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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]

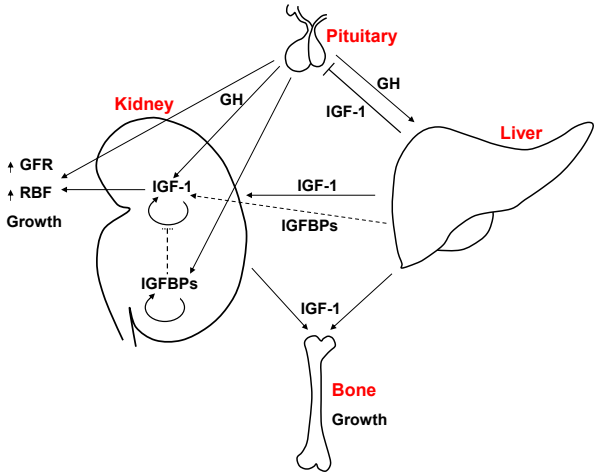

Figure 1. The anterior pituitary gland secretes growth hormone (GH) that acts on the liver to synthesize insulin-like growth factor 1 (IGF-1) from where it has endocrine actions on kidney and bone to mediate longitudinal growth. Additionally, circulating IGF-1 suppresses GH secretion in a negative feedback 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