Does elastin deficiency cause chronic kidney disease?

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Elastin deficiency in aging and disease is linked to increased vascular stiffness and hypertension, which are both associated with chronic kidney disease. Owens et al. show that alterations in renal arteries and kidney structure precede or are independent of hypertension in elastin haploinsufficient mice. This commentary addresses the authors’ findings in light of the relationships between elastin amounts, vascular stiffness, and pressure wave reflection and transmission in the kidney vasculature.

Kidney International (2017) 92, 1036–1038; http://dx.doi.org/10.1016/j.kint.2017.05.027
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Elastin is necessary for energy storage and pulse dampening in the conduit arteries. Elastin deficiency in disease or aging is associated with conduit artery stiffening. Aortic stiffness, as measured by (PWV), may be a causal factor in isolated systolic hypertension (ISH) due to altered pressure wave reflection in the cardiovascular system. Hypertension, a leading cause of chronic kidney disease (CKD), leads to a state of chronically elevated renal vascular resistance (RVR) that can cause reductions in the glomerular filtration rate (GFR) due to renal hypoperfusion. Conversely, alterations in kidney function can also lead to hypertension.

In this issue of the journal, Owens et al. (2017) address the cause-and-effect relationship between hypertension and kidney function by examining renal arteries and kidney structure and function in a mouse model of elastin haploinsufficiency (Eln+/−) before and after hypertension is fully established. The authors found that renal vascular tone is increased in Eln+/− mice at postnatal day (P) 30, before hypertension is present. Increased tone in Eln+/− renal arteries is mediated by increased activation of AT1R, which has been implicated as a mechanosensor in the cell membrane. Increased vascular tone leads to increased RVR and decreased renal blood flow in Eln+/− mice at P30. By 12 weeks of age, ISH is fully established and Eln+/− mice show kidney fibrosis and abnormalities in podocyte foot processes. Abnormalities in podocyte foot processes are present with and without treatment with the vasodilator hydralazine that abolishes ISH development in Eln+/− mice. The results of Owens et al. suggest that alterations in renal arteries and kidney structure and function due to elastin deficiency contribute to hypertension development and that hypertension then further damages the kidney in a positive feedback cycle.

Hypertension in Eln+/− mice has been attributed to increased stiffness of the aorta, which is detectable by PWV, and to altered reactivity of the resistance vasculature. The study by Owens et al. suggests that alterations in kidney hemodynamics also contribute to hypertension in Eln+/− mice. It remains to be seen whether the changes observed in the kidney are directly related to deficiency of the elastin protein or to global changes in hemodynamics related to alterations in the vasculature. Changes in hemodynamics include alterations in the pressure and flow waveforms in different regions of the arterial tree due to geometric and material property alterations caused by elastin deficiency.

The incident pressure pulse wave generated by the left ventricle moves at a finite velocity (PWV) through the systemic arteries. PWV depends on the intrinsic material stiffness, thickness, and diameter of the arterial wall and is increased in disease and aging. At arterial branch points and with changes in geometry and material stiffness of different regions of the arterial tree, the pressure pulse wave is partly transmitted and partly reflected. Reflected waves interact with the next incident wave and alter resulting pressure wave characteristics in different regions of the arterial tree. Increased PWV can cause reflected waves to augment systolic pressure and is one mechanism for ISH. Increased PWV can also increase pulse pressure, which is then propagated to the microvasculature and leads to...
damage from increased pulsatile stress or strain on the arterial wall. As low-resistance organs, arteries in the brain and kidney are especially susceptible to alterations in pulse pressure. Increased PWV is associated with the development and progression of CKD as well as with a higher incidence of all-cause mortality and the risk of cardiovascular events in CKD patients. Changes in the pulse pressure waveform due to changes in the geometry and material stiffness of the arterial tree, without measurable changes in blood pressure, may be predictive of target organ damage. In young, healthy individuals, stiffness increases in distal arteries so that the resistance arteries are much stiffer than conduit arteries, creating a stiffness mismatch and promoting wave reflection at those sites, which protects the downstream microvasculature. In elastin deficiency with disease or aging, stiffness of the conduit arteries may be increased disproportionately to the resistance arteries, reducing the stiffness mismatch and preventing the protective wave reflection. Hence, small changes in stiffness of the conduit arteries can propagate large changes in hemodynamics and subsequent vascular remodeling in target organs.

