Beyond Preeclampsia, Soluble FLT1 in Kidney Disease

By Isaac Yang and Tomokazu Souma

Vascular endothelial growth factor (VEGF or VEGF-A) is a powerful vascular growth factor and is important for maintaining glomerular health. Clinically, an anti-VEGF state induces glomerular injury. For example, excess placental production of soluble Fms-like tyrosine kinase (sFLT1), a decoy receptor for VEGF, causes preeclampsia. Moreover, patients treated with VEGF inhibitors show glomerular pathologies and hypertension. Recently, Wewers et al. report a comprehensive review on the role of circulating sFLT1 in kidney diseases other than preeclampsia (1).

The kidney vasculature is particularly dependent on VEGF-VEGF receptor 2 (VEGFR2) signaling for its development and maintenance (1, 2). Podocyte-derived VEGF is critical for glomerular health, and tubular epithelial cell-derived VEGF is essential for developing peritubular capillaries. Although downregulation of VEGF signaling causes glomerular injury, excess VEGF is also detrimental to renal pathologies, including diabetic nephropathy (1). Therefore, VEGF expression must be regulated tightly for healthy glomerular and vascular functions, and the role of sFLT1 reflects the specific role of VEGF in each condition. Importantly, sFLT1 exerts its function locally and systemically. sFLT1 can be introduced into circulation and inhibits the proangiogenic function of VEGF in remote organs. sFLT1 can also control cellular functions locally by modulating local VEGF availability and directly activating intracellular signaling pathways independent of VEGFR signaling (1, 2).

To summarize the results of clinical studies testing the roles of circulating sFLT1 in multiple kidney diseases, the authors selected peer-reviewed articles published between 2009 and 2020, which investigated the association of sFLT1 and kidney function in chronic kidney disease, acute kidney injury (AKI), and kidney transplantation. Most studies show that the elevated circulating sFLT1 level is associated with adverse outcomes, such as lower estimated glomerular filtration rate (eGFR), slower recovery from AKI, and delayed graft function. However, one report suggests that a high level of sFLT1 could be more beneficial than harmful in coronary artery disease in patients with kidney disease (Figure 1) (1). Finally, the authors discuss several unanswered questions that need to be addressed before considering therapeutic removal of circulating sFLT1. For example, it is essential to answer whether sFLT1 is a pure biomarker of metabolic disturbances, or its elevation is harmful and causing disease. In summary, this review establishes the status quo for future mechanistic and clinical studies to better understand the role of sFLT1 in kidney diseases. ■

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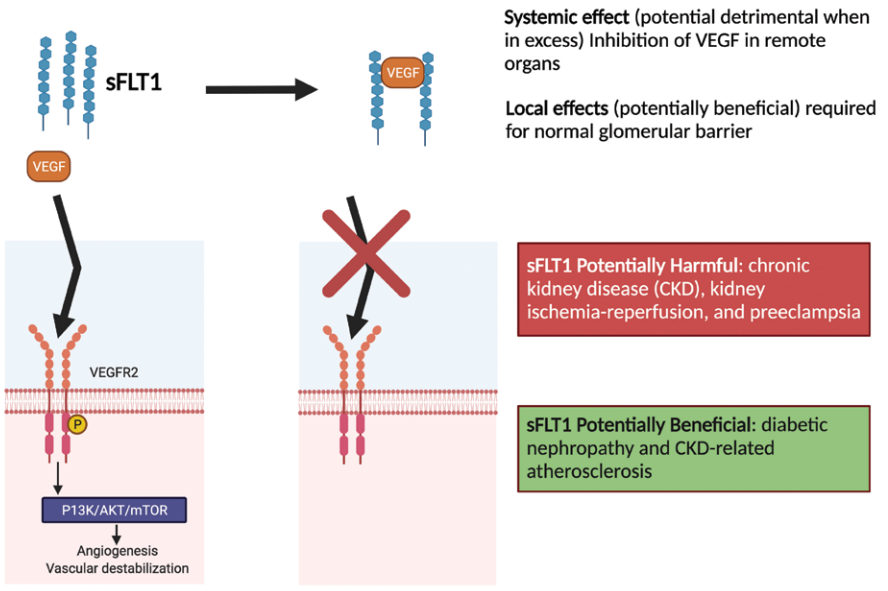
Figure 1. sFLT1 is a natural antagonist for vascular endothelial growth factor (VEGF)



PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin.

High Complication Rates in Youth with Type 2 Diabetes

Sixty percent of patients with youth-onset type 2 diabetes experience diabetic complications by the time they reach young adulthood, according to long-term follow-up data published in *The New England Journal of Medicine* (1).

[The] risk of complications… increases with age, such that a majority of patients are affected by their mid-20s.

In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, patients with youth-onset type 2 diabetes were assigned to metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention. Patients were then transitioned to metformin alone or metformin plus insulin. The current analysis presents observational follow-up data from 2011 to 2020 in 500 patients.

About 65% of participants were female; 73% were Hispanic or non-Hispanic Black. At follow-up, mean age was 26.4 years and mean time since diabetes diagnosis was 13.3 years. Participants had annual follow-ups for diabetic complications, including annual assessment of diabetic kidney disease, hypertension, dyslipidemia, and nerve disease, plus two assessments for retinal disease.

During follow-up, at least one diabetic complication occurred in 60.1% of patients and at least two complications in 28.4%. Cumulative incidence was 67.5% for hypertension, 54.8% for diabetic kidney disease, 51.6% for dyslipidemia, and 32.4% for nerve disease. Prevalence of retinal disease increased from 13.7% in the follow-up period 2010–2011 to 51.0% in 2017–2018.

Rates of adjudicated, clinically identified complications were 3.73 per 1000 person-years for heart, vascular, and cerebrovascular events; 12.17 per 1000 person-years for all eye disease events; 6.70 per 1000 person-years for liver, pancreas, or gallbladder events; 2.35 per 1000 person-years for nerve events; and 0.44 per 1000 person-years for kidney events, including end-stage kidney disease.

Risk for developing any microvascular complication was about 50% higher for Hispanic and non-Hispanic Black participants, compared to non-Hispanic White patients. In adjusted models, significant risk factors included glycated hemoglobin level, body mass index, insulin sensitivity, hypertension, and dyslipidemia.

As the prevalence of youth-onset type 2 diabetes continues to rise, there is little information about the associated risk of diabetic complications. These longitudinal data show a high risk of complications that increases with age, such that a majority of patients are affected by their mid-20s.

Patients of minority race/ethnicity are at higher risk of complications. The researchers call for studies exploring early aggressive management of glycemia and risk factors in youth-onset type 2 diabetes. ■

Reference

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