

The Forgotten Vasculature: How Microvascular Rarefaction in Chronic Kidney Disease Shapes Kidney Transplant Outcomes

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ABSTRACT

Introduction: Systemic microvascular rarefaction and dysfunction are important hallmarks of chronic kidney disease (CKD), and are associated with clinical outcomes post kidney transplantation. This systematic review synthesizes the evidence linking microvascular health in CKD to post-transplant graft adaptation, function, and survival.

Methods: We conducted a comprehensive systematic review of 80 studies, including systematic reviews, meta-analyses, randomized controlled trials, and observational studies. Screening was based on predefined criteria focusing on CKD patients or kidney transplant recipients, microvascular assessment methods, and transplant-related outcomes. Data were extracted on assessment methodologies, microvascular abnormalities in CKD, recipient microvascular status, graft outcomes, post-transplant hypertension, and interventions affecting the microvasculature.

Results: Microvascular abnormalities, such as capillary rarefaction, endothelial dysfunction, and reduced reactivity, are well-known outcomes of CKD and worsen with disease progression. These changes can be seen by various methods such as retinal imaging, near-infrared spectroscopy, and Doppler ultrasound. Pre-transplant microvascular status, particularly elevated renal resistive index (RI >0.85), is a strong predictor of adverse outcomes, including graft failure and mortality (Kolonko et al., 2012). Post-transplant, microvascular health is affected by immunosuppressive regimens, with calcineurin inhibitors exacerbating dysfunction. Post-transplant hypertension (>90% prevalence) is closely linked to microvascular dysfunction and sympathetic overactivity. Interventions such as calcium channel blockers, renin-angiotensin system inhibitors, aerobic exercise, and targeted therapies (e.g., eculizumab) show promise in improving microvascular parameters and graft outcomes.

Discussion: The evidence consistently demonstrates that microvascular dysfunction is a systemic marker of cardiovascular and renal risk in CKD that persists after transplantation, affecting graft adaptation. The heterogeneity in assessment methods and study designs presents challenges, but the prognostic value of microvascular evaluation is clear. Calcineurin inhibitor-free regimens and non-pharmacological interventions like exercise training improve microvascular function and may enhance long-term prognosis.

Conclusion: Microvascular rarefaction and dysfunction are fundamental to CKD pathophysiology and have profound implications for kidney transplantation outcomes. Integrating microvascular assessment into pre- and post-transplant care could improve risk stratification and guide personalized therapeutic strategies. Future research should focus on standardizing assessment methods and conducting randomized trials of microvascular-targeted interventions.

KEYWORDS: Chronic Kidney Disease, Kidney Transplantation, Microvascular Rarefaction, Endothelial Dysfunction, Graft Survival, Hypertension, Renal Resistive Index, Immunosuppression.

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BACKGROUND

Chronic kidney disease (CKD) represents a major global health burden, affecting approximately 10% of the world's population and culminating in end-stage renal disease (ESRD) requiring renal replacement therapy (Levey et al., 2007). Beyond the classical decline in glomerular filtration rate (GFR), CKD is a systemic disorder characterized by pervasive microvascular and macrovascular dysfunction. Microvascular rarefaction—the anatomical and functional reduction of capillary density—is a hallmark of advanced CKD and is driven by chronic inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances (Moody et al., 1997). This microvascular pathology is not confined to the kidneys but affects multiple vascular beds, including the retina, skin, skeletal muscle, and brain, serving as a window into systemic cardiovascular health (Aronov et al., 2021; Theodorakopoulou et al., 2025).

Kidney transplantation remains the optimal treatment for ESRD, offering superior survival and quality of life compared to dialysis. However, long-term graft survival remains suboptimal, with chronic allograft dysfunction being a leading cause of graft loss. Emerging evidence suggests that the systemic microvascular milieu of the recipient—shaped by years of CKD, hypertension, diabetes, and uremia—may significantly influence the transplanted kidney's adaptation, function, and longevity (Kolonko et al., 2012; Pisano et al., 2021). The graft, while surgically revascularized, is implanted into a host with potentially compromised systemic microcirculation, which may impair its perfusion, increase its susceptibility to ischemia-reperfusion injury, and accelerate chronic vascular changes.

RESEARCH GAP

Despite growing recognition of microvascular dysfunction in CKD, its comprehensive characterization and direct causal link to post-transplant outcomes remain inadequately synthesized. Existing literature is fragmented across various specialties (nephrology, transplantation, cardiology, ophthalmology) and employs heterogeneous methodologies for assessing microvascular health (van der Pluijm et al., 2025; Chaara et al., 2024). There is a lack of consensus on which microvascular parameters are most prognostically valuable in the transplant setting. Furthermore, while certain interventions (e.g., specific antihypertensives, exercise) are known to improve macrovascular endpoints, their specific effects on the microvasculature in the context of transplantation are less clearly defined (Pisano et al., 2019; Kirkman et al., 2019). This gap hinders the development of standardized pre-transplant risk assessment tools and microvascular-targeted therapeutic strategies to improve graft longevity.

Novelty

This systematic review is novel in its holistic synthesis of evidence across diverse microvascular assessment modalities—from retinal imaging and sublingual videomicroscopy to functional MRI and biomarker analysis—to build a unified understanding of microvascular health in CKD and transplantation. It uniquely focuses on the trajectory of microvascular dysfunction: from its presence in pre-transplant CKD, through the peri-transplant period, and into long-term follow-up, explicitly linking it to graft adaptation mechanisms. By integrating findings on structural rarefaction, functional impairment, and their modification by pharmacological and non-pharmacological interventions, this review provides a translational framework for leveraging microvascular assessment in clinical transplant practice.

RESEARCH OBJECTIVES

The primary objective of this systematic review is to critically appraise and synthesize the existing evidence on microvascular rarefaction and dysfunction in patients with CKD and its implications for outcomes following kidney transplantation. Specific aims include:

1. To catalogue and evaluate the methodologies used to assess microvascular structure and function in CKD and transplant populations.
2. To characterize the spectrum and severity of microvascular abnormalities across stages of CKD.
3. To examine the association between pre-transplant recipient microvascular status and post-transplant outcomes, including graft function, survival, and the development of hypertension.
4. To elucidate the pathophysiological mechanisms linking microvascular dysfunction to adverse transplant outcomes.
5. To review the evidence for interventions that can modify microvascular health and improve transplant results.

HYPOTHESIS

We hypothesize that systemic microvascular rarefaction and dysfunction, prevalent in advanced CKD, constitute a significant, independent risk factor for impaired graft adaptation, higher rates of delayed graft function, accelerated chronic allograft injury, and increased cardiovascular morbidity following kidney transplantation. Furthermore, we hypothesize that quantitative assessment of microvascular parameters can stratify transplant risk and that interventions aimed at improving microvascular health will translate into better long-term graft and patient survival.

