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In Translation

# Insulin-like Growth Factors and Kidney Disease

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Insulin-like growth factors (IGF-1 and IGF-2) are necessary for normal growth and development. They are related structurally to proinsulin and promote cell proliferation, differentiation, and survival, as well as insulin-like metabolic effects, in most cell types and tissues. In particular, IGFs are important for normal pre- and postnatal kidney development. IGF-1 mediates many growth hormone actions, and both growth hormone excess and deficiency are associated with perturbed kidney function. IGFs affect renal hemodynamics both directly and indirectly by interacting with the renin-angiotensin system. In addition to the IGF ligands, the IGF system includes receptors for IGF-1, IGF-2/mannose-6-phosphate, and insulin, and a family of 6 high-affinity IGF-binding proteins that modulate IGF action. Disordered regulation of the IGF system has been implicated in a number of kidney diseases. IGF activity is enhanced in early diabetic nephropathy and polycystic kidneys, whereas IGF resistance is found in chronic kidney failure. IGFs have a potential role in enhancing stem cell repair of kidney injury. Most IGF actions are mediated by the tyrosine kinase IGF-1 receptor, and inhibitors recently have been developed. Further studies are needed to determine the optimal role of IGF-based therapies in kidney disease.
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***INDEX WORDS:*** Insulin-like growth factor (IGF); growth hormone (GH); kidney development; kidney function; kidney disease; diabetic nephropathy; chronic kidney disease (CKD).

## BACKGROUND

Insulin-like growth factors (IGF-1 and IGF-2) are necessary for normal growth and development.[1] They are related structurally to proinsulin and promote cell proliferation, differentiation, and survival, as well as insulin-like metabolic effects, in a wide range of cell types and tissues. IGFs are expressed in many cell types and have autocrine, endocrine, and paracrine actions. In particular, IGFs are important for normal pre- and postnatal kidney development. IGF-1 mediates many of the actions of growth hormone (GH), and both GH excess and deficiency are associated with perturbed kidney function. IGFs affect renal hemodynamics both directly and indirectly by interacting with the renin-angiotensin system. In addition to the IGF ligands, the IGF system includes receptors for IGF-1, IGF-2/mannose-6-phosphate, and insulin, and a family of 6 high-affinity IGF-binding proteins (IGFBPs).[2,3] Most actions of IGFs are mediated by the tyrosine kinase IGF-1 receptor, whereas the IGF-2/mannose-6-phosphate receptor predominantly acts as a clearance receptor for IGF-2. IGFBPs primarily inhibit IGF actions, although they may enhance them in some circumstances. More recently, IGF-independent actions of a number of IGFBPs have been reported. IGFBPs are cleaved by specific proteases, resulting in release of bound IGFs with consequently increased activity.[3] Disordered regulation of the IGF system has been implicated in a number of kidney diseases, including diabetic nephropathy, polycystic kidneys, proteinuric chronic kidney disease (CKD), and Wilms tumors.[4,5]

## CASE VIGNETTE

A 48-year-old man with type 1 diabetes for 30 years presents with end-stage kidney disease. He first was found to have microabuminuria 20 years earlier and was managed with an angiotensin-converting enzyme inhibitor. Over the years, his glycemic control has fluctuated, with hemoglobin $A_{1c}$ levels of 7.6%-8.8%, most recently being 7.9%. Despite the angiotensin-converting enzyme inhibitor, he developed hypertension 15 years ago, and low-dose hydrochlorothiazide and then amlodipine were added. Microalbuminuria progressed to overt proteinuria, and his kidney function began to deteriorate 8 years ago. Despite maintenance of blood pressure at <135/85 mm Hg, his kidney function decreased to the point that creatinine clearance is now 15 mL/min. He reports easy fatigability, nausea, mild anorexia, and some shortness of breath. On examination, he has mild ankle edema. His hemoglobin level is 10.8 (reference range, 12-18) g/dL. He takes calcium carbonate, and phosphorus and calcium levels are 5.0 (range, 3.0-4.5) mg/dL and 8.4 (range, 9.0-10.5) mg/dL, respectively. Serum albumin level is 3.1 (range, 3.5-5.0) g/dL, and 24-hour urinary protein excretion is 0.8 (threshold, <0.15) g/24 h.

