focus on VEGF overexpression in early DN, to a contemporary understanding of VEGF-A/VEGFR-2 downregulation as a driver of advanced renal microvascular degeneration.

Molecular Interconnectivity and Endothelial-Podocyte Axis Collapse

The downregulation of VEGF-A disrupts canonical downstream signaling cascades, notably the PI3K/AKT/eNOS axis and the MAPK/ERK pathway, leading to endothelial apoptosis, reduced nitric oxide (NO) bioavailability, and microvascular rarefaction. Such perturbation does not occur in isolation but is potentiated by glycated end-product accumulation, activation of PKC isoforms, and TGF-β overactivity, collectively contributing to a hypoxic and pro-fibrotic glomerular microenvironment. Compromised VEGFR-2 activity impairs the endothelial response to hemodynamic shear stress, promoting capillary dropout, intraglomerular ischemia, and mesangiolysis.

Moreover, the podocyte-endothelium crosstalk — once stabilized by VEGF-A–VEGFR-2 paracrine loops — becomes functionally decoupled. Podocytic structural proteins (nephrin, synaptopodin) are destabilized, and slit diaphragm architecture collapses, resulting in overt proteinuria. This transition is morphologically evidenced by foot process effacement and actin cytoskeletal disarray, and biochemically characterized by a loss of VEGF-induced nephrin phosphorylation, a critical step in cytoskeletal dynamics and adhesion complex stability.

Capillary Rarefaction and Tubulointerstitial Fibrogenesis

VEGF-A suppression has downstream repercussions on peritubular capillary (PTC) integrity, as evidenced by significant CD31 and VE-cadherin depletion in advanced DN specimens. The reduction in PTC density synergizes with hypoxia-inducible factor-1α (HIF-1α) overexpression, fostering a pro-fibrogenic response via upregulation of connective tissue growth factor (CTGF) and collagen type IV, culminating in tubulointerstitial fibrosis (TIF). Notably, interstitial fibrosis is no longer seen as a mere consequence of glomerulopathy, but as a parallel and independent prognostic determinant of CKD progression — intricately linked to sustained VEGF axis suppression.

Furthermore, the endothelial-to-mesenchymal transition (EndMT), increasingly reported in the diabetic kidney, may be mechanistically rooted in VEGFR-2 loss, since its suppression removes inhibitory control over Snail1, TWIST1, and other transcriptional repressors of endothelial identity. Such phenotypic transitions amplify the myofibroblastic transformation of GECs and further promote fibrotic matrix deposition.

Temporal Dynamics and Clinical Implications

The dichotomous behavior of VEGF-A — initial upregulation followed by deleterious downregulation — is a temporally contingent phenomenon, highly stage-specific and responsive to the duration of diabetic exposure. This temporal plasticity challenges therapeutic targeting, as premature VEGF inhibition (e.g., with anti-angiogenic agents such as bevacizumab) can exacerbate renal injury, while delayed VEGF repletion may have limited efficacy due to irreversible nephron loss and capillary extinction.

Clinically, the extent of VEGFR-2 suppression correlates with refractoriness to RAS blockade, accelerated GFR decline, and transition to ESRD. Therefore, its evaluation could be pivotal in constructing predictive nephrological algorithms that stratify diabetic patients beyond conventional albuminuria staging, incorporating molecular nephroangioscores derived from VEGF expression indices.

Therapeutic Modulation: A Double-Edged Sword

Therapeutic targeting of VEGF-A/VEGFR-2 remains a formidable challenge due to the angiogenic paradox: both excess and deficiency are deleterious. Nanocarrier-based VEGF delivery systems, epigenetic modulators of VEGFR-2 promoter methylation, and CRISPR-Cas9–mediated editing of VEGF regulators (e.g., miR-200b, SIRT1) are under experimental exploration. However, a pressing concern remains — the potential for iatrogenic neoangiogenesis, endothelial leakiness, and glomerular hyperfiltration if VEGF modulation is not tissue-specific and temporally constrained.

Additionally, combinatorial regimens pairing VEGF reactivation with anti-inflammatory (e.g., IL-6 blockade) or antioxidant (e.g., Nrf2 activators) strategies may synergize to recalibrate the renal angiocrine milieu. Renal organoids and kidney-on-chip systems offer preclinical platforms to simulate humanized responses and pharmacokinetically profile VEGF-targeting compounds with vascular compartmental resolution.

The downregulation of VEGF-A/VEGFR-2 in diabetic nephropathy is emblematic of a broader angiocrine failure syndrome, whereby glomerular and tubulointerstitial compartments descend into a state of molecular hypoxia, architectural collapse, and fibrogenic momentum. Interventions must transcend symptomatic management and instead aim to restore molecular homeostasis within the glomerular vascular niche. Future success hinges upon harnessing multi-omics signatures, integrating VEGF-pathway phenotyping, and deploying precision therapeutics that re-establish endothelial-

podocyte symbiosis while forestalling maladaptive angiogenesis.