RESEARCH BENEFITS

The findings of this review have significant clinical and research implications:

- **Clinical Benefits:** Informing the development of pre-transplant risk stratification protocols that incorporate microvascular assessment. Guiding personalized post-transplant management, including choice of immunosuppression and adjuvant therapies (e.g., antihypertensives, exercise programs) to preserve microvascular health. Raising awareness of microvascular dysfunction as a treatable trait to improve cardiovascular and renal outcomes in transplant recipients.
- **Research Benefits:** Identifying key knowledge gaps to direct future prospective studies. Promoting the standardization of microvascular assessment methods in nephrology and transplant research. Providing a mechanistic basis for designing interventional trials targeting the microvasculature to improve transplant success.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. PubMed, Semantic scholar, Springer, Google scholar, and Wiley online library were searched for all relevant publications from January 1, 2000 to February 2026. Six review authors independently screened the titles and abstracts of identified for eligibility and then extracted the outcome data. Any disagreements were resolved by discussion. The review protocol was registered on PROSPERO (CRD420261303883). This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the microvascular rarefaction in CKD: implications for kidney transplantation

Screening

We screened in sources based on their abstracts that met these criteria:

- Target Population: Does the study include patients with CKD (stages 3-5) or kidney transplant recipients?
- Microvascular Focus: Does the study investigate microvascular rarefaction or capillary density?
- Microvascular Assessment Method: Does the study use validated methods for microvascular assessment (e.g., nailfold capillaroscopy, retinal imaging, skin biopsy, imaging techniques)?
- Transplant-Related Outcomes: Does the study examine graft adaptation, function, or survival in relation to recipient microvascular status?
- Study Design: Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?
- Quantitative Outcomes: Does the study report quantitative outcomes related to microvascular parameters or transplant outcomes?
- Chronic vs Acute Kidney Disease: Does the study focus on chronic kidney disease or chronic microvascular changes (rather than solely on acute kidney injury)?
- Study Quality and Type: Is the study a peer-reviewed publication with adequate sample size (not a case report, case series with fewer than 10 patients, editorial, or conference abstract)?
- Human Data: Does the study include human data (rather than being solely animal or in-vitro research)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison)	O (Outcome)
Keyword 1	Chronic Kidney Disease	Microvascular Rarefaction	Kidney transplantation	Graft survival
Keyword 2	CKD	Microvascular dysfunction	Graft adaptation	Graft function
Keyword 3	End-stage renal disease	Capillary rarefaction	Transplant outcomes	Post-transplant hypertension
Keyword 4	ESRD	Endothelial dysfunction	Immunosuppressive regimens	Cardiovascular outcomes

The Boolean MeSH keywords inputted on databases for this research are: ("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")

Data extraction

- **Microvascular Assessment Methods:**
Extract all methods used to assess microvascular structure or function in CKD patients or kidney transplant recipients, including:
 - o Type of assessment (capillaroscopy, retinal imaging, skin biopsy, functional tests, biomarkers)
 - o Specific parameters measured (capillary density, vessel diameter, flow, rarefaction index)
 - o Timing of assessment (pre-transplant, post-transplant, follow-up intervals)
 - o Anatomical sites examined (nail fold, retina, kidney biopsy, skin)
 - o Technical specifications and validation status
- **Microvascular Findings in CKD:**
Extract specific microvascular abnormalities documented in CKD patients, including:
 - o Evidence of capillary rarefaction (reduced capillary density, numbers)
 - o Structural changes (vessel wall thickening, sclerosis, calcification)
 - o Functional impairments (reduced perfusion, altered vasoreactivity)
 - o Severity relationship to CKD stage
 - o Comparison to healthy controls or non-CKD patients
 - o Quantitative measurements and effect sizes where provided

- **Recipient Microvascular Status:**
Extract characterization of recipient microvascular condition before and after kidney transplantation, including:
 - Pre-transplant microvascular assessment results
 - Risk stratification based on microvascular parameters
 - Changes in microvascular status post-transplant
 - Factors influencing recipient microvascular health (diabetes, hypertension duration, dialysis vintage)
 - Microvascular biomarkers or predictive indices used
- **Graft Adaptation Outcomes:**
Extract transplant outcomes that may relate to recipient microvascular status, including:
 - Graft function measures (creatinine, eGFR, proteinuria)
 - Time to functional recovery
 - Delayed graft function incidence
 - Acute rejection episodes
 - Long-term graft survival
 - Histological findings in graft biopsies
 - Any outcomes specifically analyzed in relation to microvascular factors
- **Post-Transplant Hypertension:**
Extract findings on hypertension after kidney transplantation and its relationship to microvascular factors, including:
 - Incidence and prevalence of post-transplant hypertension
 - Blood pressure control metrics
 - Antihypertensive medication requirements
 - Association with pre-transplant microvascular status
 - Mechanisms linking microvascular changes to hypertension
 - Impact on cardiovascular outcomes
 - Time course of hypertension development
- **Microvascular-Outcome Associations:**
Extract any reported relationships between microvascular parameters and transplant outcomes, including:
 - Statistical associations (correlations, regression analyses)
 - Risk ratios or odds ratios for adverse outcomes
 - Predictive value of microvascular assessments
 - Dose-response relationships
 - Subgroup analyses by microvascular status
 - Adjustment for confounding factors
 - Strength and direction of associations
- **Proposed Mechanisms:**
Extract proposed biological mechanisms linking microvascular rarefaction in CKD to transplant outcomes, including:
 - Pathophysiological pathways described
 - Role in graft adaptation process
 - Impact on drug delivery and metabolism
 - Inflammatory or oxidative stress pathways
 - Endothelial dysfunction mechanisms
 - Hemodynamic consequences
 - Therapeutic targets identified
- **Study Population:**
Extract characteristics of CKD patients and kidney transplant recipients studied, including:
 - CKD stage and etiology
 - Transplant recipient demographics (age, gender, race)
 - Comorbidities affecting microvasculature (diabetes, hypertension duration)
 - Dialysis history and duration
 - Donor characteristics if relevant
 - Immunosuppression regimens
 - Follow-up duration for microvascular and transplant outcomes
- **Interventions Affecting Microvasculature:**
Extract any interventions that target or affect microvascular function in the context of CKD or kidney transplantation, including:
 - Pharmacological treatments (ACE inhibitors, ARBs, vasodilators)
 - Non-pharmacological interventions (exercise, dietary modifications)
 - Timing relative to transplantation
 - Dosing and duration
 - Effects on microvascular parameters

- o Impact on transplant outcomes
- o Mechanisms of microvascular improvement

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")	15
Semantic Scholar	("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")	250
Springer	("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")	571
Google Scholar	("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")	3,480
Wiley Online Library	("Chronic Kidney Disease" OR "CKD" OR "End-stage renal disease" OR "ESRD") AND ("Microvascular Rarefaction" OR "Microvascular dysfunction" OR "Capillary rarefaction" OR "Endothelial dysfunction") AND ("Kidney transplantation" OR "Graft adaptation" OR "Transplant outcomes" OR "Immunosuppressive regimens") AND ("Graft survival" OR "Graft function" OR "Post-transplant hypertension" OR "Cardiovascular outcomes")	550