As part of a research protocol, the patient's urine is examined for IGFBPs, revealing almost complete cleavage of IGFBP-3. Abnormal regulation of the GH/IGF factor system has been implicated at various stages in the development of diabetic nephropathy: increased renal IGF activity is reported early in the disease, whereas GH/IGF resistance is found in patients with CKD.

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## PATHOGENESIS

### Normal Kidney Development

The GH/IGF-1 system plays a key role in normal kidney development and function (Fig 1). During embryogenesis, IGF-1 and -2 are required for normal metanephric development.[6] As the kidney develops, IGF ligands, IGF receptors, and IGFBPs are expressed in specific sites throughout the nephron, which suggests specific autocrine and paracrine roles at these locations.[7-10] Genetic models also support a role for IGFs in kidney growth and development. GH receptor knockout mice, though small, have kidneys that are disproportionally small.[11] In contrast, IGF-1 knockout mice are born at ~60% of usual body weight, and their weight subsequently declines to ~30% of normal with proportionally small kidneys and decreased glomerular size and nephron number.[12,13] Overexpression of IGF-2 cannot surmount the generalized growth deficit of IGF-1 knockout mice; however, significantly increased kidney weight and decreased renal p38 mitogen-activated protein kinase (MAPK) phosphorylation suggest that IGF-2 has a particular role in kidney growth.[12] In support of this notion, transgenic mice overexpressing IGF-2 on a wild-type background have disproportionately enlarged kidneys relative to body weight.[14] By comparison, transgenic mice overexpressing IGF-1 are larger than wild-type mice, have proportionately enlarged kidneys,[15] and have enlarged glomeruli without sclerosis.[16]

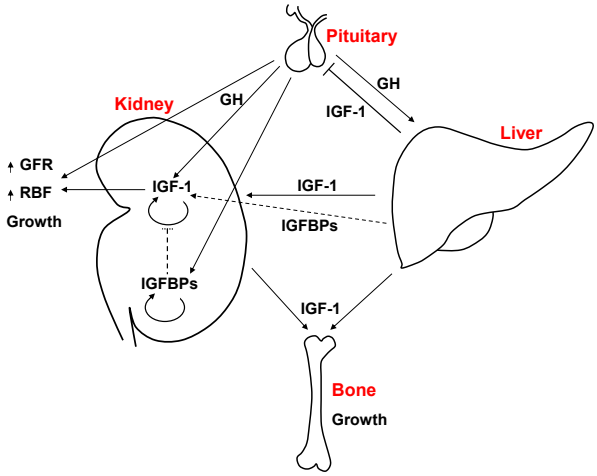


**Figure 1.** The anterior pituitary gland secretes growth hormone (GH) that acts on the liver to synthesize insulin-like growth factor 1 (IGF-1) from where it has endocrine actions on kidney and bone to mediate longitudinal growth. Additionally, circulating IGF-1 suppresses GH secretion in a negative feedback loop. GH also acts on the kidney both directly and by increasing local IGF-1 production, which acts through autocrine or paracrine mechanisms. Circulating and locally synthesized IGF-binding proteins (IGFBPs) modulate IGF-1 actions, usually in an inhibitory manner, and also may have IGF-independent actions within the kidney. GH and IGF-1 result in kidney growth, increased renal blood flow (RBF), and increased glomerular filtration rate (GFR).

In 1957, Salmon and Daughaday[17] formulated the somatomedin hypothesis, which stated that GH actions on longitudinal bone growth are mediated by a circulating factor that many years later was shown to be IGF-1.[18] Because the liver is the primary source of circulating IGF-1, it was surprising to find that liver-specific deletion of the gene encoding IGF-1 in mice had no impact on postnatal growth; however, kidney size was modestly decreased.[19,20] Another study showed that IGF-1 production in the liver is necessary for GH-mediated kidney growth in addition to normal development of lean body mass and bone mineral density.[21] Liver-specific deletion of the IGF-1 gene had no impact on creatinine clearance or kidney histology, but increased urinary sodium and potassium excretion.[20] Interestingly, liver-specific deletion of the IGF-1 gene decreased renal expression of the IGF-2 gene, but not other IGF system genes,[20] consistent with the previously discussed studies, which suggested a particular role for IGF-2 in kidney growth and function.

