Vascular Endothelial Growth Factor Therapy for the Kidney: Are We There Yet?

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CKD is a progressive disorder affecting almost 14% of the general population. The prevalence of CKD has continuously increased over the past two decades, coincident with the obesity and diabetes epidemics. Indeed, CKD is an independent risk factor for cardiovascular morbidity and mortality, as the prevalence of CKD has doubled in recent years to a staggering 40.8% in patients with diagnosed cardiovascular disease. Patients with CKD have higher rates of hospitalization, greater mortality, and shorter life expectancy. Significant efforts have been devoted to discovering therapeutic strategies that may reverse, stop, or at least slow the progressive nature of CKD, which frequently results in irreversible loss of renal function, ESRD, and the need of RRTs.

Regardless of the etiology, an almost universal pathologic feature of CKD/ESRD is a progressive alteration of the renal microcirculation. Indeed, microvascular dysfunction, damage, and even loss are hallmarks of renal disease in humans, which correlate with the development of renal dysfunction and injury and may both initiate and promote interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Unlike nephrons, with numbers that are determined at birth and (still) cannot be regenerated or recreated de novo, the vessels in the kidney are subject to changes in their diameter, remodeling, and possibly, repair and regeneration. Development of new vessels in the kidney is not limited to the developmental phase of the organ and serves as compensatory mechanism in response to insults that could also be activated or stimulated by therapeutic interventions. Previous studies in chronic renal disease with different etiologies have shown that renoprotective effects of experimental and clinically available drugs, such as antioxidants, endothelin or angiotensin receptor blockers, and statins, to name a few, are associated with a preservation of the renal microvasculature. Furthermore, therapeutic interventions using angiogenic cytokines or progenitor cells which are known to have a primary effect on vascular proliferation, have also led to marked improvements in renal function and damage accompanied by recovery of the microvascular architecture, underscoring the potential of the renal microcirculation as a therapeutic target.

Vascular endothelial growth factor (VEGF) is a prominent endogenous angiogenic cytokine that plays pivotal roles in the maintenance of the vascular networks in virtually every tissue. The kidney is both a source and a target of VEGF. Major sources of renal VEGF are tubular epithelial cells and podocytes, whereas endothelial cells and podocytes (acting in both autocrine and paracrine fashions) are major targets. Recent studies showed that renal levels of VEGF are altered in pathologic situations, such as chronic and acute renal ischemia, diabetic—induced renal injury, atherosclerosis, or metabolic syndrome, suggesting a potential pathologic role of this cytokine to promote profound microvascular dysfunctional and morphologic changes. Elegant seminal studies by the laboratories of Johnson and colleagues and Basile and colleagues showed that VEGF therapy reduced renal damage and protected the microvasculature in rodent models of chronic renal disease. Our recent studies also show a renoprotective effect of VEGF administration in a swine model of chronic renal artery stenosis, where a progressive decrease in the renal expression and bioavailability of VEGF is associated with microvascular rarefaction and renal failure. We showed that intrarenal VEGF therapy in both preventive (i.e., from the onset of disease) and interventional (i.e., advanced renal disease and established injury) fashions substantially preserves the renal microvasculature, improves renal function, and reduces renal fibrosis in this model, implying that loss of VEGF is mechanistically important and not a mere bystander in the development of renal damage. The findings of these studies are further supported by the contributions from the laboratory of Quaggin and colleagues that showed that VEGF inhibition is deleterious for podocyte health and overall renal function. All together, these data support a pathophysiologic role for reduced VEGF and suggest the potential for therapeutic application of VEGF therapy for the kidney. Nevertheless, despite this promising evidence, concerns remain about the potential for the administration of this ubiquitous cytokine. Indeed, the potential for promoting abnormal or dysfunctional neovascularization as well as accelerating tumor growth warrants careful selection of potential patients and may likely play a role in delaying clinical testing of VEGF therapy.
Polycystic kidney disease (PKD) is the most common hereditary kidney disease characterized by a pathologic growth of cysts that starts in utero and relentlessly continues throughout life. It is the fourth leading cause of CKD in adults and causes 5%–10% of all ESRD, without preference for sex or race. The current therapeutic strategies focus on the management of chronic pain and hypertension as well as the unequivocal signs of renal compromise, which eventually develops and may lead to progressive renal failure and ESRD in adulthood in up to 60% of patients.23 In this issue of JASN, Huang et al.24 provide supportive data for the development of a potential strategy for treating PKD using VEGF-C therapy. The growth of the pathognomonic cysts in PKD carries an expansion of the vasculature to supply newly developed structures, which are driven by enhanced renal angiogenic activity likely triggered by local hypoxia. The work by Huang et al.24 focuses on VEGF-C using mouse models of autosomal dominant Pkd1−/− and a recessive form of PKD (Cys1484Stop). Even in the absence of a sustained reduction in VEGF-C activity (only observed very early), administration of exogenous VEGF-C stimulates the downstream signaling of this cytokine, with a functional and structural consequence on the effect of PKD, because less damage and improvement in some markers of renal function were observed. One of the most intriguing findings is the proposed role of the VEGF-C/vascular endothelial growth factor receptor 3 (VEGFR3) pathway as an organizer of neovascularization in PKD, which may have been achieved by the beneficial effect of VEGF-C therapy on the development of both the lymphatic and the vascular networks. The VEGF-C/VEGFR3 participates in the sprouting of the lymphatic endothelium during development and regulates angiogenesis of the lymphatic vasculature.25 The augmented phosphorylation of the VEGFR3 induced by VEGF-C therapy (without modifying renal VEGF-C levels) implies that translational or posttranslational mechanisms in the renal VEGF pathway may have been somehow restored by exogenous VEGF-C in this model. Although PKD-induced neovascularization results in a disorganized and dysfunctional vascular network, previous studies showing antiangiogenic interventions in PKD by inhibition of VEGF did not result in improvements and may even accelerate the progression of the disease and renal deterioration. Therefore, the work by Huang et al.24 supports the notion that an intact VEGF-C pathway is pivotal in the pathophysiology of PKD and that the restarting of the VEGF-C/VEGFR3 pathway by VEGF-C therapy likely slowed the progression of renal injury and prolonged the survival of the treated animals.

One potential limitation of the study is the relatively short timeframe in which these experiments were performed.24 Although these models rapidly develop PKD, this study is most relevant to using VEGF-C as an intervention during very early stages of PKD in humans.24 Thus, longer observation and/or administration of VEGF-C therapy at later stages of PKD (with greater development of renal damage) will be necessary to determine the true potential of this intervention. Another potential limitation is that Huang et al.24 did not study markers of podocyte injury, which are a critical component of the glomerular filtration barrier and a major target of the VEGF-C/VEGFR3 pathway,26,27 or measure proteinuria in their study. Therefore, whether VEGF-C therapy may also preserve the integrity and function of podocytes is uncertain and requires additional studies to further elucidate the mechanisms, extent, and potential of this strategy to preserve or delay the development and progression of renal injury in PKD.

Whether renal VEGF therapy is ready for clinical use remains to be determined. However, important proof-of-concept studies, such as the one described by Huang et al.24 in this issue of JASN, provide hope for a novel (sole or adjuvant) therapeutic development to protect the kidney and may contribute to defining a comprehensive therapeutic strategy to slow or halt the progression of renal damage in patients with PKD. Furthermore, studies such as these give important insight for potential new avenues for application of renal VEGF therapy in not only PKD but also, other diseases associated with microvascular abnormalities that present and are possibly driven by defective generation, expression, and activity of the VEGF pathway.

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DISCLOSURES

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REFERENCES


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