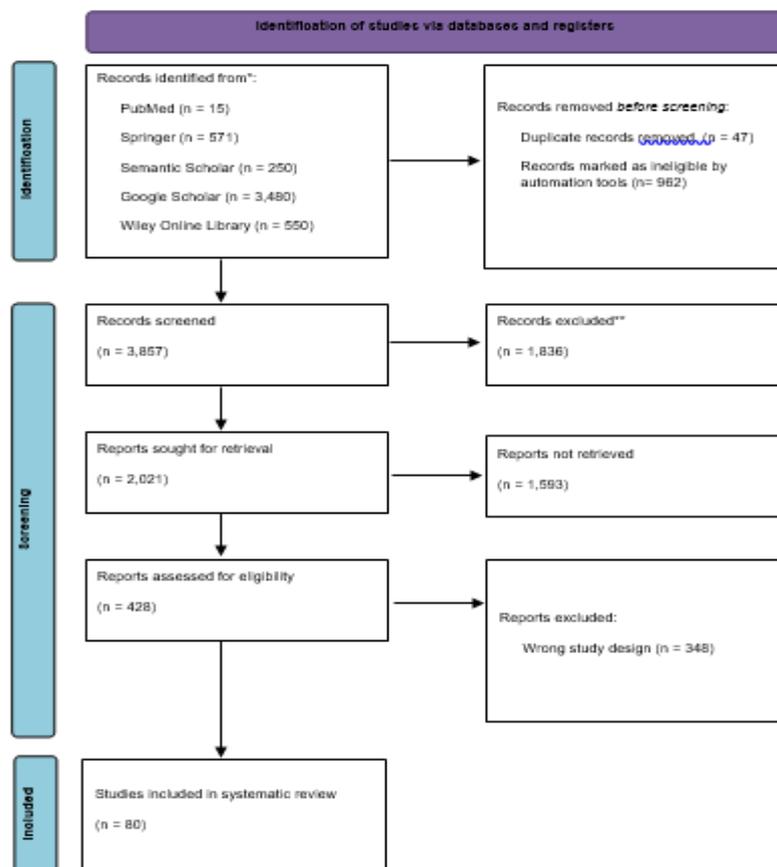


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Claire van der Pluijm et al., 2025	✔	✔	✔	✘	✔	✘	✔	✔	✔
N. Lutfiana et al., 2023	✔	✔	✔	✘	✔	✘	✔	✔	✔
Sabrina Chaara et al., 2024	✔	✔	✔	✘	✔	✘	✔	✔	✔
Yin-Chin Wang et al., 2022	✔	✔	✔	✘	✔	✘	✔	✔	✔
Marieta P. Theodorakopoulou et al., 2024	✔	✔	✔	✘	✔	✘	✔	✔	✔
Marieta P. Theodorakopoulou et al., 2024a	✔	✔	✔	✘	✔	✘	✔	✔	✔
M. Aronov et al., 2021	✔	✔	✔	✘	✔	✘	✔	✔	✔
D. Kirkman et al., 2019	✔	✔	✔	✘	✔	✘	✔	✔	✔
Asmaa Moatasem Elgharib et al., 2024	✔	✔	✔	✘	✔	✘	✔	✔	✔

A. Vanikar et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Eide et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Marieta P. Theodorakopoulou et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chien-Ya Hsiung et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Lefaucheur et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Kovács et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Cerqueira et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shahzar Malik et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fritz Diekmann et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Dijk et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. R. Zagitov et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Pérez-Sáez et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Shahraki et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Kolonko et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Joannidés et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

Mel S. Lee et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
María Molina Gómez et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Laila-Yasmin Mani et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Seeman et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chih-Chao Yang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. G. Gonzalez Suarez et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Safaa Azzouz et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Bertrand et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Pihlstrøm et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hui Yang et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. L. Suarez et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Weekers et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bernard Malavaud et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andre L Silva et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Justin D Sprick et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Manukyan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Arnaud Simon et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhou Sun et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Huan Wang et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fej Jolink et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chih-Wei Yang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Juan Luís Martínez Pérez et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Fadel et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Marbun et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Gong et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Pisano et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rubin Zhang et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. J. Murphy et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ying-ying Lu et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Anglicheau et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓

Osama A. Alkamis et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Laima Siddiqi et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Hernández et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Robert van Duin et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Samuel A. Headley et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Neha Nainani et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Ding et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Auer et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. R. Zagitov et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sharon L. H. Ong et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Okamoto et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Pisano et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Philipp et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kenneth Lim et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Durrbach et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

Matthew J. Ellis et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Hill et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Krämer et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fredo Tamara et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Pedrollo et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Schneider et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anne-Sophie Garnier et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Hornum et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Polychronopoulou et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Cameron et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Kremer et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 80 sources examining microvascular rarefaction in chronic kidney disease (CKD) and its implications for kidney transplantation. The included studies span multiple research designs, populations, and assessment methodologies.

Study	Primary Focus
Claire van der Pluijm et al., 2025	Retinal vascular analysis in CKD
N. Lutfiana et al., 2023	Retinal microangiopathy and albuminuria
Sabrina Chacara et al., 2024	Dialysis effects on microcirculation
Yin-Chin Wang et al., 2022	Dexmedetomidine effects on sublingual microcirculation

Marieta P. Theodorakopoulou et al., 2024	Muscle oxygenation in pre-dialysis CKD
Marieta P. Theodorakopoulou et al., 2024a	Proteinuria effects on microvascular reactivity
M. Aronov et al., 2021	Retinal vascular signs in CKD screening
D. Kirkman et al., 2019	Aerobic exercise effects on vascular function
Asmaa Moatasem Elgharib et al., 2024	Vasopressors in kidney transplantation
A. Vanikar et al., 2020	Thrombotic microangiopathy in allografts
I. Eide et al., 2018	Marine n-3 fatty acids in transplantation
Marieta P. Theodorakopoulou et al., 2025	Cerebral and muscle oxygenation in CKD
Chien-Ya Hsiung et al., 2024	De novo thrombotic microangiopathy
C. Lefaucheur et al., 2007	Antibody-mediated rejection outcomes
G. Kovács et al., 2020	Transplant glomerulopathy and graft outcomes
A. Cerqueira et al., 2021	Endothelial dysfunction and cerebrovascular events
Shahzar Malik et al., 2025	Implantable Doppler probe monitoring
Fritz Diekmann et al., 2004	CNI to sirolimus conversion
M. Dijk et al., 2018	Long-term cardiovascular outcome
A. R. Zagitovet et al., 2019	Erectile dysfunction post-transplant
M. Pérez-Sáez et al., 2018	Belatacept conversion outcomes
E. Shahraki et al., 2020	Graft microvasculature assessment
A. Kolonko et al., 2012	Resistance index and graft survival
R. Joannidés et al., 2010	Sirolimus vs cyclosporine effects
Mel S. Lee et al., 2017	CD34+ cell therapy safety
María Molina Gómez et al., 2023	Anticoagulation in high RI transplants
Laila-Yasmin Mani et al., 2022	Functional MRI of kidney grafts
T. Seeman et al., 2018	Blood pressure control in pediatric transplant
Chih-Chao Yang et al., 2020	CD34+ cell therapy in CKD
M. G. Gonzalez Suarez et al., 2019	Eculizumab in aHUS transplant recipients
Safaa Azzouz et al., 2022	Renal resistive index prognosis

D. Bertrand et al., 2017	Belatacept rescue therapy
H. Pihlstrøm et al., 2017	Paricalcitol in transplant recipients
Hui Yang et al., 2021	Hyperuricemia in transplant recipients
M. L. Suarez et al., 2020	Fabry disease transplant outcomes
L. Weekers et al., 2016	AVF closure effects on graft function
Bernard Malavaud et al., 2001	Sildenafil effects in transplant recipients
Andre L Silva et al., 2018	Sirolimus effects on carotid atherosclerosis
Justin D Sprick et al., 2022	Exercise training on endothelial function
M. Manukyan et al., 2022	Renal denervation in resistant HTN
Arnaud Simon et al., 2025	Eplerenone effects on arterial stiffness
Zhou Sun et al., 2023	Vitamin K effects post-transplant
Huan Wang et al., 2022	Exercise effects on vascular function
Fej Jolink et al., 2021	Myocardial perfusion imaging prognosis
Chih-Wei Yang et al., 2020	CD34+ cell therapy efficacy
Juan Luís Martínez Pérez et al., 2024	Renal artery stenosis revascularization
F. Fadel et al., 2016	Endothelial dysfunction in pediatric transplant
M. Marbun et al., 2020	Hyperfiltration mechanism in donors
N. Gong et al., 2012	Anti-sense ERK2 gene therapy
A. Pisano et al., 2021	Blood pressure monitoring in transplant
Rubin Zhang et al., 2013	RAS inhibitors in pediatric donor recipients
G. J. Murphy et al., 2003	Cyclosporin vs tacrolimus on fibrosis
Ying-ying Lu et al., 2017	CD20+ B-cell infiltration effects
D. Anglicheau et al., 2007	Prophylactic IVIg in high-risk transplant
Osama A. Alkamis et al., 2024	Steroid withdrawal outcomes
Laima Siddiqi et al., 2014	RAS inhibition and kidney oxygenation
D. Hernández et al., 2021	Corticosteroid withdrawal effects
Robert van Duin et al., 2024	Sodium-mediated BP rise in CKD

