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Title: The multiple functions of Insulin-like Growth Factor 1 in kidney disease

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Highlights

- Renal compensatory hypertrophy induced by contralateral nephrectomy is largely mediated by local increase of Insulin-like Growth Factor 1 (IGF-1) production. These renal anabolic effects of the IGF-1 have been extensively studied in order to enhance glomerular filtration rate and prevent acute renal injury.
- Circulating IGF-1 concentration have shown to be useful as a marker of malnourishing in patients with advanced chronic kidney disease (CKD), since the lower IGF-1 levels are associated with the lower uptake of protein/calories, as well as reduced muscle strength.
- IGF-1 plays a key role in the regulation of phosphate resorption and the renal activation of vitamin D by increasing 1- α hydroxylase activity, effects that are triggered independently of the parathyroid hormone levels. Moreover, IGF-1 also participates directly in bone growth and bone remodeling, particularly bone formation.
- Moreover, IGF-1 is an important factor promoting erythroid cell proliferation, playing a relevant role in the prevention of anemia, even when erythropoietin levels are below the normal range. In addition, IGF-1 controls vascular nitric oxide synthesis, indicating a contribution of this factor on the regulation of vasodilation.
- However, while IGF-1 plays a crucial role in the context of renal disease, resistance to IGF-1 has been observed in renal insufficiency, which may potentially contribute to the complications associated with CKD, underscoring the need for further research.

Abstract

Unilateral nephrectomy (Uni-Nx) produces compensatory hypertrophy of the remnant kidney. In this anabolic process, the up-regulation of renal insulin-like Growth Factor 1 (IGF-1) plays a key role, which has inspired numerous studies considering the potential regenerative actions of the IGF-1 and the subsequent increase in the glomerular filtration rate. Thus, IGF-1 administration has shown to be able to induce renal hypertrophy, increase glomerular size and enhance glomerular filtration rate, without reaching glomerulosclerosis. Moreover, protein uptake also contributes to renal hypertrophy by increasing renal and circulating IGF-1 levels. In this respect, circulating IGF-1 concentration has been used as a marker of the nutritional status in end-stage CKD patients and has been associated with hormones that participate in the regulation of appetite. Moreover, IGF-1 regulate mineral metabolism, participating in phosphate resorption and calcitriol production by increasing 1- α -hydroxylase activity. Furthermore, IGF-1 is key for bone growth in pediatric patients, acting directly in chondrocyte, osteoblasts and in a lesser manner in osteoclasts. In addition, IGF-1 is an important inductor of erythroid proliferation, being able to maintain erythrocytic homeostasis in anephric patients.

Nevertheless, the actions of the IGF-1 are attenuated in the context of renal disease, which may be promoted by the presence of inhibitory factors, such as the IGF binding proteins, and inability to trigger intracellular downstream signaling despite of normal IGF-1 receptor expression in cell surface.

This review highlights the importance of the IGF-1 in the context of CKD and its potential contribution to renal and also systemic disorders.

Resumen

La nefrectomía unilateral (Uni-Nx) produce hipertrofia compensatoria del riñón remanente. En este proceso anabólico, la regulación positiva del factor de crecimiento similar a la insulina 1 (IGF-1) juega un papel clave, lo que ha inspirado numerosos estudios considerando las posibles acciones regenerativas del IGF-1 y el consiguiente aumento de la tasa de filtración glomerular. Así, la administración de IGF-1 ha demostrado ser capaz de inducir hipertrofia renal, aumento del tamaño glomerular y un

consecuente aumento de la tasa de filtración glomerular, sin llegar a desarrollar glomeruloesclerosis. Además, la ingesta de una dieta alta en proteínas también contribuye a la hipertrofia renal mediante el aumento de los niveles de IGF-1, tanto a nivel renal como en la circulación. En este sentido, la concentración sérica de IGF-1 se ha utilizado como marcador del estado nutricional en pacientes con enfermedad renal crónica (ERC) terminal y se ha asociado con hormonas que participan en la regulación del apetito. Además, el IGF-1 regula el metabolismo mineral, participando en la resorción de fósforo y la producción de calcitriol al aumentar la actividad de la 1- α -hidroxilasa. Además, el IGF-1 es clave para el crecimiento óseo en pacientes pediátricos, actuando directamente en condrocitos, osteoblastos y en menor medida en osteoclastos. Además, el IGF-1 es un importante inductor de la proliferación eritroide, pudiendo mantener la homeostasis de los eritrocitos en pacientes anéfricos.

No obstante, las acciones del IGF-1 se atenúan en el contexto de la enfermedad renal, que puede verse favorecida por la presencia de factores inhibidores, como las proteínas de unión al IGF, y la incapacidad de activar la señalización intracelular a pesar de una expresión normal del receptor de IGF-1 en la superficie celular.

Esta revisión destaca la importancia del IGF-1 en el contexto de la ERC y su potencial contribución a los trastornos renales y también sistémicos.

Keywords: Insulin-like Growth Factor 1, chronic kidney disease, compensatory renal hypertrophy.

Palabras clave: Factor de Crecimiento similar a la insulina 1, Enfermedad Renal Crónica, hipertrofia renal compensatoria.

Introduction

The insulin-like growth factor 1 (IGF-1) is a hormone that is widely expressed throughout the body and plays a crucial role in promoting anabolic processes. By binding to the IGF-1 receptor (IGF1R), IGF-1 initiates the phosphorylation of phosphatidyl-inositol 2-phosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which activates

downstream signaling pathways involving AKT and mTOR. This cascade is essential for processes such as cell proliferation, survival, and metabolic regulation, impacting various organs and systems. The kidney expresses both, IGF-1 and IGF1R, where they contribute significantly to renal function and disease. IGF-1 is particularly abundant in the medullary collecting ducts, with lower expression in the cortical collecting ducts, proximal tubular cells, and the glomerulus. The binding sites for IGF-1 are widely distributed across the kidney, with higher concentrations observed in the inner medulla.¹

Importantly, unilateral nephrectomy (uni-Nx) induces an increase in IGF-1 production in contralateral kidney, which promotes compensatory renal hypertrophy.² Similarly, both the exogenous administration of recombinant growth hormone (GH), a major stimulus for IGF-1 synthesis during development, and uni-Nx compensatory renal hypertrophy by both, exogenous administration of recombinant growth hormone (GH), which is a principal stimulus for IGF-1 synthesis during development, or uni-Nx result in enhanced renal IGF-1 expression, a critical factor in renal hyperplasia.³ The kidney also produces a variety of IGF-1 binding proteins (IGFBPs), which bind and capture free soluble IGF-1, inhibiting its mitogenic effects.⁴ To date, six closely related high-affinity IGFBPs have been identified, and all are expressed in the kidney. These include IGFBP-1 to IGFBP-6, each expressed at different sites. Among them, IGFBP-5 is the most abundant in renal tissue, while IGFBP-3 is the most prevalent in circulation. In contrast, IGFBP-6 exhibits the lowest renal expression.⁵ Notably, although IGFBP-7 is minimally expressed in healthy kidney and has low affinity for IGF-1, its production is significantly upregulated in renal biopsies from CKD patients, making it a potential marker for acute kidney injury.^{6,7}

In addition to its regulatory binding proteins, serum IGF-1 levels decline with aging in the general population.⁸ This reduction may also contribute to the decreased renal anabolic capacity observed in older adults, as well as the progressive decrease of the kidney function.