Lowering systolic blood pressure with hydralazine did not reverse podocyte abnormalities in Eln+/− mice. This raises the intriguing possibility of elastin involvement in kidney development, which should be further investigated. The persistent podocyte abnormalities could also be due to subtle changes in pressure wave reflection that were not captured in the blood pressure measurements. Due to the nonlinear mechanical behavior of arteries, the material stiffness, and hence PWV, should decrease with applied blood pressure. However, arteries with a high material stiffness will show less dependence of PWV on blood pressure. It has been shown that CKD patients with high PWV that is insensitive to antihypertensive therapy have worse outcomes than CKD patients with high PWV that is sensitive to antihypertensive therapy. The evidence points to persistent cardiovascular and renal effects of elastin deficiency and the resulting changes in large and small artery hemodynamics.

High PWV is associated with a decreased GFR in older individuals. A component of the relationship between PWV and GFR is partly attributable to an association between PWV and the flow pulsatility index of the renal vasculature. An increased pulsatility index may cause constriction, damage, or loss of small arteries, which decreases arterial volume in the cortex, increases RVR, and compromises kidney function. After adjusting for the upstream effects of the pulsatility index, RVR still has a significant independent relationship with the GFR, so other factors besides increased pressure and flow pulsatility may contribute to compromised kidney function in individuals with a high PWV. These “other factors” may also play a role in the persistent podocyte abnormalities in Eln+/− mice, even after ISH was abolished with hydralazine.

Increased PWV causes changes in the timing of transmitted and reflected pressure waves, which alters the resulting blood flow and perfusion of target organs. Blood flow generally moves forward, away from the heart, but there is evidence of aortic flow reversal during diastole that is exaggerated with increased PWV. Flow reversal in the aorta reduces the volume of blood available to the kidneys during diastole. It has been shown that an increase in aortic flow reversal leads to reduced

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**Figure 1** | Interrelationships between elastin deficiency, large- and small-artery hemodynamics, blood pressure, and chronic kidney disease (CKD). AVC, arterial volume in the cortex; GFR, glomerular filtration rate; PWV, pulse wave velocity; RBF, renal blood flow; RVR, renal vascular resistance.
renal blood flow and a decreased GFR.\textsuperscript{7} Aortic flow reversal is correlated with PWV, aortic distensibility, augmentation index, aortic arch length, and aortic diameter, with aortic diameter having the strongest predictive value.\textsuperscript{6} 

Eh−+/− aortas have a decreased diameter, an increased length, and decreased distensibility as early as P7, which may all contribute to altered pulsatile pressure and flow in the renal vasculature and reduced renal blood flow that lead to the observed changes in renal vascular tone, RVR, and kidney structure and function.\textsuperscript{3}

The data presented by Owens et al.\textsuperscript{3} suggest that elastin deficiency and the resulting alterations in large- and small-vessel hemodynamics cause compromised kidney function independent of the effects on individual blood pressure metrics (i.e., systolic or mean pressure). The study also suggests that elastin deficiency may be a cause and not a consequence of CKD. It is important to remember, however, that the relationship is probably not unidirectional. Elastin degradation may contribute to CKD through alterations in large and small arteries, but CKD also likely contributes to elastin degradation in a positive feedback cycle. Individuals with CKD have higher serum levels of elastin-derived peptides, indicative of elastin degradation, than healthy controls.\textsuperscript{9} There is a significant temporal relationship between changes in serum elastin-derived peptide concentration and PWV, and elastin-derived peptide levels are independently associated with all-cause mortality in CKD patients. Inflammation, oxidative stress, and mineral imbalance due to CKD have been suggested as factors leading to the observed elastin degradation, increased PWV, and resulting cardiovascular disease.

Owens et al.\textsuperscript{3} provide insight into the interrelationships between CKD, hypertension, and vascular hemodynamics in the context of elastin insufficiency, as summarized in Figure 1. Important questions to be addressed in future work include experimental measurements or computational simulations of the pressure and flow waveforms at different arterial locations in the mouse to address hypotheses about altered wave reflections. The stimuli leading to altered mechanosensitivity of AT1R in the renal vasculature are unknown and represent a possible therapeutic target for modulation of renal vascular tone and resulting RVR. The direct role of elastin in the kidney, separate from its role in large and small artery hemodynamics, must also be addressed. This could be investigated through cell type–specific modulation of elastin expression.

**DISCLOSURE**

The author declared no competing interests.

**REFERENCES**


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**Going single but not solo with podocytes: potentials, limitations, and pitfalls of single-cell analysis**

Mario Schiffer\textsuperscript{1}

Single-cell RNA-sequence (RNA-seq) is a widely used tool to study biological questions in single cells. The discussed study identified 92 genes being predominantly expressed in podocytes based on a 5-fold higher expression compared with endothelial and mesangial cells. In addition to technical pitfalls, the question that is discussed in this commentary is whether results of a single-cell RNAseq study are able to deliver expression data that truly characterize a podocyte.

Kidney International (2017) 92, 1038–1041; http://dx.doi.org/10.1016/j.kint.2017.05.033

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