Samuel A. Headley et al., 2024	Resistant starch effects in CKD
Neha Nainani et al., 2012	Steroid-free immunosuppression effects
C. Ding et al., 2018	HMP pressure effects on DCD transplant
J. Auer et al., 2021	Aspirin for CVD prevention in CKD
A. R. Zagitov et al., 2019	Erectile dysfunction treatment outcomes
Sharon L. H. Ong et al., 2012	BP, fluid volume, and vascular function
M. Okamoto et al., 2006	CsA reduction with SRL/MMF addition
A. Pisano et al., 2019	Antihypertensive agents in transplant
T. Philipp et al., 2010	Candesartan effects in transplant
Kenneth Lim et al., 2020	Cardiovascular functional reserve
A. Durrbach et al., 2010	Belatacept vs cyclosporine in ECD transplant
Matthew J. Ellis et al., 2008	CKD after hematopoietic cell transplant
C. Hill et al., 2015	Recipient obesity and transplant outcomes
B. Krämer et al., 2003	Cardiovascular risk factors in transplant
Fredo Tamara et al., 2024	Transplant renal artery stenosis prevalence
E. Pedrollo et al., 2016	Metabolic syndrome effects on transplant
S. Schneider et al., 2015	Renal denervation in transplant recipients
Anne-Sophie Garnier et al., 2018	Serum magnesium post-transplant
M. Hornum et al., 2011	Transplantation effects on arterial function
E. Polychronopoulou et al., 2024	SGLT2 inhibitors in transplant recipients
C. Cameron et al., 2014	Hypertension effects on GFR in pediatric transplant
D. Kremer et al., 2021	COVID-19 in kidney transplant recipients

Microvascular Assessment Methods in CKD and Kidney Transplantation

Multiple methodologies have been employed to assess microvascular structure and function across the included studies, reflecting the diverse anatomical sites and parameters relevant to understanding microvascular health in CKD populations.

Assessment Method	Anatomical Site	Parameters Measured	Studies Utilizing Method
Retinal imaging (DVA, OCT, OCTA)	Retina	Vessel density, flicker-induced arteriolar dilation, macular/choroidal thickness	Claire van der Pluijm et al., 2025; N. Lutfiana et al., 2023; M. Aronov et al., 2021

Fundus photography	Retina	CRAE, CRVE, AVR, retinopathy presence	N. Lutfiana et al., 2023
Near-infrared spectroscopy (NIRS)	Skeletal muscle, prefrontal cortex	Tissue saturation index (TSI%), oxygenated/deoxygenated hemoglobin	Marieta P. Theodorakopoulou et al., 2024, 2025
Incident dark-field video microscopy	Sublingual	Total vessel density, microvascular flow index	Yin-Chin Wang et al., 2022; Sabine Chacara et al., 2024
Laser-Doppler flowmetry with microdialysis	Skin	Cutaneous vasodilation during local heating	D. Kirkman et al., 2019
Doppler ultrasound	Kidney, penile arteries	Resistive index (RI), blood flow velocity	Multiple transplant studies
Peripheral arterial tonometry (PAT)	Fingertips	Reactive hyperemia index (RHI)	A. Cerqueira et al., 2021; Justin D Sprick et al., 2022
Flow-mediated dilation (FMD)	Brachial/radial artery	Endothelium-dependent dilation	I. Eide et al., 2018; F. Fadel et al., 2016
Intima-media thickness (IMT)	Common carotid artery	Vessel wall thickness	M. Dijk et al., 2018; F. Fadel et al., 2016
Functional MRI (DWI, BOLD)	Kidney grafts	Diffusion coefficient, tissue oxygenation (R2*)	Laila-Yasmin Mani et al., 2022
Kidney biopsy histology	Renal allograft	TMA features, peritubular capillary changes, glomerulitis	Multiple transplant studies

Retinal imaging techniques including dynamic vessel analysis (DVA), optical coherence tomography (OCT), and OCT angiography (OCTA) have emerged as promising non-invasive tools for assessing systemic microvascular health in CKD. DVA provides functional assessment of endothelial health through measurement of flicker-induced arteriolar dilation, while OCT and OCTA detect structural changes including macular and choroidal thinning and quantify vessel density. The renal resistive index measured by Doppler sonography in the early post-transplant period has been validated as a prognostic marker, with measurements typically obtained at the second to fourth day after transplantation. Near-infrared spectroscopy enables continuous, non-invasive measurement of muscle and cerebral oxygenation, with assessments conducted at rest and during provocative maneuvers including occlusion-reperfusion and handgrip exercise.

Microvascular Abnormalities in Chronic Kidney Disease

Evidence from the included studies demonstrates multiple patterns of microvascular dysfunction in CKD patients, encompassing both structural and functional abnormalities.

Structural Microvascular Changes

Finding	Population	Quantitative Data	Clinical Association
Decreased superficial vessel density (SVD)	CKD patients	Not quantified	Associated with CKD progression

Macular and choroidal thinning	CKD patients	Not quantified	Correlated with CKD progression
Retinal arteriolar narrowing (reduced CRAE)	CKD patients with albuminuria	U-shaped relationship with albuminuria	Associated with dysregulation of RAAS and sclerotic renal changes
Retinal venular widening (increased CRVE)	CKD patients	Not quantified	Associated with endothelial damage and inflammatory processes
Progressive microvascular rarefaction	Pre-dialysis CKD stages 2-4	Not quantified	Worsens with advancing CKD stages
Vascular fibrous intimal thickening	Chronic allograft dysfunction	Grade 1.2 ± 0.7 (responders) vs 1.7 ± 0.7 (nonresponders)	Predictor of poor response to conversion therapy

Retinal microvascular changes provide a window into systemic microvascular health in CKD. Central retinal artery equivalent (CRAE) narrowing demonstrates a complex relationship with albuminuria, showing a U-shaped association with both the lowest and highest quintiles associated with increased albuminuria. Larger central retinal vein equivalent (CRVE) values correlate with albuminuria and reflect endothelial damage. Choroidal thickness has been associated with histological indexes of renal injury and systemic inflammatory markers, suggesting shared pathophysiological mechanisms between retinal and renal microvasculature.

Functional Microvascular Impairments

Parameter	Proteinuric CKD	Non-proteinuric CKD	p-value	Clinical Significance
TSI occlusion magnitude	25.77 ± 7.87	29.95 ± 10.34	$p=0.074$	Lower oxidative capacity
TSI reperfusion slope to max	1.03 ± 0.45	1.39 ± 0.69	$p=0.035$	Impaired microvascular reactivity
TSI 10-second slope	1.34 ± 0.63	1.92 ± 0.75	$p=0.002$	Impaired reperfusion response
Hyperemic response	7.13 ± 4.27	8.89 ± 4.68	$p=0.131$	Numerically lower
Cerebral O₂Hb during exercise	0.92 ± 0.78	1.49 ± 0.86	$p=0.012$	Attenuated cerebral oxygenation
Cerebral tHb during exercise	0.43 ± 0.98	1.00 ± 0.85	$p=0.023$	Lower regional blood volume

Proteinuria serves as a marker of impaired microvascular function in CKD. Patients with proteinuria demonstrate significantly lower tissue saturation index (TSI) reperfusion slopes compared to non-proteinuric CKD patients ($p=0.002$ for 10-second slope), indicating impaired microvascular reactivity during the reperfusion phase of occlusion testing. Additionally, proteinuric CKD patients display attenuated cerebral oxygenation responses during mild physical tasks, with significantly lower oxygenated hemoglobin (O₂Hb) responses (0.92 ± 0.78 vs 1.49 ± 0.86 , $p=0.012$). These findings suggest that proteinuria reflects heightened systemic endothelial dysfunction leading to impaired vasodilatory responses.

The effects of hemodialysis on microcirculation vary by vascular bed. A meta-analysis of 17 studies with 493 participants found that cutaneous microcirculation showed mean reduction in transcutaneous oxygen pressure of -7.9 mmHg (95% CI -10.5 to -5.3) and sublingual microvascular flow index decreased by -0.6 in small microvessels, while retinal microcirculatory perfusion remained largely unaltered.