In this review, we aim to provide a comprehensive overview of the renal actions of IGF-1 signaling, highlighting its role in the pathophysiological complications associated with chronic kidney disease (CKD) at systemic level. This review is structured into two main sections: the first one explores the effects of IGF-1 on renal physiology and pathophysiology and the second one highlights the key role of IGF-1 in systemic complications associated with renal dysfunction.

IGF Effects on Renal Patho-physiology

IGF-1 in Normal Kidney Function and Compensatory Renal Hypertrophy

The GH is a key stimulus for both, whole-body and renal growth. Studies in rats have shown that administration of recombinant GH or carrying a GH-producing tumor results in increased body weight and kidney size compared to control animals. Additionally, rats under high GH conditions showed increased serum levels and renal expression of IGF-1, with sclerotic glomeruli. These findings suggest that overproduction of renal IGF-1 may contribute, at least in part, to kidney abnormalities observed in acromegaly.⁹ In a similar context, mutant mice with GH overproduction develop renal hypertrophy, increased glomerular size and mesangial sclerosis. This condition progresses to glomerulosclerosis and albuminuria, along with interstitial infiltration, further emphasizing the role of excessive GH and IGF-1 signaling in renal pathophysiology. However, mutant mice overproducing IGF-1 do not develop glomerulosclerosis, despite exhibiting increased kidney size and mild glomerular hypertrophy. This suggesting that activation of the renal IGF-1 signaling may not be directly involved in the GH-induced pathological effects on the kidney.^{10,11} The mild glomerular changes observed, such as cell proliferation, could be mediated directly by renal IGF-1, as mesangial and other glomerular cells express the IGF1R.¹² Interestingly, other studies have observed increased kidney weight following IGF-1 or GH administration in rats. In the case of GH, this effect is partially mediated through stimulation of renal IGF-1, leading to enhanced glomerular and tubular cell proliferation. Although, the increase in kidney size was only significant in IGF-1 treated animals when expressed relative to total body weight.¹³

In healthy human subjects, the stimulatory effects of GH on renal plasma flow and glomerular filtration rate (GFR) exhibits a significant delay following exogenous GH administration. This delay is likely due to the time required for subsequent increases in renal IGF-1 levels, suggesting that locally produced IGF-1 may play a crucial role as a mediator of GH's renal effects.¹⁴ Of note, IGF-1 injection alone is sufficient to induce renal actions in animals with pituitary gland ablation, further supporting the importance of IGF-1 in this context.^{15,16} Additionally, IGF-1 administration led to an increase in GFR in healthy volunteers while simultaneously decreasing GH levels and insulin secretion. This contrasts with the typical effects of GH, which usually induces hyperinsulinemia.¹⁷

Compensatory renal hypertrophy induced by contralateral nephrectomy is accompanied by increased expression of IGF-1 in the remnant kidney, but not by serum or liver expression.¹⁸ This suggests that the renal anabolic effects of IGF-1 are likely triggered locally, through binding to specific receptors in the kidney. This compensatory mechanism is highly sensitive to changes in renal function, as even partial unilateral infarction, induced by ligation of one-half of the renal arteries, can be sufficient to increase IGF-1 expression in the contralateral kidney.¹⁹ Mechanistically, the upregulation of renal IGF-1 expression is stimulated by epidermal growth factor (EGF) in the renal collecting ducts, indicating a paracrine regulatory mechanism, as both IGF-1 and EGF are produced locally within the kidney.²⁰ Moreover, the renal anabolic effects of IGF-1 are partly mediated through activation of the AKT-calcineurin-NFATc1 signaling pathway, which is involved in the regulation of vascular endothelial growth factor (VEGF).^{21,22}

More recently, studies using single-cell RNA sequencing, have revealed that renal hypertrophy in mice activates sterol regulatory element-binding protein 2 (SREBP2) and increases cholesterol biosynthesis in medullary thick ascending limb cells. This signaling pathway is essential for the hypertrophic effects of IGF-1.²³ Notably, IGF-1 has also been shown to promote intracellular lipid accumulation in mesangial cells, a phenotype similar to foam cells, which leads to reduced contractility in response to angiotensin-II.^{24,25} Furthermore, kidney samples from patients with advanced CKD and mouse models with renal fibrosis have defective fatty acid oxidation and higher lipid accumulation than controls without fibrosis. Interestingly, restoring fatty acid metabolism has been found to prevent tubulointerstitial fibrosis in mouse models of renal injury.²⁶

Recent studies have demonstrated that upregulation of peroxisome proliferator-activated receptor α (PPAR α) plays a crucial role in renal hypertrophy,²⁷ highlighting the importance of lipid metabolism on renal hyperplasia. Notably, compensatory renal hypertrophy following Uni-Nx is prevented in mice over-expressing α -klotho. This fact is associated with the reduction in renal IGF-1 production, while plasma IGF-1 levels remain unaffected. Moreover, the study shows that *in vitro* overexpressing of α -klotho in human proximal tubular cells decreases IGF-1-induced AKT phosphorylation. This indicates that the inhibitory effects of α -klotho on compensatory renal hypertrophy may, at least in part, be mediated through reduced IGF-1 signaling.²⁸

Notably, inhibition of the GH receptor by the specific antagonism G120K-PEG blocks renal IGF-1 upregulation and subsequent kidney hypertrophy in Uni-Nx animals. Despite this, total body weight, food intake and serum levels of GH and IGF-1 remain similar to those in the vehicle-treated Uni-Nx group, suggesting direct renal effects.²⁹ In contrast, continuous infusion of IGF-1 during one-week results in increased glomerular volume and decreased renal vascular resistance, leading to a higher GFR. Inhibition of the GH-releasing hormone, however, does not promote kidney growth or glomerular volume, but reduces renal plasma flow and vascular resistance.³⁰ In the Figure 1 are shown the main regulatory factors of the IGF-1 signaling, as well as the principal downstream pathways related to kidney hypertrophy.

Sexual differences in renal characteristics have been observed, with male mice having larger kidneys and glomerular area compared to females. In terms of renal hypertrophic capacity, female mice exhibit larger kidney size and weight, as well as greater glomerular area, despite similar levels of renal IGF-1 and proliferating cell nuclear antigen (PCNA) expression.³¹ These sex differences in kidney size were attenuated in female mice lacking the estrogen receptor; although their glomerular area remained similar to that of wild-type females. Interestingly, the loss of estrogen receptor function did not affect compensatory renal hypertrophy following Uni-Nx in male mice.

Role of IGF-1 in Renal Ischemia

Post-ischemic regeneration leads to increased renal IGF-1 expression, promoting proliferation of tubular and non-tubular cells at the kidney regenerative zones by binding IGF1R.³² Studies using animal models of ischemic acute renal injury have shown that IGF-1 administration is useful to reduce renal protein catabolism, resulting in enhanced renal cell proliferation, accelerated recovery of renal function, and improved kidney histology.^{33,34} These regenerative effects after ischemia-induced acute tubular necrosis are also achieved by exogenous administration of recombinant IGF-1, resulting in a lower mortality in comparison with animals treated with vehicle or GH.^{34,35}

However, despite these promising results in animal models, administration of recombinant IGF-1 (100µg/12h;sc) did not improve renal outcomes in patients with acute renal failure, compared to placebo, after a mean period of 10 days.³⁶ To account for confounding factors in acute renal injury, recombinant IGF-1 administration was also tested in transplant patients receiving a cadaveric kidney allograft.³⁷ In these patients, treatment

with IGF-1 similarly failed to significantly improve renal function compared to placebo, suggesting that the regenerative effects of IGF-1 observed in animal models of renal ischemia may not be directly scalable to patients with acute renal failure.