Consistent with the role of IGFBPs as inhibitors of IGF action, their generalized overexpression predominantly results in growth retardation. Mice engineered to overexpress IGFBP-1 have small kidneys in proportion to body weight and decreased nephron number[22,23]; they later develop glomerulosclerosis without glomerular hypertrophy.[22] Transgenic mice that overexpress IGFBP-2 also have small kidneys essentially in proportion to body weight.[24] Mice overexpressing IGFBP-3 have disproportionally small kidneys,[25] whereas those overexpressing a mutant of IGFBP-3 with impaired IGF binding have normal postnatal growth and kidney size,[26] suggesting that the effects on the kidney seen in the former are due to inhibition of IGF actions. In contrast, overexpression of IGFBP-5 or a mutant with decreased IGF binding both demonstrated decreased kidney size in proportion to body weight, suggesting that this binding protein has IGF-independent and IGF-dependent effects on kidney growth and development.[27] Transgenic mice with increased IGFBP-4 levels in kidney, lung, spleen, and thymus, but not serum, have no change in body or kidney weight.[28] The effects of IGFBP-6 overexpression on kidney size or function have not been reported.

### Kidney Function and Solute Handling

Injection of IGF-1 in rodents and humans increases renal plasma flow and glomerular filtration rate (GFR).[29,30] Micropuncture studies showed that IGF-1 increases single-nephron GFR and blood flow by increasing the ultrafiltration coefficient and decreasing efferent arteriolar resistance.[31] Using in vitro

preparations of blood-perfused juxtamedullary nephrons, IGF-1 has been found to stimulate vasodilation of preglomerular but not postglomerular juxtamedullary microvessels; the difference between this result and those from micropuncture studies may be due to the latter technique sampling superficial nephrons.[32] The preglomerular vasodilatory effect is mediated at least in part by IGF-1–stimulated nitric oxide (NO) production and cyclooxygenase.[32] GH/IGF also are involved in tubular function, including solute handling.[33,34] Both GH and IGF-1 increase sodium reabsorption in the distal nephron, whereas GH-stimulated phosphate reabsorption in the proximal tubule is mediated by IGF-1. GH- and IGF-1–stimulated calcium reabsorption is mediated mainly by increased calcitriol production.

## Compensatory Growth

Following unilateral nephrectomy, the remaining kidney undergoes compensatory growth. This growth is GH dependent, and IGF-1 messenger RNA (mRNA) and protein levels rapidly increase in the remaining kidney.[33,34] Some studies also have found increased levels of transcripts coding for the IGF-1 receptor in the remaining kidney.[33] Klotho is an antiaging protein that is renoprotective in mice with glomerulonephritis and induces resistance to IGF-1. Compensatory kidney growth is suppressed and serum creatinine level is increased after unilateral nephrectomy in transgenic mice that overexpress klotho, suggestive of loss of functional kidney compensation.[35] Kidney IGF-1 signaling was compromised in these animals, so it appears that klotho inhibits the compensatory IGF response.

## Mechanisms of Kidney Disease

Synthesis of IGF-1 at multiple locations in the kidney was confirmed first by a number of research groups more than 20 years ago.[36] At that time, mesangial cells were the only glomerular cells shown to produce IGF-1 in vitro.[37] These cells were widely believed to be central to the development of kidney disease with IGF-1 signaling enhanced in many disease states, including diabetes.[38-41] IGF-1 is a potent mesangial cell mitogen and stimulates migration and production of extracellular matrix proteins[33,42] while also inhibiting apoptosis induced by high glucose levels.[43,44]

More recently, the podocyte increasingly has become a primary focus owing to its importance in the prevention of albuminuria and association with progressive kidney damage in disease.[45,46] This cell type expresses GH receptors through which GH induces rearrangement of the actin cytoskeleton while also increasing levels of reactive oxygen species, which may stimulate apoptosis.[47] These changes may result in a compromised filtration barrier, leading to progressive proteinuria, a hallmark of many kidney diseases. Podocyte depletion also is associated with abnormal glomerular IGF expression.[48-50] However, the podocyte produces IGF-1,[51] which, via the IGF-1 receptor and phosphoinositide 3-kinase (PI3K) pathway, is a key factor in the survival of the developing podocyte (Fig 2).[52,53] The balance between protective and deleterious actions of the GH/IGF system in podocytes requires further study.

