HbAS provides some protection from mortality, then that also would elevate the observed prevalence of HbAS in this sample.

Implications for care are also raised by the authors’ suggesting a possible need for additional monitoring of dialysis access and possible modifications for anemia management. This assertion is likely a bit premature, because we do not have any evidence that practices specific to patients with HbAS alter outcomes related to either of these key components of dialysis care; no data regarding erythropoietin-stimulating agents or hemoglobin levels are presented in this study. Additional research is needed before calling for modification of clinical practice. There also is not enough convincing evidence for universal screening for sickle cell hemoglobinopathies in patients with kidney disease. Overall, the therapeutic approach is the same whether it is for CKD or dialysis therapy. Again, until additional research provides evidence for efficacy of a unique approach for patients with HbAS and CKD, screening has little utility.

One other important point made by the authors addresses the issue of prevention. If the presence of HbAS affects the outcome of renal function in patients who are at risk for the development of ESRD from all causes, then the question becomes whether screening all black individuals, so that they are aware of their genotype, might change outcomes. The data presented by Derebail et al. are too preliminary to suggest that kind of screening effort to prevent renal disease, but it suggests that further study is required for full understanding of the risk to this population.

Finally, if we agree with assumptions presented in this study—that HbAS actually contributes significantly to development of ESRD—then we may need to reevaluate what this means for live-donor kidney transplants. A recent survey of transplant centers in the United States found that 83% have no policy for screening for HbAS, and 63% exclude such a donor rarely or never.4 The justification for this indifference is the lack of studies examining this important question—calling for more work in this area.

This study is an important contribution to break the ice, but additional examination of HbAS is needed in larger, well-characterized, and geographically diverse populations with advanced kidney disease. It may also be interesting to examine the interaction of HbAS with other, recently identified genetic risks for ESRD in black individuals, such as the MHY9 gene.5 We look forward to better understanding of the role of sickle cell gene abnormalities in renal disease and translating this to improved care for our patients.

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DISCLOSURES

None.

REFERENCES


Dependence of Renal Microvessel Density on Angiotensin II: Only in the Fetus?

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During renal development, coordinate positioning and lengthening of the postglomerular microvasculature takes place as the tubular compartment expands and lengthens to form the renal papilla.1 The three-dimensional relationship of peritubular capillaries and vasa rectae to their specific nephron segments1,2 is essential for effective water and solute reabsorption in balance with glomerular filtration,3 for regulated salt excretion through the pressure natriuresis mechanism,4,5 and for formation of hypertonic urine.6,7 Conversely, rarefaction of the peritubular vasculature associated with tubulointerstitial fibrosis is a hallmark of chronic allograft nephropathy8 and probably most other progressive renal diseases.9,10 Hence, there is an obvious need to understand mechanisms that control the formation and maintenance of the peritubular vasculature.

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In this issue of *JASN*, Madsen *et al.* describe the critical importance of signaling through angiotensin receptor 1 (ATR1) for development of a normal density and position of the postglomerular renal microvasculature. They administered the angiotensin II (AngII) receptor antagonist candesartan to rat pups during the first 2 postnatal weeks in rat pups, a window that corresponds roughly to gestational weeks 24 through 36 for human fetal kidney development, and found a dramatic reduction in peritubular microvessel density. The reduced microvessel density accompanies a dramatic and very specific reduction of inner medulla size and an accumulation of interstitial myofibroblasts in the outer medulla. Consequently, the diffusion distance from a nephrone to the nearest capillary is significantly greater in rat pups treated with candesartan than in controls. Moreover, the medullary fibrosis persists and renal blood flow continues markedly reduced 2 weeks after removal of the ATR1 inhibitor. In rodents, ATR1 is expressed as two isoforms, ATR1A and ATR1B, and both are blocked by candesartan. Previous work using ATR1A/ATR1B double-null mice had already shown that the inner medulla does not develop in the absence of ATR1 signaling. Madsen *et al.* now extend their findings to ATR1A/ATR1B-deficient mice and show that endothelial-specific transcripts Tie-2 and Flk-1, measures of endothelial cell density, are reduced in kidneys from double-null mice, as in the medulla of candesartan-treated rat pups. Their findings that ATR1A and the vascular endothelial growth factor (VEGF) are prominently expressed in the thick ascending loop of Henle and collecting duct and that VEGF expression in these nephron segments is profoundly reduced during candesartan treatment lead them to conclude that coordinate development of the medullary vasculature during the period of collecting duct and loop of Henle lengthening is very likely due to specific activation of ATR1 in these epithelia, stimulating VEGF production, which in turn drives lengthening and proper positioning of peritubular microvessels and vasa rectae.