Subsequent studies in rats have shown that subcutaneous administration of recombinant IGF-1 may be associated with exacerbation of the ischemic renal damage through stimulation of neutrophil infiltration and inflammation.³⁸ This mechanism could explicate the unfavorable results in patients with acute renal failure.

IGF-1 in Renal Cancer

The anabolic effects of IGF-1 signaling activation can be particularly negative in the context of renal cell carcinoma (RCC). *In vitro* studies have demonstrated that RCC cells exhibit high expression of both IGF-1 and IGFBP3, which have opposing effects: inhibition of IGF-1 reduces RCC cell proliferation, while blocking IGFBP3 increases it.³⁹ This occurs because IGF-1 signals through IGF1R, triggering proliferative effects and promoting IGFBP3 expression, which subsequently exerts antiproliferative actions. Importantly, IGF1R expression also determines RCC aggressiveness, while patients with clear-cell RCC shown kidney IGF1R expression higher than 50% have shorter survival, a difference that becomes particularly significant after two years of follow-up.⁴⁰

Moreover, after adjustment for age and stage at diagnosis, those patients with renal IGF1R expression higher than 50% had a 4.2 increased risk of death compared to those with lower renal IGF1R expression. Similarly, other studies have demonstrated a direct association between kidney IGF1R expression and the severity of RCC.^{41,42} *In vitro* studies using RCC cell lines have shown that treatment with neutralizing antibodies against IGF1R can reduce IGF1R expression and inhibit cell proliferation. This effect is enhanced when combined with the mTOR inhibitor temsirolimus.⁴³

Importantly, loss-of-function mutations in the gene encoding the tumor suppressor Von Hippel-Lindau (VHL) are commonly observed in RCC.⁴⁴ These mutations have been associated with increased activation of renal IGF-1 signaling and elevated IGF1R expression, resulting in a more aggressive tumor phenotype compared to RCC with wild type VHL. This fact is directly induced by inhibition of IGF1R transcription and occurs independently of VHL's role in suppressing the hypoxia pathway.⁴⁵⁻⁴⁷

Despite of the clear association between activation of renal IGF-1 signaling and RCC occurrence and progression, low circulating IGF-1 levels have been linked to an increased risk of renal cancer, particularly in a cohort of male smokers after at least five years of follow-up.⁴⁸ This finding raises doubts about the utility of circulating IGF-1 as a reliable biomarker for renal cancer risk.

In addition, discordant (opposite) differential mRNA expression of genes associated to the IGF-1 signaling pathway has been observed in kidney samples from mice undergoing post-ischemic renal repair, compared to gene expression profiles reported in human renal cell carcinoma. Particularly, IGFBP1 and IGFBP3 are upregulated in cancer, while IGFBP8 and IGFBP10 (which has lower affinity for IGF-1).⁴⁹ Thus, whereas 77% of differentially expressed genes were similarly regulated in both renal regeneration and cancer, some genes related to IGF-1 signaling follow divergent molecular pathways in these contexts. This suggests that IGF-1 signaling may not play a common role in both physiological and pathophysiological proliferative processes in the kidney.

Implication of IGF-1 in other Renal Pathologies

The beneficial effects of IGF-1 treatment have also been observed in rats with acute renal tubulointerstitial injury induced by ureteral obstruction.⁵⁰ Likewise, *in vivo* studies using this mouse model of obstructive nephropathy have demonstrated that IGF-1 administration reduces apoptosis, an effect that was abolished by inhibition of the ERK/MAPK signaling pathway.⁵¹

Of particular interest, renal hypertrophy in diabetes is also associated with elevated kidney IGF-1 production, similar to the compensatory hypertrophy observed in the contralateral kidney following Uni-Nx.⁵² In fact, while rats subjected to Uni-Nx show increased size of the remnant kidney size by 30%, animals undergoing streptozotocin-induced diabetes show a 32% increase in renal size, reaching a 46% increase when the diabetic rats were subjects to Uni-Nx, which was consistent with the increased kidney IGF-1 expression.⁵³ These effects of IGF-1 on compensatory renal growth are reduced by administration of an IGF1R antagonism in both, diabetic and Uni-Nx rats,⁵⁴ as well as *ex-vivo* compensatory hyperfiltration in kidney samples from Uni-Nx rats.⁵⁵ Similar results have been observed in non-obese diabetic mice treated with an antagonist of the GH receptor.⁵⁶ These studies demonstrate that diabetes is an inductor of renal hypertrophy

through activation of the kidney IGF-1 levels. Table 1., shows the main renal effects of IGF-1 in studies with animal models.

In clinical studies, treatment with recombinant IGF-1 has been shown to improve renal function in patients with moderate renal insufficiency or end stage renal disease (ESRD), as evidenced by increased GFR, lower plasma creatinine and BUN levels, and enhanced inulin clearance. Additionally, IGF-1 administration has been associated with increased tubular phosphate reabsorption.^{57,58} In the same way, other clinical studies have reported beneficial effects of recombinant IGF-1 on GFR in ESRD patients scheduled to begin renal replacement therapy or patients undergoing peritoneal dialysis.^{59,60}

In vitro studies have supported the renal protective effects of IGF-1. Specifically, treatment with IGF-1 prevented etoposide-induced podocyte apoptosis, whereas these protective actions were blocked by inhibition of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, highlighting the critical role of this signaling pathway as a key downstream mechanism.⁶¹ Moreover, *in vitro* studies have shown that IGF-1 signaling is crucial for mesenchymal stem cell-mediated recovery of renal function and tubular cell structure following cisplatin-induced damage.⁶² Notably, mesenchymal stem cells overexpressing IGF-1 significantly improved outcomes in a rat model of acute kidney injury, enhancing renal function and preventing apoptosis, oxidative stress and inflammation.⁶³

Based on the studies mentioned above, treatment with IGF-1 appears to be beneficial for renal function. However, the mechanisms underlying IGF-1 signaling seem to be complex. To note, aged rats with GH inhibition, which leads to reduced plasma IGF-1 levels, exhibit improved age-associated renal changes, including lower glomerulosclerosis, altered myofibroblast, reduced collagen content and less macrophage infiltration.⁶⁴ Additionally, it has been observed that blocking IGF-1 signaling by inhibition of the IGF1R results in prevention of renal inflammation, tubular damage and fibrosis in a mouse model of diabetic kidney disease.⁶⁵ These findings emerge the controversy regarding potential negative effects of IGF-1, suggesting that its role in kidney disease may not be entirely protective.