## Specific Diseases

### *Acromegaly*

Patients with acromegaly have kidney hypertrophy, increased GFR, and increased renal plasma flow.[34]

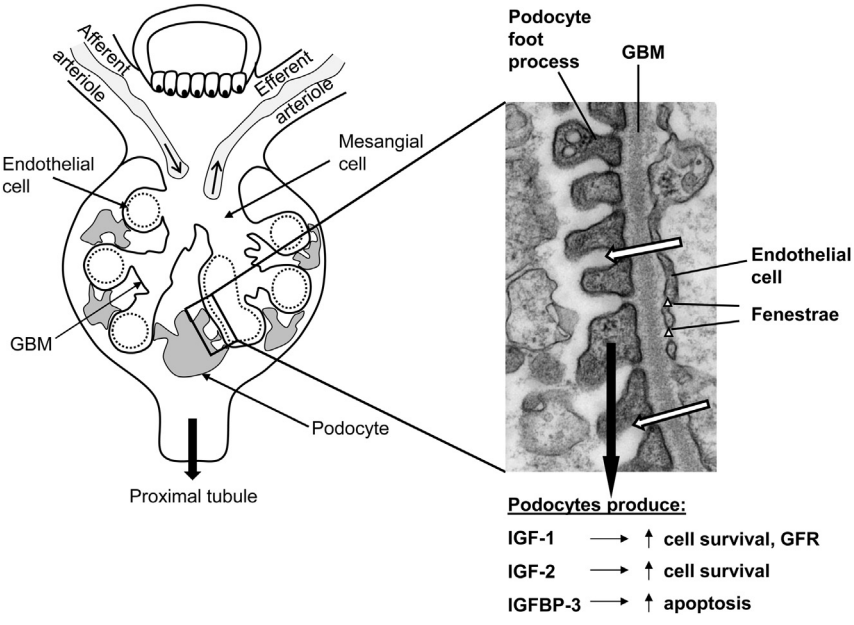


**Figure 2.** Insulin-like growth factor (IGF) system in the podocyte. The podocyte is a crucial component of the glomerular filtration barrier. Recent evidence indicates that podocytes synthesize IGF-1 and -2, both of which promote cell survival. They also synthesize IGF-binding protein 3 (IGFBP-3), which promotes apoptosis, at least in part by inhibiting IGF actions. White arrows show filtration pathway across the slit diaphragm. Abbreviations: GBM, glomerular basement membrane; GFR, glomerular filtration rate.

They commonly are volume expanded and hypertensive, which in part may be an indirect effect by activation of the renin-angiotensin-aldosterone system. Recent evidence also shows that GH and IGF-1 cooperatively stimulate sodium transport by epithelial sodium channels in cortical collecting ducts.[54] These findings are supported by studies showing that treatment of GH/IGF-1 excess in acromegalic patients decreases epithelial sodium channel activity.[55] GH and IGF-1 also have roles in phosphate and calcium homeostasis.[33] IGF-1 increases renal calcitriol synthesis and stimulates tubular phosphate reabsorption. It recently was shown that IGF-1–mediated calcitriol synthesis in acromegalic patients results in enhanced distal tubular calcium reabsorption, absorptive hypercalciuria, and increased fasting plasma calcium levels.[56]

### GH Deficiency

GH deficiency is associated with decreased GFR and renal plasma flow, along with low body sodium and water levels.[34] Replacement therapy with GH or IGF-1 at least partially normalizes these parameters; higher dose replacement may acutely result in clinically significant fluid retention manifesting as edema, weight gain, and carpal tunnel syndrome.

### Diabetic Nephropathy

Excessive production of GH and exaggerated GH responses to certain stimuli are common findings in poorly controlled type 1 diabetes mellitus.[57] In contrast, GH secretion is diminished in type 2 diabetes,[58] whereas involvement of the IGF system in diabetic nephropathy has been acknowledged for some time.[59] IGF-1 accumulates in kidneys prior to the onset of hypertrophy in diabetic rodent models, including the streptozotocin-induced diabetic rat,[60,61] streptozotocin-diabetic mouse,[62] and nonobese diabetic (NOD) mouse.[63-65] Most[46,50,51] but not all[66] studies have shown that this local accumulation is not associated with increased renal IGF-1 mRNA levels, which suggests that levels in the kidney increase because IGF-1 is sequestered from the circulation or that its increased synthesis is cell-type specific. In the diabetic rat kidney, IGFBP levels, particularly IGFBP-1, also increase early in the disease process,[67-70] and it has been postulated that this could contribute to IGF-1 accumulation. IGF-1 receptor levels also are increased in animal models of diabetic nephropathy.[71] In patients with diabetic nephropathy, urinary IGFBP-3 protease activity correlates with the degree of albuminuria, and it was postulated that this could contribute to kidney damage due to increased local IGF-1 activity.[72]