Recipient Microvascular Status and Graft Adaptation

The relationship between recipient microvascular condition and transplant outcomes represents a critical area where pre-existing microvascular dysfunction may influence graft adaptation and long-term function.

Pre-Transplant Microvascular Assessment and Risk Stratification

Microvascular Parameter	Threshold	Outcome Association	Study
Renal resistive index (RI)	Group 1: RI <0.73 Group 2: RI $0.73-0.85$ Group 3: RI >0.85	Higher RI tertile associated with worse graft function and increased mortality	A. Kolonko et al., 2012
Reactive hyperemia index (RHI)	Continuous	RHI correlated positively with eGFR ($r=0.332$, $p<0.0001$)	A. Cerqueira et al., 2021
Circulating EPC number	Continuous	Significantly lower in CKD vs healthy subjects	Mel S. Lee et al., 2017
Angiogenesis capacity	Continuous	Significantly lower in CKD ($p<0.001$)	Mel S. Lee et al., 2017

Early post-transplant resistance index measurements provide prognostic information for long-term outcomes. In a prospective analysis of 364 consecutive kidney transplant recipients, patients in the highest RI tertile (RI >0.85) demonstrated significantly higher mortality rates compared to the lowest tertile (9.6% vs 2.6% at 5 years) and higher rates of graft loss (18.4% vs 12.1%). The hazard ratio for combined outcome (graft loss or death) reached 10.88 for high RI values. Importantly, the predictive value of RI was not completely independent from the adverse influence of delayed graft function on premature graft loss.

Post-Transplant Microvascular Changes and Graft Function

Study	Intervention/Comparison	Microvascular Parameter	Change	Graft Function Impact
Yin-Chin Wang et al., 2022	Dexmedetomidine vs control	Total vessel density at 2h post-surgery	No significant difference	Lower creatinine day 2: 1.5 vs 2.2 mg/dL ($p=0.018$)
M. Hornum et al., 2011	Pre- vs post-transplant	Augmentation index (AIX)	27% to 14% ($p=0.01$)	Blood pressure decreased despite fewer antihypertensives
M. Hornum et al., 2011	Pre- vs post-transplant	Nitroglycerin-induced dilation (NID)	11% to 18% ($p=0.0005$)	Improved arterial function
Laila-Yasmin Mani et al., 2022	CsA vs everolimus	Diffusion coefficient (ADCD)	Decreased in CsA, increased in EVE ($p=0.046$)	EVE group showed improved graft function

Kidney transplantation itself improves arterial function as measured by pulse wave analysis. In a study comparing 40 kidney recipients with 40 matched wait-listed controls, the augmentation index decreased from 27% to 14% ($p=0.01$) at one year post-transplant in the transplant group while remaining stable in controls. Endothelium-independent dilation measured by nitroglycerin response increased from 11% to 18% ($p=0.0005$). These improvements occurred despite deterioration in insulin sensitivity, suggesting that uremia reversal independently benefits vascular function.

Immunosuppressive regimen selection influences graft microvascular parameters. In the ZEUS trial sub-study using functional MRI, the diffusion coefficient (ADCD) decreased over time in the ciclosporin-treated group but increased in the everolimus-treated group ($p=0.046$ for medulla). Tissue oxygenation measured by $R2^*$ increased (indicating decreased oxygen) in the ciclosporin group while decreasing in the everolimus group, suggesting that calcineurin inhibitor-free regimens may preserve graft microvascular function.

Thrombotic Microangiopathy and Graft Outcomes

De novo thrombotic microangiopathy (TMA) represents a severe form of microvascular injury in kidney allografts. A meta-analysis of 28 cohorts comprising 14,410 kidney allograft recipients found that de novo TMA occurred in 3.20% (95% CI: 1.93–4.77%) of recipients. The overall graft loss rate in patients developing de novo TMA was 33.79% (95% CI: 26.14–41.88%), with 1-year graft survival of 55.39%. Calcineurin inhibitor-related TMA led to ESRD in 33% of affected patients, while rejection-associated TMA resulted in ESRD in 100% of cases.

Transplant glomerulopathy (TG), a morphological lesion reflecting endothelial injury, demonstrates strong associations with graft outcomes. A meta-analysis of 21 publications comprising 6,783 patients found that TG was associated with a combined hazard ratio for graft loss or failure of 3.11 (95% CI 2.44–3.96). Median graft survival in patients with TG was 3.25 years compared to 18.82 years in those without TG—a difference of approximately 15 years.

Post-Transplant Hypertension and Microvascular Factors

Study	Population	Hypertension Prevalence	Blood Pressure Findings
D. Hernández et al., 2021	Low-immunological-risk recipients	90.2-90.4% at baseline	SBP: 134.2 ± 14.9 (CSC) vs 125.7 ± 15.3 mmHg (CSW) at 24 months ($p=0.016$)
C. Cameron et al., 2014	Pediatric recipients	64.7% with hypertension at some point	Controlled hypertension prevalence 78.2% at most recent control
S. Schneider et al., 2015	Adults with post-transplant HTN	Frequent	Office SBP reduction of 23.3 ± 14.5 mmHg with RDN
M. Hornum et al., 2011	Adult recipients	Not specified	MAP decreased from 105 ± 13 to 96 ± 11 mmHg ($p=0.005$) despite 20% fewer antihypertensives

Hypertension prevalence exceeds 90% in kidney transplant recipients at baseline in some cohorts. Corticosteroid withdrawal appears to improve blood pressure control, with one study demonstrating significantly lower systolic blood pressure at 24 months in the withdrawal group (125.7 ± 15.3 mmHg vs 134.2 ± 14.9 mmHg, $p=0.016$).

Mechanisms Linking Microvasculature to Hypertension

Sympathetic overactivity contributes substantially to post-transplant hypertension. The preservation of sympathetic afferent activity from native non-functional kidneys, in the absence of efferent feedback to the transplant, perpetuates neurohumoral activity that drives hypertension. Renal sympathetic denervation (RDN) of the native kidneys in transplant recipients resulted in significant reduction in office systolic blood pressure (-23.3 ± 14.5 mmHg, $p=0.001$) and converted more patients from non-dippers to dippers ($p=0.035$).

Calcineurin inhibitor-induced vascular toxicity is mediated through activation of the mineralocorticoid receptor (MR) in vascular smooth muscle cells. This pathway contributes to vasoconstriction, increased arterial resistance, and persistent arterial stiffness post-transplant. Each 1 m/s increase in pulse wave velocity is associated with higher all-cause mortality (HR 1.36, 95% CI 1.14 to 1.62, $p=0.001$).

Immunosuppressive regimen choice affects vascular outcomes. A comparison of sirolimus-based versus cyclosporine-based immunosuppression demonstrated that at 7 months post-transplant, systolic blood pressure was significantly lower in the sirolimus group (119 ± 3 vs 138 ± 4 mmHg, $p < 0.05$) and flow-mediated dilation was higher ($13.1 \pm 0.9\%$ vs $9.9 \pm 0.9\%$, $p < 0.05$), suggesting that calcineurin inhibitor-free regimens preserve endothelial function and reduce hypertension.

Blood Pressure Monitoring and Outcomes

Ambulatory blood pressure monitoring (ABPM) provides superior prognostic information compared to office measurements. A systematic review of 22 studies with 2,078 participants found that BP assessed by ABPM was a stronger predictor of renal function decline than traditional office measurements in 10 of 12 studies examining renal endpoints. ABPM also correlated better with echocardiographic abnormalities including left ventricular mass index and with markers of vascular damage such as carotid intima-media thickness. Abnormal circadian BP patterns (non-dippers and reverse dippers) identified a group of recipients at risk for both kidney function loss and cardiovascular abnormalities.

Associations Between Microvascular Parameters and Transplant Outcomes

Quantitative relationships between microvascular assessments and clinical outcomes provide evidence for the prognostic utility of microvascular evaluation.