Studies in rats undergoing subtotal nephrectomy (5/6Nx) have shown that IGF-1 administration failed to increase GFR in this model of renal insufficiency.⁶⁶ Close to this finding, patients undergoing hemodialysis or peritoneal dialysis, recombinant IGF-1

administration induces a dose-dependent decrease in plasma levels of insulin, C-peptide, amino acids and glucose. However, this response was blunted compared to normal subjects, despite higher plasma IGF-1 concentrations, indicating partial resistance in advanced CKD.⁶⁷ This reduced response is likely due to a decrease in the distribution and shortened half-life of the IGF-1 in dialysis patients.⁶⁸ Furthermore, resistance to the GH-mediated bioactive IGF-1 stimulation has been demonstrated in non-diabetic hemodialysis patients, suggesting the presence of additional inhibitory mechanisms.⁶⁹ In predialysis patients, increased production of IGFBPs has been observed, which may bind free IGF-1 and contribute to the attenuation of its renal effects.⁷⁰ Therefore, as previously mentioned, elevated levels of renal IGFBPs in conditions of renal insufficiency may act as inhibitors of IGF-1 contributing to resistance in the proximal tubular cells.⁴

On the other hand, the renal anabolic actions of IGF-1 can be detrimental in the context of polycystic kidney disease (PKD), as it promotes renal cell proliferation and kidney enlargement. Studies have shown that renal epithelial cells from patients with autosomal dominant polycystic kidney disease (ADPKD) exhibit increased sensitivity to IGF-1 compared to those from healthy individuals, indicating the involvement of this signaling pathway in cyst formation.⁷¹ In addition, increased expression of IGF-1-related genes, such as IGF-1, IGF1R, and IGFBP5, along with the metalloproteinase Pregnancy-Associated Plasma Protein A (PAPPA), has been detected in kidney samples from PKD1 mutant mice, a model of PKD, compared to wild-type controls. PAPPA levels were also elevated in kidney samples from ADPKD patients, where it was found to cleave IGFBP4, an inhibitor of the IGF-1, producing a consequent overactivation of the IGF-1 signaling. This overactivation contributes to increased cyst number and area.⁷²

Despite the controversy surrounding the various actions of the IGF-1, lower serum IGF-1 levels have been associated with shorter survival rates in patients undergoing one year on dialysis,⁷³ whereas hemodialysis patients with low serum IGF-1 levels had a higher mortality rate, an association that remained significant after adjusting for demographic factors, inflammatory markers, co-morbidities, and biomarker of renal function.⁷⁴ These studies suggest that, systemic IGF-1 may play a role in preventing mortality in ESRD patients, and could serve as an useful circulating marker of survival in this population.

Clinical trials investigating the renal effects of recombinant human IGF-1 are shown in Table 2. It is important to highlight that numerous studies in small groups of patients with kidney disease have demonstrated significant improvements in GFR following

recombinant IGF-1 administration; however, these benefits are not observed in clinical studies with larger numbers of kidney patients. Since this discrepancy could be due, at least in part, to the heterogeneity of kidney patients in larger studies, there is a possibility that a particular profile of kidney patients may benefit from IGF-1 treatment.

Role of IGF-1 in renal dysfunction-associated complications

IGF-1 and nutritional status

Protein intake is an important stimulus for renal growth. In rats, kidney size increases according to protein consumption and it acts synergically with compensatory renal hypertrophy following Uni-Nx.⁷⁵ Of relevance, switching to low or high protein diet leads to decreased or increased renal IGF-1 production, respectively, being directly associated with renal growth. These effects are observed even in rats deficient in GH or vasopressin.⁷⁶ Uni-Nx-induced renal enlargement occurs similarly in both normal and GH-deficient rats when fed a diet with moderate protein content. However, when provided a high-protein diet, only normal rats showed further renal growth. This is because GH-deficient rats on the moderate-protein diet had lower baseline renal and plasma IGF-1 levels, but their IGF-2 levels increased similarly after Uni-Nx. In contrast, a high-protein diet enhanced renal IGF-1 levels only in normal rats, suggesting that the additional effects of a high-protein intake on compensatory renal hypertrophy are partially mediated by GH signaling.⁷⁷ In fact, the renal anabolic effects of the high-protein diet are attenuated by the inhibition of the GH receptor.⁷⁸

Particularly, protein and energy wasting (PEW) is commonly observed in hemodialysis patients and likely associated with a lower protein and caloric intake.⁷⁹ In this respect, circulating IGF-1 has been well-established as a marker for nutritional deficiency in hemodialysis patients for decades.^{80,81} Thus, hemodialysis patients with decreased muscle mass and a history of infections often show decreased serum IGF-1 levels, showing high sensitivity (77%) and moderate specificity (52%) as a marker of nutritional status.⁸²

Compared to controls on a low-protein diet, rats fed a high-protein diet show increased serum, liver and glomerulus IGF-1 levels, but not in the renal cortex, which result in higher total body and kidney weight but not liver. In addition, high protein intake also increases renal flow and GFR as compared with rats fed a low protein diet, while

decreased renal vascular resistance, actions that were associated with the higher serum IGF-1 levels.⁸³ As previously mentioned, the glomerular hemodynamic effects of IGF-1 are mainly due to increased glomerular ultrafiltration coefficient and decreased efferent arteriolar resistance. However, these effects are prevented in fasted animals due to a reduction in the increment of the glomerular transcapillary hydrostatic pressure.¹⁵ Additionally, a protein-rich diet also stimulates VEGF signaling, which promotes glomerular hypertrophy.⁸⁴ In contrast, low-protein diet leads to reduced serum GH and IGF-1 levels in rats, which could help preventing glomerulosclerosis.⁸⁵

It is important to note that appetite-regulating endocrine factors, such as leptin, a hormone that induces satiation, may be linked to IGF-1 production in renal patients. Serum IGF-1 levels correlates with the circulating leptin concentration in patients undergoing peritoneal dialysis and hemodialysis, but not in patients treated with conservative therapy.⁸⁶ Interestingly, administration of recombinant IGF-1 decreases serum leptin concentration in patients undergoing hemodialysis; however, when recombinant IGF-1 is co-administrated with recombinant GH, circulating leptin levels are unexpectedly elevated, likely due to GH stimulatory effects on insulin production.⁸⁷ Moreover, treatment with recombinant GH increases IGF-1 levels in hemodialysis patients with low protein intake, resulting in a positive nitrogen balance and suggesting an anabolic response, which may also contribute to increase the leptin levels.⁸⁸ Of note, among the multiple factors, circulating IGF-1 is strongly associated with loss of appetite in dialysis patients, a condition linked to poor clinical outcomes.⁸⁹ However, very low IGF-1 levels have been associated with a higher mortality in CKD patients with poor muscle strength, whereas those with higher muscle strength showed improved survival despite of the reduced IGF-1 concentration.⁹⁰ This suggest that muscle effects, potentially influenced by physical exercise habits or muscle-derived cytokines (myokines), may play a role in these outcomes.