Further investigation into the relationship between the IGF system and kidney growth in diabetes recently was performed, focusing on the role of NO synthesis.[73] In the first week after streptozotocin induction of diabetes in rats, L-NAME (L-nitro-arginine-methyl-ester), an NO synthase inhibitor, significantly reduced kidney weight and hyperfiltration. L-NAME also prevented decreases in both serum IGFBP-3 and IGFBP-4 levels in the diabetic animals, and the authors concluded that NO synthase attenuates kidney hypertrophy and hyperfiltration by decreasing the kidney bioavailability of IGF-1.[73] Accumulation of advanced glycation end products is another proposed mechanism for the development of diabetic nephropathy. In the streptozotocin-induced model of diabetes, aminoguanidine, a glycation inhibitor, has been reported to inhibit the usual effects on renal expression of IGF-1, IGFBP-1, and IGFBP-4 mRNAs, suggesting that normalization of the renal IGF system may play a part in its renoprotective effects.[74]

A number of interventions targeting the GH/IGF system ameliorate experimental diabetic nephropathy. These include pegvisomant, a GH antagonist[62]; octreotide, a somatostatin analogue[75]; and genetic disruption of the GH receptor.[76] In contrast, short-term administration of IGFBP-1, which might be expected to inhibit IGF-1, has been reported to have no effect on renal growth or albuminuria.[77] Octreotide also has been reported to decrease kidney size and hyperfiltration in patients with type 1 diabetes over 12 weeks.[78]

### Chronic Kidney Disease

CKD results in many perturbations of the GH/IGF system that cumulatively result in resistance to GH and IGF-1 (Box 1). These changes result in significant clinical effects, including growth retardation in children and catabolism and malnutrition in adults.[34,79] Children with CKD present with normal or even elevated GH levels in the circulation, indicating acquired GH resistance.[80-82] The serum half-life of GH also is increased significantly in these patients.[33] Mechanisms of GH resistance in CKD include decreased GH receptor expression and postreceptor defects in JAK/STAT (Janus kinase 2/signal transducer and activator of transcription) signaling.[79]

IGF-1 resistance plays an additional role in decreased growth of children with CKD.[79] Increased circulating IGFBPs in those with CKDs,[83-86] at least in part due to increased liver production of IGFBP-1 and -2,[87] as well as impaired IGFBP clearance, contribute to IGF insensitivity by reducing bioavailability and impairing IGF delivery to target tissues.[88,89] Postreceptor defects in IGF signaling pathways also contribute to IGF insensitivity.[79] Decreased AKT phosphorylation due to insulin/IGF-1 resistance also have been implicated in the development of muscle wasting in patients with CKD by

**Box 1.** Changes in the IGF System in Kidney Disease

**IGF-1**
↓ in serum and liver, ↑ in kidney in diabetes
Normal in serum in CKD

**IGF-2**
Normal in serum in CKD
↑ levels in Wilms tumor and regulated by WT1

**IGF-1R**
Regulated by WT1

**IGF-2R**
↑ in kidney and liver in diabetes at 24-48 h, ↓ by 3-4 d

**IGFBP-1**
↑ in serum and kidney in diabetes
↑ in serum and liver in CKD
↑ loss into urine in FSGS patients
↑ levels in serum and kidney in IgA nephropathy

**IGFBP-2**
↑ in serum and liver in CKD

**IGFBP-3**
↓ in serum and kidney in diabetes → prevented by NOS inhibitor
↑ in serum in CKD
↑ loss into urine in FSGS patients

**IGFBP-4**
↓ in serum and kidney in diabetes → prevented by NOS inhibitor
↑ in serum in CKD

**IGFBP-5**
↑ in kidney in diabetes
Normal in serum in CKD

**IGFBP-6**
↑ in serum in CKD

Abbreviations: CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IGF, insulin-like growth factor; IGF-1R, IGF-1 receptor; IGFBP, insulin-like growth factor binding protein; NOS, nitric oxide synthase.