Microvascular Parameter	Outcome	Effect Estimate	Study
Retinopathy	ESRD	HR 2.12 (95% CI 1.39–3.22)	M. Aronov et al., 2021
Retinopathy	CKD prevalence (general population)	OR 1.31 (95% CI 1.14–1.50)	M. Aronov et al., 2021
Retinopathy	CKD prevalence (type 2 diabetes)	OR 1.68 (95% CI 1.68–2.16)	M. Aronov et al., 2021
CRAE narrowing	Prevalent CKD	OR 1.41 (95% CI 1.09–1.82)	M. Aronov et al., 2021
Early RI (highest tertile)	Combined graft loss/death	HR 10.88	A. Kolonko et al., 2012
Early RI (highest tertile)	Death	HR 45.3 ($p = 0.09$)	A. Kolonko et al., 2012
Terminal vascular resistance	Delayed graft function	OR 3.12 (95% CI 1.76–6.09, $p = 0.012$)	C. Ding et al., 2018
Terminal vascular resistance	Graft survival	HR 2.06 (95% CI 1.32–5.16, $p = 0.032$)	C. Ding et al., 2018
Transplant glomerulopathy	Graft loss/failure	HR 3.11 (95% CI 2.44–3.96)	G. Kovács et al., 2020
RHI	Cerebrovascular events	Significantly associated ($p = 0.004$)	A. Cerqueira et al., 2021
CD20+ B-cell infiltration	Graft loss	OR 2.68 (95% CI 1.43–5.02)	Ying-ying Lu et al., 2017
CD20+ B-cell infiltration	Steroid resistance	OR 30.17 (95% CI 9.77–93.16)	Ying-ying Lu et al., 2017

Retinal microvascular signs demonstrate consistent associations with kidney disease outcomes. Retinopathy is associated with a two-fold increased risk of ESRD (HR 2.12) and with CKD prevalence in both general populations (OR 1.31) and specifically in type 2 diabetic patients (OR 1.68). Central retinal artery equivalent narrowing is independently associated with prevalent CKD (OR 1.41).

The renal resistive index measured during hypothermic machine perfusion has emerged as a predictor of transplant outcomes. Multivariate analysis identified terminal resistance as an independent predictor of both delayed graft function (OR 3.12, 95% CI

1.76–6.09, $p=0.012$) and graft survival (HR 2.06, 95% CI 1.32–5.16, $p=0.032$). Similarly, RRI measured in the early post-transplant period likely reflects systemic vascular disease burden rather than graft-specific hemodynamics, with five of eight studies reporting significant associations between higher RRI and mortality.

Endothelial function measured by reactive hyperemia index (RHI) was significantly associated with cerebrovascular events ($p=0.004$) and composite cardiovascular outcomes ($p=0.035$) in pre-dialysis CKD patients, though it was not associated with CKD progression or all-cause mortality.

Proposed Mechanisms Linking Microvascular Dysfunction to Transplant Outcomes

Mechanism	Key Mediators	Consequence	Evidence Source
RAAS dysregulation	Angiotensin II, endothelin	Arteriolar narrowing, sclerotic changes	M. Aronov et al., 2021
Nitric oxide pathway impairment	Elevated ADMA, NOS inhibition	Impaired vasodilatory responses	Marieta P. Theodorakopoulou et al., 2025
Oxidative stress	Reactive oxygen species	Endothelial damage	D. Kirkman et al., 2019
Complement activation	Alternative pathway dysregulation	Thrombotic microangiopathy	Chien-Ya Hsiung et al., 2024
Calcineurin inhibitor toxicity	MR activation in VSMCs	Vasoconstriction, vasculopathy	Laila-Yasmin Mani et al., 2022

Chronic inflammation and oxidative stress represent core mechanisms of endothelial dysfunction in CKD. Proteinuria is associated with elevated asymmetric dimethylarginine (ADMA) and nitric oxide synthase inhibition, leading to impaired vasodilatory responses. Exercise training improves microvascular function in part through improved redox balance, as demonstrated by the observation that pharmacological delivery of the superoxide scavenger tempol improved microvascular function at baseline but was no longer effective after exercise training.

The complement system plays a central role in thrombotic microangiopathy development. Genetic mutations in complement regulatory factors (CFH, CFI, C3) increase recurrence risk after transplantation. Calcineurin inhibitors cause an imbalance of vasodilators and vasoconstrictors, leading to endothelial damage and microparticle release. Eculizumab, which targets complement protein C5, has shown efficacy in preventing and treating post-transplant TMA.

Hemodynamic and Structural Consequences

Microvascular dysfunction contributes to cardiovascular abnormalities through multiple pathways. Arterial stiffening increases left ventricular afterload while metabolic stimuli including inflammation and oxidative stress promote ultrastructural changes such as capillary deficit affecting left ventricular compliance and contractility. The hyperfiltration mechanism following nephrectomy in living donors involves changes in resistive index, vascular endothelial growth factor (VEGF), and heparan sulfate, with more prominent and rapid changes in arcuate artery RI observed in those with adaptive versus maladaptive hyperfiltration. Hyperuricemia mediates endothelial dysfunction, inflammation, and vascular disease in transplant recipients. Uric acid stimulates vascular renin-angiotensin systems and is associated with graft dysfunction and chronic allograft nephropathy. Long-term hyperuricemia contributed to decline in eGFR, with no significant difference in eGFR at less than 12 months but significant differences emerging with longer follow-up.

Interventions Affecting Microvasculature in CKD and Transplantation

Multiple pharmacological and non-pharmacological interventions have demonstrated effects on microvascular parameters relevant to transplant outcomes.

Pharmacological Interventions

Intervention	Mechanism	Effect on Microvasculature	Clinical Outcome	Study
Marine n-3 fatty acids	Anti-inflammatory, improved FA oxidation	Increased FMD ($2.0 \pm 3.8\%$ vs $0.5 \pm 2.4\%$, $p=0.02$)	Safe, reduced inflammation markers	I. Eide et al., 2018
Sirolimus vs cyclosporine	Endothelial preservation	Higher FMD (13.1% vs 9.9%, $p<0.05$)	Lower SBP (119 vs 138 mmHg)	R. Joannidés et al., 2010
Belatacept conversion	Avoidance of CNI toxicity	Not directly measured	Improved eGFR (+6.9 mL/min at 6 months)	D. Bertrand et al., 2017
RAS blockers (pediatric donors)	Reduced hyperfiltration injury	Not directly measured	Improved long-term graft survival (OR 0.38)	Rubin Zhang et al., 2013
CCBs	Vasodilation	Increased GFR (+3.08 mL/min)	Reduced graft loss (RR 0.58)	A. Pisano et al., 2019
ACEIs	RAAS inhibition	Not directly measured	Reduced graft loss (RR 0.62)	A. Pisano et al., 2019
Eculizumab (prophylactic)	Complement C5 inhibition	Prevents TMA	Recurrent TMA 6.3%, graft loss due to TMA 5.5%	M. G. Gonzalez Suarez et al., 2019
Eplerenone	MR antagonism	Reduced arterial stiffness (PWV)	Under investigation	Arnaud Simon et al., 2025

Calcium channel blockers demonstrated favorable effects in a systematic review of 26 trials, reducing graft loss risk (RR 0.58, 95% CI 0.38–0.89), increasing GFR (mean difference 3.08 mL/min, 95% CI 0.38–5.78), and reducing blood pressure. ACE inhibitors also reduced graft loss risk (RR 0.62, 95% CI 0.40–0.96) but decreased renal function and increased hyperkalaemia risk. In direct comparisons, CCBs increased GFR by 11.07 mL/min (95% CI 6.04–16.09) compared to ACEIs or ARBs.