It is already well established that inhibition of angiotensin-converting enzyme during pregnancy results in renal dysplasia. Furthermore, that deletion of various components of the renin-angiotensin system (RAS), including *ATRIA/ATR1B*, *ACE*, and *angiotensinogen* but not *ATR2*, are associated with renal medullary dysplasia leaves little room for doubt that signaling through ATR1 is necessary for development of the renal medulla. Teratogenic effects of RAS inhibition during pregnancy were initially ascribed to inhibition of uterine prostaglandin synthesis and a consequent reduction in uterine blood flow or to significant maternal hypotension. Of course, in the work of Madsen *et al.*, maternal and uterine factors do not play a role.

The notion that ATR1 signaling regulates development of the renal vasculature through more direct, local effects has received scant attention thus far. Nonetheless, a marked reduction in the density of the peritubular vasculature, profoundly limited formation of vasa recta bundles, and interstitial fibrosis in a fetus of a mother who continued angiotensin receptor blocker therapy during pregnancy has been reported and is entirely consistent with the observation by Madsen *et al.* Also, Tufro-McReddie *et al.* previously reported abnormalities in afferent arteriolar and glomerular development in neonatal rat pups treated with ATR1 inhibitors.

It could still be argued that abnormal renal vascular development in the study by Madsen *et al.* is accounted for by an indirect effect resulting from systemic inhibition or inactivation of ATR1. In fact, the BP in *ATRIA/ATR1B*-null mice is approximately 46 mmHg lower than in wild-type controls, so renal hypoperfusion could potentially produce this effect. Madsen *et al.* argue that hypoperfusion is not a likely mechanism leading to failure of renal microvascular development because other classes of antihypertensive agents are not associated with renal dysplasia. There also is mounting evidence that AngII stimulates VEGF expression in a wide variety of tissues, including proximal tubular epithelium, all in keeping with the hypothesis that ATR1 blockade inhibits local ATR1-dependent VEGF synthesis. Still, proof that local angiotensin-stimulated VEGF synthesis regulates coordinate vasa recta development during expansion and growth of the renal medulla will require conditional deletion of ATR1A/ATR1B specifically in the ascending limb of Henle and/or collecting duct. Despite this qualification, this work adds substantial weight to the evidence that AngII, acting on ATR1, plays a critical role in the normal development of the renal vasculature.

It is also of note that quantification of renal microvessel density as a measure of progressive parenchymal damage is challenging, given that other compartments, for instance the interstitium and nephron mass, tend to change simultaneously. The stereologic technique used by Madsen *et al.* is the most robust approach to establish the fractional volume and length of the renal microvasculature and sets a new bar for the evaluation of renal microvessel density.

Finally, we use inhibitors of the RAS with abandon for the treatment of hypertension and prevention of vascular dysfunction, among them progressive renal failure associated with proteinuria, and diabetic nephropathy in particular. The study by Madsen *et al.* reemphasizes that utmost care must be exercised in the use of these agents in women of child-bearing age. Furthermore, mechanisms that stimulate renal vascular development in the fetus also reemerge in response to injury, for instance diabetic nephropathy and acute kidney injury. Although angiotensin-driven VEGF synthesis may be detrimental in diabetic nephropathy, this article raises the important question of whether RAS inhibition is potentially detrimental in other forms of renal injury repair.

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18. ZO-1 and ZONAB Interact to Regulate Proximal Tubular Cell Differentiation

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Renal tubular segments are specialized structures with selective functions defined by the specificity of highly differentiated epithelial cells. All polarized epithelial cells in tubular structures have distinct apical and basal plasma membrane domains as well as lateral surfaces that connect sister cells by specialized cellular junctions. The basal membrane of epithelial cells adhere to the extracellular matrix primarily by integrins and syndecans, whereas the lateral surfaces of the epithelial cells interact with each other through lateral cellular junctions. Among these junctions, the apical tight junction complex controls paracellular transport, the adherens junctions localized below the tight junctions allow cells to adhere to each other, and gap junctions often found below the