In addition, ghrelin, a stomach-derived hormone involved in appetite stimulation, increases renal IGF-1 levels and improves renal function in a mouse model of ischemia-reperfusion.⁹¹ Consequently, a ghrelin receptor agonist has been studied in hemodialysis patients, being efficient in increasing serum IGF-1 levels after three months of treatment, suggesting that the ghrelin receptor activation should be useful to prevent PEW in these patients.⁹²

IGF-1 and CKD-MBD

GH induces increased tubular phosphate reabsorption and 1,25-dihydroxyvitamin D3 production, which should be at least partially induced by the subsequent renal IGF-1 production. Thus, continuous administration of exogenous IGF-1 in rats with pituitary gland ablation enhances renal phosphate reabsorption, 1,25-dihydroxyvitamin production, reduces renal sodium excretion and increases GFR. These effects of the IGF-1 persisted even in thyroparathyroidectomized rats, suggesting a PTH-independent mechanism.⁹³ In addition, 1-alpha hydroxylase activity is synergically increased by IGF-1 administration in rats fed a phosphorus deficient diet, which suggest also distinct mechanisms.⁹⁴ *In vitro* experiments with renal proximal tubular cells have demonstrated the direct stimulatory effects of IGF-1 and P depletion on calcitriol synthesis.⁹⁵

In patients undergoing hemodialysis, recombinant GH administration results in a subsequent increase in plasma IGF-1 concentration, accompanied by reductions of the blood urea nitrogen (BUN), urea generation, protein catabolic rate, phosphate, and intact parathyroid hormone plasma (iPTH) concentrations,⁹⁶ likely reflecting improved renal function. In prepubertal children with advanced CKD and severe growth retardation, GH administration has shown significant benefits, leading to increased serum IGF-1 levels.⁹⁷ However, despite improved growth in children treated with GH and the non-apparent progression of renal damage, bone maturation seems to be unaffected despite of the increased plasma IGF-1 levels after 6 months, maybe due to the concomitant decrease of IGFBP1 and increase of IGFBP3, which occurred in a lower extent than the IGF-1 changes.⁹⁸ In the same way, circulating levels of IGF-1 are not correlated with bone formation parameters in non-dialysis CKD patients, which apparently excludes a role of the IGF-1 in bone turnover or a dependence on bone-derived growth factors.⁹⁹

Recent studies have demonstrated that low serum IGF-1 levels are associated with lower weight and bone mineral density in pediatric CKD patients.¹⁰⁰ Importantly, a combination of recombinant GH and IGF-1 has been found to be more effective in preventing growth retardation than GH alone, suggesting an impaired response to the GH effect on IGF-1 stimulation.¹⁰¹ In a study of young rats with renal insufficiency, despite having similar serum GH levels, the animals exhibited lower IGF-1 concentrations, which may contribute to bone growth retardation. This reduced bone response to the stimulatory effects of GH via IGF-1 has been linked to decreased VEGF expression and diminished vascularization in the primary ossification zone of rats with renal insufficiency.¹⁰² In the same way, intensive treadmill exercise improves linear bone growth in a rat model of

renal insufficiency (5/6Nx). This effect was associated with increased expression IGF-1 and VEGF in the primary ossification zone.¹⁰³

Altogether, the bone anabolic actions of the GH can be, at least in part, mediated by paracrine IGF-1 signaling, which enhances osteoblast activity.¹⁰⁴ In fact, the only administration of recombinant IGF-1 to healthy participants results in an increase in circulating levels of bone remodeling markers. In these participants, GH administration increases circulating phosphate levels by enhancing phosphate resorption, while IGF-1 treatment does not significantly modify phosphate concentrations.¹⁰⁵ These effects of recombinant IGF-1 on bone remodeling and calcitriol production have been also observed in patients with GH deficiency, being more notable on osteoblast activity than in bone resorption.¹⁰⁶

Calcium influx from the bone store appears to be an important regulator of IGF-1 production, since patients with pycnodysostosis, who have a loss-of-function mutation of the Cathepsin K gene and develop osteosclerosis, show low levels of IGF-1, which may be associated with impaired osteoclastic activity.¹⁰⁷ In addition, continuous infusion of PTH or PTH-related protein (PTHrP) increase circulating IGF-1 levels, along with plasma levels of calcium and calcitriol, as well as bone resorption.¹⁰⁸ Of interest, the osteoanabolic effects of PTH are reduced in mice with IGF-1 knockout mice, as well as in osteoblasts derived from this mutant strain, while administration of exogenous recombinant IGF-1 increased *in vitro* proliferation.¹⁰⁹ In contrast, total parathyroidectomy abolishes the effects of high dietary protein supplementation on the stimulation of renal and liver IGF-1 expression, as well as its actions on the compensatory kidney hypertrophy. However, administration of calcitriol or activation of renal calcium reabsorption by a retinoid derivate restored plasma IGF-1 levels.¹¹⁰

Importantly, chondrocytes isolated from rats with renal insufficiency also show decreased response to the anabolic effects of IGF-1 compared to chondrocytes from rats with normal renal function,¹¹¹ suggesting that intracellular alterations as causing factors for IGF-1 resistance. Moreover, rats undergoing subtotal nephrectomy (5/6Nx), which impairs long bone growth, show reduced IGF-1 expression in the growth plate. The exacerbation of secondary hyperparathyroidism due to high dietary phosphate further worsens bone alterations and decreases growth plate width. These bone defects are associated with a reduced expression of both IGF-1 and PTH receptor expression in the growth plate.¹¹²

Altogether, these studies suggest a connection between mineral metabolism parameters and bone IGF-1 signaling.

The bone effects of IGF-1 have been demonstrated in elderly women,¹¹³ where treatment with a low dose of recombinant IGF-1 led to increased osteoblast activity with only a minor increase in bone resorption, also decreased serum phosphate after 3 weeks. Similarly, associations among serum IGF-1 concentration and serum levels of phosphate, calcium, FGF23 and bone mineral density have been shown in patients with advanced CKD, which also supports the interconnection between mineral metabolism and IGF-1 regulation in CKD patients.⁷³

In patients with acromegaly, higher renal IGF-1 is associated expression with increased serum and urinary calcium levels, elevated serum phosphate and calcitriol concentrations, along with decreased serum PTH levels. In these patients, treatment with the diuretic agent furosemide decreases serum IGF-1 concentration and normalizes mineral parameters, but did not further increase urinary calcium excretion, suggesting that these effects are mediated by IGF-1.¹¹⁴ Another factor that reduces IGF-1 levels is metabolic acidosis that often may accompany CKD,¹¹⁵ highlighting the complexity of the IGF-1 regulation. Studies demonstrating the effects of IGF-1 in mineral and bone metabolism are shown in Table 3.

IGF-1 and Cardiovascular Complications

Most studies have reported a protective effect of IGF-1 on cardiovascular health in CKD. In hemodialysis patients, higher circulating levels of IGF-1 are independently associated with a lower ventricular mass and an improved ejection fraction.¹¹⁶ However, under hypertensive conditions, increased IGF-1 expression is observed in the left ventricle but not in the right ventricle. The highest IGF-1 expression occurs in the subendocardial layer, where the wall stress is more pronounced,¹¹⁷ suggesting a possible role as a mediator of left ventricular hypertrophy. In the same way, left ventricular IGF-1 expression is increased in the early stages of hypertrophy,^{118,119} which may raise the possibility of an involvement of the IGF-1 anabolic actions in the exacerbation of cardiac insufficiency. Remarkably, while recent studies have reported an association between low serum IGF-1 levels and all-cause mortality in hemodialysis patients, serum IGF-1 concentration was not useful as a predictor of cardiovascular events.¹²⁰

In the vasculature, studies in animal models have shown that IGF-1 induces vasodilatory effects mediated by increasing nitric oxide synthesis in vascular endothelial cells.^{121,122} Moreover, *in vitro* studies with rat vascular smooth muscle cells have demonstrated that treatment with recombinant IGF-1 directly reduces the endogenous production of nitric oxide induced by exogenous administration of interleukin-1 β or TNF- α , suggesting a role of IGF-1 on the regulation of nitric oxide synthase at the sites of vascular injury.¹²³ A list of preclinical and clinical studies on the actions of IGF-1 in cardiovascular diseases is shown in Table 4.

