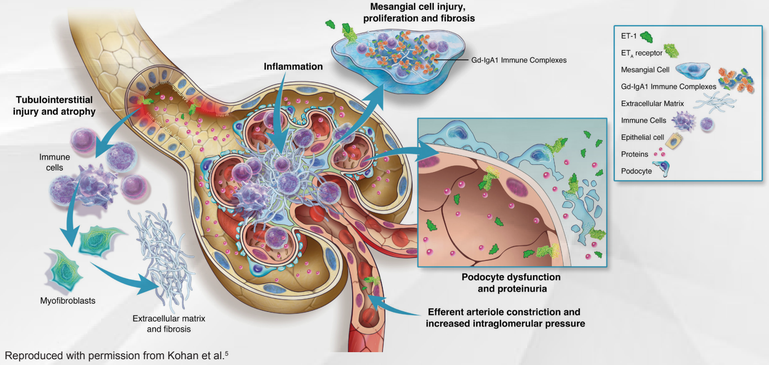
ENDOTHELIN SYSTEM ACTIVATION IN IGA NEPHROPATHY

INCREASED KIDNEY ET-1 PRODUCTION AND ETA RECEPTOR ACTIVATION MAY CONTRIBUTE TO GLOMERULAR INJURY IN IGA NEPHROPATHY[1-5]

- ET-1 is a relatively stable peptide produced in nearly every kidney cell type, with effects on various biological systems.[5-7] ET-1 is important in maintaining fluid and electrolyte homeostasis and blood pressure[5,6]
- The 2 endothelin receptors, ETA and ETB, mediate a wide range of complementary or opposing actions[5,8]
- ET-1 binds to and activates ETA receptors to bring about numerous pathophysiologic effects[5,6]
- In IgA nephropathy, immune complex deposition in the mesangium (Hit 4 of the multihit model) can trigger activation of the endothelin system, resulting in increased ET-1 production and ETA receptor activation[5,9]
- Overactivation of the ETA receptor leads to glomerular injury, fibrosis, and progression to CKD, which are all hallmarks of IgA nephropathy[5,8]
- ET-1, proteinuria, and angiotensin II can act in a positive feedback loop that may contribute to renal injury, inflammation, and disease progression[4,5]



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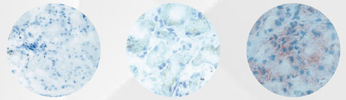
ENDOTHELIN SYSTEM ACTIVATION IS ASSOCIATED WITH DISEASE PROGRESSION IN IGA NEPHROPATHY[1-3,5]

- Patients with significant proteinuria showed an increase in glomerular and tubulointerstitial ET-1 staining compared to controls[1]



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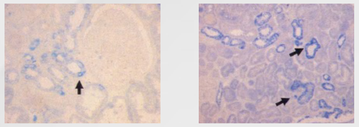
- Patients with IgA nephropathy had more intense and diffuse tubular epithelial ETA receptor staining compared to controls[2]



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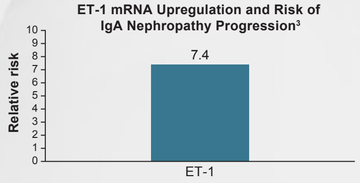
- Elevated total kidney ET-1 mRNA expression was associated with risk of progression in patients with IgA nephropathy[3,a]



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CKD, chronic kidney disease; ET-1, endothelin-1; ETA, endothelin A; ETB, endothelin B; IgA, immunoglobulin A; mRNA, messenger RNA; UPCR, urine protein-creatinine ratio.

[a]At 12 months following kidney biopsy.

ENDOTHELIN SYSTEM ACTIVATION CAN DRIVE PROTEINURIA AND KIDNEY INJURY VIA DIFFERENT CELL TYPES[4]

- Increased ET-1 production and ETA receptor activation can drive proteinuria and kidney injury through various mechanisms that involve the following cell types:[4,5]

Mesangial cells

- Pathological effects of ET-1 on mesangial cells mediated by ETA receptors include enhanced proliferation, contraction, and extracellular matrix accumulation, which contribute to kidney disease progression[5,10]
- ET-1, via autocrine or paracrine mechanisms, activates many intracellular signaling mechanisms in mesangial cells that sustain pathological effects[5]

Podocytes

- Activation of podocyte ETA receptors promotes actin cytoskeleton disruption, slit diaphragm dysfunction, inflammation, apoptosis, and fibrosis, compromising the filtration barrier[4,5,11]
- Podocyte-mesangial cell cross talk promotes proteinuria[5]

Endothelial cells

- In a preclinical model, ET-1 led to increased heparanase production, resulting in endothelial glycocalyx degradation[5,12]
- Cross talk between endothelial cells, podocytes, and mesangial cells along with ET-1 and ETA receptor activation are thought to drive kidney injury[5]

Inflammatory cells

- ETA receptor activation leads to overproduction of proinflammatory cytokines and chemokines, which contributes to kidney damage and proteinuria[4,5,8]

Kidney tubules

- A positive feedback loop between proximal tubule-derived ET-1 and proteinuria may cause kidney damage[4,5]

1. Lehrke I et al. *J Am Soc Nephrol*. 2001;12(11):2321-2329. doi:10.1681/ASN.V12112321 2. Zanatta CM et al. *Ren Fail*. 2012;34(3):308-315. doi:10.3109/0886022X.2011.647301 3. Tycová I et al. *Physiol Res*. 2018;67(1):93-105. doi:10.33549/physiolres.933670 4. Kohan DE, Barton M. *Kidney Int*. 2014;86(5):896-904. doi:10.1038/ki.2014.143 5. Kohan DE et al. *Kidney Int Rep*. 2023;8(11):2198-2210. doi:10.1016/j.ekir.2023.07.023 6. Kohan DE et al. *Compr Physiol*. 2011;1(2):883-919. doi:10.1002/cphy.c100039 7. Wang L et al. *Biophys J*. 2022;121(13):2490-2502. doi:10.1016/j.bpj.2022.06.006 8. Raina R et al. *Kidney Dis (Basel)*. 2020;6(1):22-34. doi:10.1159/000504623 9. Rizk DV et al. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504 10. Barton M, Sorokin A. *Semin Nephrol*. 2015;35(2):156-167. doi:10.1016/j.semnephrol.2015.02.005 11. Barton M. *Biochem Biophys Acta*. 2010;1802(12):1203-1213. doi:10.1016/j.bbadis.2010.03.012 12. Rabelink TJ et al. *Nat Rev Nephrol*. 2017;13(4):201-212. doi:10.1038/nrneph.2017.69

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