The intersection between diabetic nephropathy and neurocognitive decline in diabetes is increasingly being recognized as a manifestation of shared microvascular pathology, with the VEGF-A/VEGFR-2 signaling axis occupying a pivotal mechanistic role in both domains. The study by Biessels et al. (2021) provides robust epidemiological evidence that patients with longstanding type 2 diabetes mellitus exhibit progressive cognitive deterioration, particularly in executive and processing speed domains, which are typically vulnerable to microvascular compromise. The authors highlight that cerebral hypoperfusion and endothelial dysfunction may serve as central mechanisms underpinning this cognitive decline. Although the study does not directly interrogate VEGF-A signaling, the vascular etiopathogenesis aligns with the known role of VEGF-A in maintaining microvascular homeostasis and neurovascular coupling. In parallel, the mechanistic insights offered by Zhou et al. (2022) reveal that VEGF-A/VEGFR-2 downregulation in diabetic murine models leads to hippocampal neurovascular unit (NVU) disruption, blood-brain barrier permeability, and cognitive deficits — all of which are ameliorated with exogenous VEGF-A administration. This establishes a direct causal link between VEGF-A signaling deficiency and neurovascular instability in diabetes, paralleling similar molecular cascades seen in diabetic nephropathy. Taken together, these findings suggest that VEGF-A is not merely a renal angiogenic factor but a systemic vascular guardian whose dysregulation contributes to a spectrum of diabetic complications, from glomerular injury to cognitive dysfunction. Moreover, these studies underscore the concept of a "diabetic endotheliopathy," where a unified vascular signaling deficit gives rise to multiorgan microvascular damage. This expands the clinical horizon of diabetic care, suggesting that therapeutic interventions aimed at restoring VEGF-A/VEGFR-2 signaling may yield dual neuro-renal benefits. It also accentuates the urgency to adopt a more holistic, systems-based approach in diabetes management, one that transcends glycemic control and targets the underlying microvascular pathobiology. Importantly, the translational implication of these findings rests in the potential repurposing or modulation of VEGF-targeted therapies to not only mitigate renal decline but also to preserve cognitive function in diabetic populations at risk of neurodegenerative sequelae.

Conclusion

The pathogenesis of diabetic nephropathy (DN) is no longer to be viewed solely through the lens of hyperglycemia-induced mesangial expansion or proteinuria. Rather, it is increasingly clear that microvascular derangements, particularly those governed by the VEGF-A/VEGFR-2 signaling axis, serve as a linchpin in disease progression. The cumulative evidence from the reviewed studies converges on the notion that downregulation of VEGF-A and VEGFR-2 is not merely epiphenomenal but rather constitutes a primary pathobiological driver of glomerular endothelial dysfunction, capillary dropout, and podocyte detachment.

From a clinicopathological perspective, this downregulation manifests as a spatiotemporal cascade — initiating with capillary rarefaction, progressing through glomerular ischemia, and culminating in global glomerulosclerosis and interstitial fibrosis. Histopathological findings such as effaced foot processes, endothelial dedifferentiation, and the collapse of slit diaphragm integrity are not isolated occurrences but direct consequences of sustained VEGF-A/VEGFR-2 insufficiency. This correlates robustly with clinical parameters including eGFR decline, increasing albuminuria, and insensitivity to standard renoprotective therapy (e.g., ACEi/ARB regimens).

From a nephrological standpoint, the significance of VEGF-A/VEGFR-2 lies in its bidirectional control of endothelial homeostasis and podocyte viability. The loss of VEGFR-2 expression or signaling leads not only to impaired angiogenic repair and microvascular tone, but also to the deterioration of podocyte–endothelial crosstalk, the breakdown of glomerular permselectivity, and the escalation of inflammatory and fibrotic responses. The pathophysiological continuum from early DN to ESRD is thus, in part, governed by a gradual but decisive withdrawal of this vascular trophic support.

The therapeutic implications of this axis are profound yet paradoxical. While anti-VEGF strategies have shown utility in ocular diabetic complications, their indiscriminate systemic use has proven deleterious to renal architecture. Conversely, the therapeutic reconstitution of VEGF-A signaling presents as a viable strategy, but it demands exquisite precision. Any attempt to restore VEGF-A/VEGFR-2 must be tightly regulated — spatially confined to the renal microvasculature and temporally aligned with specific disease stages to avoid exacerbation of glomerular hyperfiltration, neovascular leakage, or proteinuria.

In the era of precision nephrology, future directions must prioritize the integration of transcriptomic and proteomic biomarkers (e.g., VEGFR-2 mRNA levels, soluble VEGF isoform ratios), functional renal imaging, and non-invasive vascular profiling to stratify patients and guide therapeutic timing. Furthermore, organotypic models, such as human kidney organoids and bioengineered glomeruli, should be leveraged for high-throughput testing of

VEGF-modulatory therapies, enabling personalized and compartment-specific intervention paradigms.

While VEGF-A has traditionally been viewed through the lens of renal angiogenesis and glomerular maintenance, accumulating evidence, as exemplified by Zhou et al. (2022) and Biessels et al. (2021), suggests that its influence transcends the kidney, exerting critical effects on cerebral microvascular integrity, blood-brain barrier stability, and hippocampal function. The convergence of renal and cognitive pathology under a shared umbrella of microvascular compromise underscores a systemic endothelial dysfunction, conceptually framed as a "diabetic endotheliopathy."

In summary, VEGF-A/VEGFR-2 downregulation is a fulcrum of endothelial and podocyte destabilization in DN, acting as both a predictive molecular sentinel and a targetable pathogenic inflection point. Restoring its balance offers a novel therapeutic frontier — one that holds promise not only in halting DN progression but potentially in reversing early structural damage and restoring nephron integrity. However, this vision demands translational precision, multi-disciplinary collaboration, and innovative delivery platforms that can navigate the fine line between physiological angiogenesis and pathological remodeling.

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