IGF-1 and Erythropoiesis

Anemia is a common complication in CKD patients, primarily caused by decreased renal erythropoietin (EPO) production. Standard treatments typically are focused on exogenous administration of recombinant EPO or EPO-stimulating agents. However, the erythropoietic activity of IGF-1 has been recognized since 1985.¹²⁴ Despite of this evidence, the potential role of the IGF-1 in the development of anemia within the context of CKD remains insufficiently explored.

In hemodialysis patients with severe secondary hyperparathyroidism, Ureña P. et al., observed that hematocrit values correlated more strongly with serum IGF-1 levels than with serum EPO levels.¹²⁵ Interestingly, residual hematopoietic function has been observed in some anephric patients, suggesting the involvement of stimulators beyond renal EPO. Serum IGF-1 has been identified as a major contributor to hematopoiesis in anephric patients with normal hematocrit. Furthermore, treatment with recombinant IGF-1 enhanced erythroid colony formation in *in vitro* culture of bone marrow cells.¹²⁶ In the same way, end-stage CKD patients undergoing hemodialysis and presenting erythrocytosis showed elevated serum IGF-1 levels, while EPO levels were variable. Serum from these CKD patients showed a greater ability to enhance proliferation of erythroid progenitors in normal marrow cultures than serum from non-CKD controls. This effect diminished after IGF-1 neutralization with a specific antibody. Of note, serum from anemic CKD patients showed similarly variable EPO levels but lower serum IGF-1 concentration than CKD patients with erythrocytosis and their uremic serum was not able to induce erythroid progenitor proliferation in normal bone marrow culture, being these effects unaffected by IGF-1 neutralization.¹²⁷ These findings underscore the significant role of IGF-1 in the erythrocytic homeostasis in CKD, particularly in those with low EPO levels.

However, a negative association between circulating IGF-1 levels and the hematocrit has been also observed in predialysis patients, suggesting that the presence of uremic inhibitors could impair the effects of IGF-1 on erythroid cell proliferation, which could be restored in patients undergoing hemodialysis.¹²⁸

In renal transplant recipients, patients developing erythrocytosis have similar serum levels of IGF-1 and EPO than those without erythrocytosis; however, elevated levels of serum IGFBP1 and IGFBP3 were found higher in the transplant patients with erythrocytosis, which have been related to decreased degradation of IGF-1.¹²⁹

In addition, recombinant EPO administration increased IGF-1 levels in hemodialysis patients, along with higher serum collagen telopeptide concentration, in comparison with untreated patients. This suggests a potential link between EPO, IGF-1, and bone resorption in CKD.¹³⁰

More recently, the association between low IGF-1 and anemia in hemodialysis patients has been also demonstrated,¹³¹ which support the principal role of the IGF-1 in hematocrit homeostasis, being a relevant topic of current research interest. Table 5 shows key studies demonstrating a role of IGF-1 signaling in the development of anemia.

Potential Actions of the IGF-1 in Skeletal Muscle Cells

Aerobic exercise, a condition known to prevents renal disease progression in CKD models,¹³² has been linked to elevated plasma IGF-1 levels, which may partially contribute to improved renal outcomes.¹³³ Moreover, IGF-1 plays a significant role in the development of CKD-associated sarcopenia. Attenuation of the IGF-1-AKT pathway in muscle satellite cells from CKD mice leads to in reduced levels of myogenic markers, resulting in poor muscle regeneration, fibrosis, and the consequent muscle wasting.¹³⁴

In hemodialysis patients, it has been recently demonstrated that the association between plasma IGF-1 and muscle strength is comparable to that of the myostatin, a well-known inhibitor of muscle growth, and both similarly predict mortality in this population.¹³⁵ In this regard, the relationship between higher plasma IGF-1, muscle strength and survival could be expected; however, the association with plasma myostatin is surprising and should be related to dialysis conditions, since these patients commonly have higher myostatin levels than general population.¹³⁶

Similar to other organs, the anabolic response to IGF-1 in skeletal muscle cells is decreased in the context of renal insufficiency.¹³⁷ This resistance is associated with both, decreased local IGF-1 production and resistance to recombinant IGF-1 administration. Despite of the increased expression of the IGF1R in the skeletal muscle cells of uremic animals, intracellular phosphorylation and downstream signaling activation is attenuated, suggesting additional inhibitory mechanisms. Studies in animal models of renal insufficiency have demonstrated that GH or work overload-induced upregulation of IGF-1 expression in the skeletal muscle is partially reduced in animals with renal insufficiency.¹³⁸ In the same way, a complementary study in patients undergoing hemodialysis has shown that IGF-1, IGF-2 and IGF-1 receptor gene expressions are reduced in skeletal muscle from hemodialysis patients as compare with normal control participant; however, at protein level, the amounts of IGF-1, IGF-2 and TNF- α in the skeletal muscle of hemodialysis patients were found elevated in comparison to the control group,¹³⁹ which may suggest impaired IGF-1 signaling activation as observed in animal models of renal insufficiency,¹³⁷ considering the decreased muscle strength in the hemodialysis patient group. In Table 6 are presented principal studies showing evidences for a role of IGF-1 signaling in sarcopenia.

Conclusion and Future Perspective

IGF-1 exhibits a wide range of functions that are significantly impacted in the context of CKD. In spite of the numerous studies on the renal actions of IGF-1, most of them conducted decades ago, emphasizing its potential role on renal regeneration, mineral and bone metabolism and red blood cell homeostasis, as well as its association with patient survival, nowadays its relevant functions are underestimated. Recent findings demonstrating the key role of fatty acid oxidation for renal cell proliferation and compensatory hypertrophy may help to understand the complex mechanisms involved in this process and whether abnormal lipid metabolism in the injured kidney may contribute to IGF-1 resistance. Moreover, the implication of a defective IGF-1 signaling in the development of adynamic bone disease or EPO-resistant anemia in CKD should be considered.

In summary, the wide-ranging actions of IGF-1 make it a compelling molecule for studying various pathological complications associated with renal disease. Understanding

the IGF-1 downstream pathways could reveal novel mechanisms underlying multiple conditions, offering the potential for the development innovative therapeutic strategies.

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

3. ¿Su trabajo incluye un ensayo clínico?:

No

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el

apartado de resultados y las conclusiones?:

Sí

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Conflict of interest

All authors declare no conflicts of interest.

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Figure 1. Schematic illustration depicting IGF-1 regulatory factors in the kidney and its downstream interaction pathways leading to renal hypertrophy. Binding of IGF-1 to the IGF-1 Receptor (IGF-1R) results in phosphatidylinositol-3-kinase (PI3K) activation, increasing phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP₂) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP₃), which in turn results in the AKT and mTOR phosphorylation, as well as NFATc1 nuclear translocation, and subsequent transcription of genes related to cell survival and proliferation. In contrast, IGF binding proteins (IGFBPs) capture free IGF-1 and inhibits IGF-1 binding to IGF-1R. Growth Hormone (GH) and Epidermal Growth Factor (EGF) bind to their specific receptors and increase RAS-mediated ERK phosphorylation, which also activates the transcription of genes involved in proliferation and survival. Activation of the IGF-1 signaling interacts with EGF and GH downstream signaling by enhancing MEK signaling and ERK phosphorylation, thereby stimulating their anabolic effects. Furthermore, activation of the GH signaling increases IGF-1 gene transcription through phosphorylation and nuclear translocation of STAT5, which further stimulates IGF-1 signaling. Altogether, IGF-1 signaling produces renal hypertrophy and increases glomerular filtration rate (GFR).