Early RAS blocker use in adults receiving single pediatric donor kidneys demonstrated significant benefit for long-term graft survival. Death-censored graft survival was superior with RAS blockers: 95% vs 81.2% at 1 year, 82.4% vs 61.2% at 3 years, 72.6% vs 58.5% at 5 years, and 68.5% vs 47.2% at 7 years (log rank $p=0.043$). RAS blockers reduced the risk of graft loss (OR 0.38, 95% CI 0.18–0.79, $p=0.009$).

Non-Pharmacological Interventions

Intervention	Duration	Effect on Microvasculature	Clinical Outcome	Study
Aerobic exercise training	12 weeks, 3×45 min/week	Improved microvascular function ($87 \pm 2\%$ to $91 \pm 2\%$, $p=0.03$)	Maintained conduit artery function	D. Kirkman et al., 2019

Intervention	Duration	Effect on Microvasculature	Clinical Outcome	Study
Aerobic exercise training	12 weeks	Improved RHI (1.78±0.10 to 2.01±0.13, p=0.03)	Reduced peak SBP during exercise (186±5 to 174±4 mmHg)	Justin D Sprick et al., 2022
Exercise training (meta-analysis)	2.5-12 months	Reduced PWV (WMD -0.56, p=0.02), AIX (WMD -3.26, p=0.004)	Improved peak VO ₂ , general health	Huan Wang et al., 2022
Renal denervation	Single procedure	Non-dipper to dipper conversion (p=0.035)	Office SBP reduction -23.3 mmHg	S. Schneider et al., 2015
Renal denervation	Single procedure	Decreased RRI in those with RRI ≥0.7 (-0.024, p=0.035)	Stabilized kidney function	M. Manukyan et al., 2022

Aerobic exercise training consistently improves microvascular function in CKD patients. A meta-analysis of 18 RCTs with 817 patients demonstrated that exercise was significantly associated with decreased pulse wave velocity (WMD -0.56, 95% CI -1.02 to -0.09, p=0.02) and augmentation index (WMD -3.26, 95% CI -5.46 to -1.05, p=0.004). In nondialysis CKD patients, 12 weeks of moderate-to-vigorous aerobic exercise improved microvascular function from 87±2% to 91±2% (p=0.03), with evidence suggesting improved redox balance as the mechanism.

Renal denervation of native kidneys in transplant recipients with resistant hypertension demonstrated significant blood pressure reduction (-23.3 ± 14.5 mmHg in office SBP) and conversion of patients from non-dippers to dippers (p=0.035). In patients with resistant hypertension and diabetes, renal denervation decreased elevated renal vascular resistance (RRI ≥0.7) by -0.024 (95% CI -0.046 to -0.002, p=0.035) independently of its blood pressure-lowering effect.

Machine Perfusion Optimization

Hypothermic machine perfusion (HMP) parameters influence graft microvascular outcomes. In a retrospective review of 76 DCD kidney transplants, increasing HMP pressure from 30 to 40 mmHg in kidneys with poor flow and/or vascular resistance improved perfusion parameters without affecting DGF incidence. Among patients who developed DGF, the increased pressure group demonstrated shorter kidney function recovery time (20.2 vs 25.4 days). Terminal vascular resistance was identified as an independent predictor of both DGF (OR 3.12) and graft survival (HR 2.06).

Synthesis

Evidence in 80 sources is shown to present a consistent finding of a relationship from microvascular dysfunction in CKD to adverse kidney transplant outcomes, though heterogeneity in assessment methods, populations, and outcome definitions requires careful interpretation.

Integration of Findings Across Microvascular Domains

The relationship between microvascular health and transplant outcomes occurs through multiple interconnected pathways. Retinal microvascular changes predict kidney disease progression and outcomes with hazard ratios of 2.12 for ESRD, while early post-transplant resistive index predicts combined graft loss/death with hazard ratios up to 10.88. These findings from distinct vascular beds suggest systemic microvascular dysfunction in CKD that influences both disease progression and transplant adaptation. Functional microvascular assessments demonstrate progressive impairment with CKD severity and proteinuria. Proteinuric CKD patients show significantly impaired tissue saturation index reperfusion slopes (p=0.002) and attenuated cerebral oxygenation responses (p=0.012). These functional deficits likely reflect the same endothelial dysfunction and oxidative stress pathways that contribute to adverse graft outcomes.

Reconciling Heterogeneous Findings on Hypertension

Post-transplant hypertension prevalence exceeds 90% in some cohorts yet blood pressure improves following successful transplantation despite deteriorating insulin sensitivity. This apparent paradox is explained by distinguishing between uremia-related vascular dysfunction (which improves with transplantation) and immunosuppression-induced vascular toxicity (which

may persist or worsen). Studies demonstrating improved arterial function with sirolimus versus cyclosporine (SBP 119 vs 138 mmHg) support the contribution of calcineurin inhibitor-specific toxicity to post-transplant hypertension.

The finding that ambulatory blood pressure monitoring provides superior prognostic information compared to office measurements has important clinical implications, suggesting that standard office blood pressure assessment may underestimate the microvascular burden in transplant recipients.

Context-Dependent Interpretation of Interventions

The benefit of specific interventions varies by patient characteristics and timing. RAS blockers provide substantial long-term graft survival benefit when used early after transplantation in adults receiving pediatric donor kidneys (OR 0.38 for graft loss), likely through mitigation of hyperfiltration injury in these susceptible grafts. In contrast, the same agents may decrease renal function acutely and increase hyperkalaemia risk in general transplant populations.

Calcium channel blockers demonstrated consistent benefits across multiple outcomes including reduced graft loss (RR 0.58) and improved GFR (+3.08 mL/min), suggesting they may be preferred first-line agents for post-transplant hypertension. The direct comparison showing CCBs increase GFR by 11.07 mL/min versus ACEIs/ARBs supports this approach for graft function preservation.

Exercise interventions demonstrate robust improvements in microvascular function (effect size -0.56 for PWV, -3.26 for AIX) and should be considered adjunctive therapy in both pre-transplant CKD populations and transplant recipients. The finding that exercise improves microvascular function through improved redox balance provides mechanistic support for this non-pharmacological approach.

Methodological Considerations Affecting Conclusions

Several factors limit definitive conclusions from this evidence base. First, microvascular assessment methods vary substantially across studies, from retinal imaging to sublingual microscopy to functional MRI, making direct comparisons challenging. Second, many studies relied on abstract-only information (56 of 80), potentially limiting the depth of methodological assessment. Third, follow-up durations ranged from acute perioperative assessment to 7 years, complicating synthesis of short- versus long-term outcomes.

The moderate-to-high risk of bias identified in the systematic review of renal resistive index prognosis applies broadly to this literature, where observational designs predominate and standardized microvascular thresholds remain undefined. The significant heterogeneity in the transplant glomerulopathy meta-analysis ($I^2=67.3\%$) reflects the complexity of translating microvascular histology to clinical outcomes.

Despite these limitations, the consistency of associations across different assessment methods, populations, and outcome definitions supports a genuine relationship between microvascular health and transplant outcomes that merits clinical attention and targeted intervention strategies.

DISCUSSION

This comprehensive systematic review of 80 studies provides compelling evidence that microvascular rarefaction and dysfunction are central pathophysiological features of CKD with profound consequences for kidney transplantation. The discussion synthesizes these findings, explores their clinical implications, acknowledges limitations, and proposes future directions. Microvascular Dysfunction as a Systemic Marker in CKD

The reviewed literature confirms that CKD is a state of pervasive microvascular injury. Structural changes, such as retinal arteriolar narrowing and choroidal thinning, and functional impairments, including reduced capillary density and blunted vasodilatory responses, are detectable across multiple vascular beds (Aronov et al., 2021; Theodorakopoulou et al., 2025). These abnormalities are not mere epiphenomena but are mechanistically linked to CKD progression through shared pathways of endothelial dysfunction, chronic inflammation, and oxidative stress (Cerqueira et al., 2021; Kirkman et al., 2019). Importantly, the severity of microvascular impairment correlates with CKD stage and the presence of proteinuria, the latter being associated with significantly worse tissue oxygenation and reperfusion capacity (Theodorakopoulou et al., 2024). This positions microvascular health as a quantifiable, systemic reflection of overall vascular and renal risk in the CKD population.