increasing muscle protein breakdown and impairing myogenesis.[90]

GH treatment of patients with kidney failure increases serum IGF-1 levels and alters the balance of IGFBPs, resulting in a marked increase in IGF-1 bioactivity with subsequent improvements in growth in children and body composition in adults.[34,91] Findings from a number of studies have concluded that the effect on growth is improved by early initiation of GH treatment.[92] Small short-term studies also show anabolic effects of GH and IGF-1 in adults with CKD, as well as improved quality of life.[93,94]

Serum IGF-1 and IGFBP-3 levels were reported not to correlate with kidney function or proteinuria in a study of 137 adult patients with CKD of different causes.[95] However, serum IGF-1 levels prior to commencing dialysis therapy were found to correlate with measures of nutritional status and bone metabolism in 365 patients with end-stage kidney disease.[96] IGF-1 levels increased in the year following commencement of dialysis therapy, and low IGF-1 levels were reported to associate with increased mortality in these patients.

### *Acute Kidney Injury*

IGF-1 is involved in the repair process following acute kidney injury. In particular, IGF-1 expression is increased in regenerating proximal tubule cells after injury in rats.[33,34] IGF-1 treatment accelerates recovery in animal models,[97] but clinical trials using IGF-1 in patients with acute kidney injury did not significantly improve kidney function or overall outcome.[98-100]

### *Polycystic Kidney Disease*

The IGF system also has been shown to play a role in polycystic kidney disease (PKD), which is the most common genetic cause of kidney failure and is characterized by massive nephromegaly due to progressive dilation of epithelial-lined cysts derived from kidney tubules.[101] Gene expression of members of the IGF-1 pathway is increased, together with other tyrosine kinase pathways, in cyst-lining epithelial cells from patients with autosomal dominant PKD.[102] IGF-1 stimulates proliferation of cyst-lining cells from patients with PKD, an effect inhibited by rosiglitazone, a thiazolidinedione that attenuates progression in animal models of PKD.[103]

### *Other Kidney Diseases*

IGFBP-3 has a recognized role in the podocyte by enhancing the proapoptotic effect of transforming growth factor-β and inhibiting the antiapoptotic effect of bone morphogenetic protein-7.[104] Urinary podocyte, IGFBP-3, and IGFBP-1 levels are increased in patients with focal segmental glomerulosclerosis, but not in patients who have minimal change disease and who display a similar level of proteinuria, indicating a possible specific role for these IGFBPs in the pathogenesis of focal segmental glomerulosclerosis.[105] IGFBP-1 levels also are elevated in the kidneys in a mouse model of experimental immunoglobulin A nephropathy and in serum of patients with immunoglobulin A nephropathy, correlating with mesangial cell proliferation and other markers of kidney damage.[106]

## RECENT ADVANCES

### IGF Receptor Inhibitors

There is substantial preclinical and clinical evidence indicating that dysregulation of the IGF system may play a role in cancer, which resulted in the development of a range of potential therapeutic agents (including monoclonal antibodies and small-molecule tyrosine kinase inhibitors) predominantly targeting the IGF-1 receptor, which mediates most IGF actions.[107] Many clinical studies have been conducted using these agents alone and in combination with other treatments. Unfortunately, initial phase 3 studies

in unselected patients did not demonstrate efficacy across a range of cancers, and there currently are intense efforts to find biomarkers that identify subgroups of patients who may respond. Toxicity also has been reported, with hyperglycemia being a major side effect. Tyrosine kinase inhibitors may cross-react with and partially inhibit the insulin receptor, whereas IGF-1 receptor antibodies may lead to GH hypersecretion and consequent insulin resistance. Nevertheless, the availability of these agents provides the possibility that they could be used to treat kidney diseases in which IGF overactivity is implicated.

### Stem Cell Therapy

As is the case in many areas of medicine, there is intense interest in the possibility that stem cell therapies will revolutionize the treatment of kidney disease.[108] Clinical trials of mesenchymal stem cells are in progress, although the precise mechanisms whereby they exert their effects are not completely understood. It appears that administered stem cells do not integrate into the kidney parenchyma, but likely act as paracrine sources of biomolecules that ameliorate damage.