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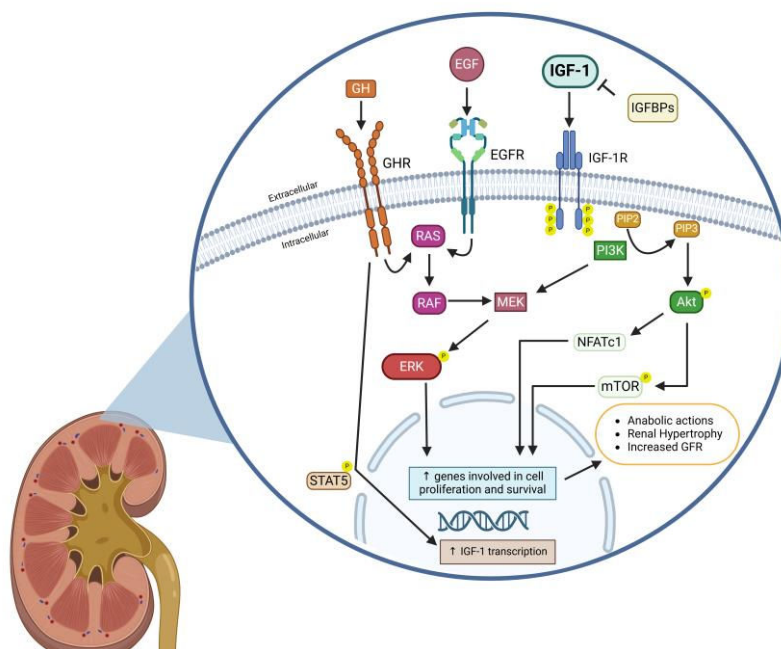


Table 1. Studies in animal models on the renal actions of IGF-1

Study (year)	Animal model	Study design	Sample size	Type of intervention	Key findings
Hirschberg R., et al (1989)	Male Sprague-Dawley and Wistar rats	~3d fasting	n=6-8	rhIGF-1 (25µg/kg;i.v.)	- ↑ renal plasma flow, GFR and ↓ renal vascular resistance in IGF-1 treated animals - rhIGF-1 effects are mediated by eicosanoids
Hirschberg R., et al (1991)	Male Wistar rats	1) 12h fasting 2) ~3d fasting	n=6-8 per group	1) rhIGF-1 (75µg/kg;i.v) and continuous rhIGF-1 infusion (250µg/kg/h) 2) rhIGF-1 (25µg/kg/i.v) and continuous rhIGF-1 (75µg/kg/h)	- ↑ serum IGF-1 levels and GFR - ↑ single nephron GFR, renal blood and plasma flow rate - rhIGF-1 administration partially prevents fasting-induced single nephron GFR reduction.
Hirschberg R., et al (1992)	Male Wistar rats	N/A	n= 7 per group	Continuous infusion of rhIGF-1 (125µg/24h;s.c) or GH antagonist.	- rhIGF-1 infusion ↑ kidney/total body weight, GFR, glomerular volume, single nephron plasma flow and ↓ renal vascular resistance - treatment with GH antagonist ↓ GFR, but not kidney weight
Doi T., et al (1988); Doi T., et al (1990)	Transgenic mice over-expressing GH and IGF-1	N/A	n= 2-36	N/A	- Both GH and IGF-1 mice ↑ glomerular volume, with the latter having a lesser effect - GH mice had severe glomerulosclerosis - IGF-1 mice had no sclerotic lesions
Miller SB., et al (1990)	Male Sprague-Dawley rats	Normal renal mass and 5/6Nx	n= 3-8 per group	Continuous infusion of 200 µg/day of rhIGF-1 or rbGH or vehicle for 10 or 17 days	- rhIGF-1 or rbGH administration ↑ GFR in rats without reduction of renal mass - Treatment with rbGH nor rhIGF-1

					do not modify inulin clearance in 5/6Nx rats
Miller SB., et al (1992)	Male Sprague-Dawley rats	Ischemic acute tubular necrosis	n= 7-9 per group	Continuous infusion of rhIGF-1 (100µg/day), rbGH, rhEGF or vehicle	- ↑ GFR and preserved renal function in rhIGF-1 treated rats - ↓ weight lost, renal injury and mortality
Rogers SA., et al (1993)	Male Sprague-Dawley rats	Uni-Nx and partial unilateral infarction	n= 4-8	Measure of IGF-1 in the tissue infarcted	- ↑ renal IGF-1 expression in the remnant kidney of Uni-Nx rats (peak at 3 days) - Partial unilateral infarction ↑ IGF-1 expression in the non-infarcted kidney
Ding H., et al (1994)	Male Sprague Dawley	Ischemic acute renal failure	n=14 per group	rhIGF-1 (50µg/100g;s.c) three times daily	- rhIGF-1 ↑ recovery of renal function at 3 days (GFR, renal plasma flow) - ↑ formation of new renal tubular cells
Haylor JL., et al. (JASN 2000)	Male Wistar rats	Uni-Nx and streptozotocin-induced diabetes		IGF-1 R inhibition (JB3, 10µg/kg/day) for 4 or 11 days	- JB3 prevents renal hypertrophy in Uni-Nx and diabetic rats.
Haylor JL., et al. (NDT 2000)	Male Wistar rats	Uni-Nx	n= 4-8 per group	IGF-1 neutralizing antibody	- ↓ renal hyperfiltration
Chevalier RL., et al (2000)	Sprague-Dawley neonatal rats	UUO	n= 21-24 per group	rhIGF-1 (2mg/kg/d; s.c.) for 3 or 7 days	- ↓ renal tubular atrophy, tubular cell apoptosis and interstitial fibrosis
Wu Z., et al. (2016)	C57BL/6 mice	UUO	n= 10 per group	rhIGF-1 (daily/i.p.; dose non-reported)	- Treatment with IGF-1 reduces renal fibrosis and apoptosis of renal epithelial cells (↑Bcl2)
Dong R., et al (2019)	Male C57BL/6J mice	Streptozotocin-induced diabetic kidney disease	n= 8-10 per group	IGF-1 R inhibition (GSK4529, 30 mg/kg/day; i.p.)	- IGF-1 R inhibition ↓ albuminuria, diabetes-induced kidney growth, glomerulomegaly, inflammatory infiltration and

					tubulointerstitial fibrosis
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Abbreviations. rhIGF-1: Recombinant human IGF-1. Uni-Nx: Unilateral nephrectomy. GFR: glomerular filtration rate. GH: growth hormone; bGH: recombinant bovine growth hormone. EGF: epidermal growth factor GH-rh: growth hormone-releasing hormone. UUO: Unilateral ureteral obstruction. IGF-1 R: IGF-1 receptor

Table 2. Clinical studies on the effects of IGF-1 on glomerular filtration rate and survival in CKD patients