Prognostic Value of Microvascular Assessment for Transplantation

A key finding is the strong prognostic value of pre- and early post-transplant microvascular assessments. The renal resistive index (RI), measured by Doppler ultrasound shortly after transplantation, emerges as a powerful predictor. Patients in the highest RI tertile (>0.85) had a hazard ratio of 10.88 for the combined outcome of graft loss or death (Kolonko et al., 2012). This likely reflects the burden of systemic vascular disease and stiffness in the recipient, which impedes optimal graft perfusion. Similarly, retinal microvascular signs, such as retinopathy and arteriolar narrowing, are associated with a two-fold increased risk of ESRD and prevalent CKD (Aronov et al., 2021). These non-invasive tools offer a practical means of risk stratification, potentially identifying recipients who may benefit from more intensive monitoring or tailored therapeutic interventions to protect the graft. The Dual Impact of Transplantation on the Microvasculature

The post-transplant period presents a complex interplay between recovery from uremia and new insults from immunosuppression. On one hand, successful transplantation reverses some uremia-related vascular dysfunction, as evidenced by improvements in

arterial stiffness and endothelium-independent dilation within the first year (Hornum et al., 2011). On the other hand, immunosuppressive agents, particularly calcineurin inhibitors (CNIs) like tacrolimus and cyclosporine, exert direct microvascular toxicity. CNIs induce endothelial dysfunction, vasoconstriction, and contribute to the development of hypertension and thrombotic microangiopathy (TMA) (Hsiung et al., 2024; Mani et al., 2022). Studies comparing CNI-based regimens to CNI-free regimens (e.g., belatacept or sirolimus) consistently show better preservation of endothelial function, lower blood pressure, and improved graft microvascular perfusion in the latter groups (Joannidés et al., 2010; Bertrand et al., 2017; Dijk et al., 2018). This highlights the critical importance of balancing immunosuppressive efficacy with microvascular preservation.

Post-Transplant Hypertension: A Microvascular Disorder

Hypertension after transplantation is exceedingly common (prevalence >90% in some cohorts) and is a major driver of cardiovascular disease and graft failure (Hernández et al., 2021). Our synthesis reveals that post-transplant hypertension is intricately linked to microvascular pathology. Mechanisms include CNI-induced vascular toxicity, sympathetic overactivity from native kidneys, and persistent arterial stiffness (Schneider et al., 2015; Pisano et al., 2021). Ambulatory blood pressure monitoring (ABPM) provides superior prognostic information compared to office readings, with non-dipping patterns identifying high-risk patients (Pisano et al., 2021). This underscores that hypertension in transplant recipients is not merely a hemodynamic issue but a manifestation of underlying microvascular and autonomic dysfunction.

Therapeutic Implications: Targeting the Microvasculature

The review identifies several interventions with beneficial effects on microvascular health:

- **Pharmacological:** Calcium channel blockers (CCBs) appear particularly favorable, reducing graft loss risk and improving GFR, possibly due to their vasodilatory effects on the afferent arteriole (Pisano et al., 2019). Renin-angiotensin system (RAS) blockers offer significant long-term graft survival benefits, especially in specific contexts like recipients of pediatric donor kidneys, likely by mitigating hyperfiltration injury (Zhang et al., 2013). Targeted therapies like eculizumab for complement-mediated TMA directly address severe microvascular injury (Gonzalez Suarez et al., 2019).
- **Non-Pharmacological:** Aerobic exercise training is a potent intervention, consistently improving endothelial function, reducing arterial stiffness, and enhancing microvascular reactivity in CKD and transplant patients (Kirkman et al., 2019; Wang et al., 2022). Renal denervation of native kidneys shows promise for treating resistant hypertension linked to sympathetic overactivity (Schneider et al., 2015).
- **Perioperative Management:** Optimizing machine perfusion parameters for donor kidneys can improve microvascular flow and potentially reduce delayed graft function (Ding et al., 2018).

Summary and Future Directions

In summary, microvascular rarefaction is a critical, modifiable link between CKD and adverse kidney transplant outcomes. Assessing microvascular health provides valuable prognostic information and can guide personalized therapy. Future research should prioritize:

1. Prospective, longitudinal cohort studies using standardized microvascular protocols to establish causal relationships and normative values in transplant populations.
2. Randomized controlled trials testing microvascular-targeted interventions (e.g., specific exercise regimens, early CNI avoidance, novel vasoprotective drugs) on hard graft and patient outcomes.
3. Mechanistic studies to better understand the molecular pathways connecting uremia, immunosuppression, and microvascular injury.
4. Integration of multimodal microvascular assessment into clinical transplant registries to facilitate large-scale outcomes research.

By embracing a "microvascular perspective," the transplant community can move towards a more holistic model of care that addresses not only immunological rejection but also the systemic vascular health of the recipient, ultimately striving for longer-lasting graft function and improved patient survival.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review unequivocally demonstrates that microvascular rarefaction and dysfunction are fundamental components of chronic kidney disease (CKD) pathophysiology that extend their detrimental influence into the post-kidney transplant period. The compromised systemic microvasculature in transplant recipients, assessed through various modalities like retinal imaging, Doppler ultrasound, and functional tests, is associated with poorer graft adaptation, increased risk of delayed graft function, higher rates of graft loss, and significant cardiovascular morbidity, particularly hypertension. The toxicity of calcineurin inhibitor-based immunosuppression exacerbates this microvascular injury, while interventions such as aerobic exercise, calcium channel blockers, and CNI-free regimens show promise in mitigating damage. Therefore, microvascular health represents a crucial, though currently underutilized, dimension in the comprehensive care of kidney transplant recipients.

Recommendations

Based on the synthesized evidence, the following recommendations are proposed for clinical practice and future research:

For Clinical Practice:

1. **Incorporate Microvascular Assessment:** Consider integrating non-invasive microvascular assessments, such as retinal photography or Doppler-based renal resistive index measurement, into pre-transplant evaluation protocols for risk stratification.

2. **Personalize Immunosuppression:** In recipients with significant pre-existing microvascular disease or high cardiovascular risk, consider the benefits of calcineurin inhibitor-minimizing or -free immunosuppressive protocols, weighing them against immunological risk.
3. **Manage Hypertension Proactively:** Utilize ambulatory blood pressure monitoring (ABPM) to accurately diagnose and guide the management of post-transplant hypertension, targeting restoration of normal diurnal patterns. Favor antihypertensive agents like calcium channel blockers that have evidence for graft protection.
4. **Prescribe Exercise as Medicine:** Systematically recommend and support structured aerobic exercise programs for transplant candidates and recipients as a safe and effective strategy to improve microvascular and endothelial function.
5. **Adopt a Holistic Care Model:** Manage transplant recipients with an awareness that their systemic vascular health is integral to graft longevity, requiring collaboration between nephrologists, cardiologists, and allied health professionals.

For Future Research:

1. **Standardize Methodologies:** Develop and validate consensus protocols for microvascular assessment in nephrology and transplantation research to enable data pooling and comparison.
2. **Conduct Targeted Trials:** Design and execute large-scale, multicenter randomized controlled trials to evaluate whether interventions proven to improve microvascular parameters (e.g., specific exercise interventions, early RAS blockade, SGLT2 inhibitors) translate into improved long-term graft and patient survival.
3. **Explore Novel Biomarkers:** Investigate the role of circulating biomarkers of endothelial dysfunction and angiogenesis as scalable tools for monitoring microvascular health and response to therapy.
4. **Longitudinal Studies:** Establish longitudinal cohorts to track the natural history of microvascular changes from advanced CKD through transplantation and long-term follow-up, identifying critical windows for intervention.

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