IGF-1 has a number of distinct effects that underlie the reparative actions of mesenchymal stem cells. Bone marrow–derived mesenchymal stem cells ameliorate proximal tubule damage induced by cisplatinum in vitro. In mice, IGF-1 secreted by these cells has been reported to significantly contribute to this effect by its proliferative and antiapoptotic actions.[109] A limitation of systemic infusion of stem cells is their inability to home to injured tissues. Preconditioning of these cells with IGF-1 has been shown to enhance their migratory response in vitro, increase both endogenous IGF-1 synthesis and the number of stem cells in the peritubular region, and improve kidney function in mice treated with cisplatin.[110] Mesenchymal stem cells secrete exosomes, which are membrane-bound vesicles containing specific mRNAs that can be transferred to recipient cells and translated into protein. mRNA for the IGF-1 receptor is enriched in these exosomes and results in IGF-1 receptor expression in cisplatin-damaged proximal tubular cells, thereby enhancing the proliferative effects of IGF-1 in these cells.[111]

### Podocyte Function

Knowledge of the action of IGFs in the podocyte recently was enhanced by a study focussing on IGF-2 (Fig 2).[112] The podocyte was found to be a major source of IGF-2 in both humans and mice into adulthood. The actions of IGF-2 were found to be mediated by the IGF-1 receptor and were observed to be crucial for podocyte cell survival and maintenance of the integrity of the glomerular filtration barrier. Mice with globally reduced IGF-2 production have abnormal glomeruli (featuring increased matrix production, sclerosis, mesangial expansion, and podocyte defects), indicating autocrine and paracrine roles for IGF-2 throughout the glomerulus.[112]

### Fibrosis

Interstitial fibrosis is a hallmark of CKD, and IGFs stimulate extracellular matrix protein accumulation in a number of cell types. Epithelial-mesenchymal transdifferentiation contributes to fibrosis and IGF-1 stimulates this process in collecting duct epithelial cells.[113] Aldosterone, a mineralocorticoid that regulates extracellular volume through sodium and potassium balance, independently contributes to the development of fibrosis and progression of CKD. Expression of the extracellular matrix protein fibronectin in kidney fibroblasts is mediated by a number of pathways, including Src-dependent phosphorylation and activation of both the IGF-1 receptor and Erk-independent of the mineralocorticoid receptor.[114] NAPDH oxidase (Nox)-dependent generation of reactive oxygen species has been implicated in kidney diseases, including diabetic nephropathy. In proximal tubule cells, IGF-1 increases fibronectin expression by a pathway involving Nox-dependent reactive oxygen species generation and Akt signaling.[115]

### Development

Studies in rodents have shown that IGFs contribute to pre- and postnatal kidney growth and development. Results from a randomized clinical trial of formula with higher versus lower protein levels during the first year of life in healthy infants show a correlation between free IGF-1 levels and kidney volume, and structural equation modeling suggests that IGF-1 in part mediates protein-induced kidney growth.[116] The authors concluded that the IGF-1 axis may contribute to nutritional programming of the renal system.

Preterm birth is associated with adverse renal outcomes, and there is interest in identifying urinary biomarkers to assess renal development in this setting. A recent study has shown that preterm infants at birth have relatively elevated levels of urinary IGFBP-1, -2, and -6.[117]

## SUMMARY

There is extensive evidence for the importance of the IGF system in normal kidney development and function. IGF activity is increased in some kidney diseases, such as early diabetic nephropathy and PKD, whereas decreased IGF activity contributes to the morbidity related to CKD, suggesting that the system must be finely balanced for optimal renal outcomes. It is heartening that GH administration has positive effects on growth without accelerating nephromegaly in children with PKD, although the

IGF system is implicated in this disease, indicating that there is a "safety margin" for intervention. New therapeutic tools such as stem cells and IGF-1 receptor inhibitors provide the possibility for modulating the IGF system to treat kidney disease. For example, early treatment of patients with diabetic nephropathy, such as the patient in the vignette, with an IGF-1 receptor inhibitor may limit kidney enlargement and reduce albuminuria. In contrast, enhancing local IGF-1 with GH or stem cells to limit catabolism and enhance kidney repair may be beneficial as CKD progresses. However, increased understanding of this complex system is required before IGF-based therapies can be implemented optimally. Further, methods to target treatments to the kidney to avoid systemic side effects would enhance the utility of this approach.

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