Study (year)	Study design	Sample size	CKD stage of participants	Type of intervention	Key findings	Potential side effects
O'Shea MH., et al (1993)	Longitudinal study	n=4	Moderate chronic renal insufficiency (CrCl 25-60mL/min)	rhIGF-1 (100µg/kg; 12h; s.c.) for 4 d	- ↑ Circulating IGF1 - ↑ Inulin clearance - ↑ Kidney size	- Tachycardia
Miller SB., et al (1994)	Longitudinal study	n=9	CrCl less than 20 mL/min/1.73 m ²	rhIGF-1 (100µg/kg; 12h; s.c.) for 4 d (short-term) and for 13-27 d (long-term)	- ↑ GFR - ↓ Plasma creatinine and BUN levels - ↑ Inulin clearance during short-term administration	- Pericardial Rub - Nasal Congestion - Jaw pain
Fouque D., et al (1995)	Longitudinal study	n=18	Stage 5	rhIGF-1 (50 or 100 µg/kg; s.c.; twice)	Dose-dependent effects: - ↓ Plasma levels of insulin - ↓ serum C-peptide, amino acids and glucose levels - Partial resistance to IGF-1 in advanced CKD	Not reported
Hirschberg R., et al (1999)	Multicenter clinical trial, randomized, double-blind, placebo-controlled	n=72	Acute renal failure, CKD stage 5	rhIGF-1 (100 µg/12h; s.c.)	rhIGF-1 did not improve renal outcomes in patients with acute renal failure	Not reported
Vijayan A., et al (1999)	a) prospective open-labeled trial; b) randomized	a) n=5 b) n=10	End-stage renal disease	rhIGF-1 (50µg/kg; 24h; s.c.) for a) 24 d or b) 31 d	- ↑ GFR during the 3 rd and 4 th week in both studies	- Peripheral edema - Local irritation at the site of

	d, double-blinded, placebo-controlled trial					drug injection
Frystyk J., et al (1999)	Cross-sectional case-control study	n=38	CrCl: 3-59 and 89 to 148 mL/min/1.73 m ²	Overnight fasting serum samples	- ↑ Production of IGFBPs - Low serum levels of IGF-1	Not reported
Hladunewich MA., et al (2003)	A randomized, placebo-controlled trial	n=47	Acute renal failure with GFR less than 20 mL/min	rhIGF-1 (100µg/kg; 12h; s.c.) for 6 d	Treatment failed to improve renal function compared to placebo	Not reported
Jia T., et al (2014)	Cohort study	n=365	CKD stage 5	Measurement of serum IGF-1 and other biochemical markers	- ↓ serum IGF-1 levels are associated with body composition and CKD-MBD parameters - serum IGF-1 levels predict increased mortality risk.	Not reported
Nilsson E., et al (2016)	Cohort study	n=265	CKD stage 5	Analysis of serum biochemistry and IGF-1 levels	- ↓ serum IGF-1 levels associate with increased mortality in HD patients	Not reported

Abbreviations. rhIGF-1: Recombinant human IGF-1. CrCl: Creatinine clearance. GFR: glomerular filtration rate. ESRD: End-stage renal disease. HD: Hemodialysis.

Table 3. Evidence on the involvement of IGF-1 in mineral and bone metabolism

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention
Caverzasio J., et al. (1990)	Animal models	Hypophysectomized and tyroparathyroidectomized male Sprague Dawley rats	5 to 8 animals	rhIGF-1 continuous infusion (10 µg/h) for 6 days
Coen G., et al. (1991)	Cross-sectional study	Non-dialysis CKD patients	n=28	Serum IGF-1 quantification
Nesbitt T., et al. (1993)	Animal models	C57BL/6J mice	Not reported	rhIGF-1 continuous infusion (0.1 to 10 µg/h) for 24h
Condamine L., et al (1994)	<i>In vitro</i> study	Kidney cells	5 to 10 replicates	rhIGF-1 (25ng/ml)
Ghiron LJ., et al. (1995)	Prospective interventional study	Healthy elderly women	n= 16	rhIGF-1 (15 or 50 µg/kg s.c) or GH for 28 days
Mak RH., et al. (1996)	<i>In vitro</i> study	Chondrocytes from 5/6Nx male Sprague-Dawley rats	n= 6	rhIGF-1 (1 to 100 ng/ml) 3 days
Johansson AG., et al (1996)	Randomized, crossover study	Idiopathic osteoporosis men	n= 12	rhIGF-1 (80µ/kg;s.c) for 1 week
Bianda T., et al. (1997)	Randomized, crossover study	Healthy young adults	n= 7	rhIGF-1 continuous infusion (8 µg/kg/h) for 2 weeks.
Bianda T., et al. (1998)	Randomized, crossover study	GH deficient adults	n= 8	Continuous infusion of rhIGF-1 (5 µg/kg/h)
Miyakoshi N., et al. (2001)	Animal models	IGF-1 deficient mice	n= 5 to 6	rhPTH (1-34) (160µ/kg;s.c) for 10 days
Karava V., et al. (2021)	Cross-sectional study	CKD children and adolescent patients	n= 46 patients	Serum IGF-1 quantification

Abbreviations: rhIGF-1: Recombinant human IGF-1. Max TRPi: maximal tubular reabsorption of phosphate; GFR: Glomerular filtration rate; BMD: bone mineral density. MAR: mineral apposition rate.

Table 4. Studies demonstrating an involvement of IGF-1 in cardiovascular diseases

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention
Haylor J., et al. (1991)	Animal models	Male Wistar rats	n= 11 to 13	rhIGF-1 (50µg/kg;i.v)
Wåhlander H., et al. (1992)	Animal models	Male Wistar rats	n= 10	Renal artery occlusion-induced hypertension
Schini VB., et al. (1994)	<i>In vitro</i> study	Rat vascular smooth muscle cells		rhIGF-1 (1 - 100 ng/ml)
Tsukahara H., et al. (1994)	<i>In vitro</i> study	Endothelial cells	n= 4 to 14	rhIGF-1 (1 - 20 ng/ml)
Guron G., et al. (1996)	Animal models	Male Wistar rats	n= 5 to 8	Renal artery occlusion-induced hypertension
Huang CY., et al. (2003)	Animal models	Male Sprague-Dawley rats	n= 4	Abdominal aorta occlusion- induced hypertension
Prelevic V., et al. (2020)	Multicentric cohort study	Hemodialysis patients	n= 102	Measurement of serum IGF-1
Nakaya R., et al. (2022)	Cross-sectional cohort study	Hemodialysis patients	n= 506	Measurement of serum IGF-1

Abbreviations. rhIGF-1: Recombinant human IGF-1. IL1β: Interleukin-1β; TNF: Tumor necrosis factor; LVH: Left ventricular hypertrophy; EF: ejection fraction; LVMI: Left ventricular mass index.

Table 5. Studies suggesting a key role of IGF-1 deficiency in the development of anemia

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention
Kurtz A., et al. (1985)	<i>In vitro</i> study	Fetal mouse liver cells	n= 21	Administration of FBS, rat or human serum and IGF-1 antiserum
Ureña P., et al. (1992)	Cross-sectional study	Hemodialysis patients with severe SHPT	n= 17	Measurement of serum EPO, IGF-1 and hematocrit values
Geffriaud-Ricouard C., et al (1993)	Cross-sectional study	Non-dialysis patients with CKD	n= 12	Analysis of serum IGF-1 levels and anemia parameters
Brox AG., et al. (1998)	Cross-sectional study	Renal transplant recipients with/out erythrocytosis	RT-E n=18 RT-nE n=23 Control n=15	Measurement of serum EPO, IGF-1, IGFBP1, and IGFBP3
Shih LY., et al. (1999)	Cross-sectional study	ESRD patients with erythrocytosis	n=8	Measurement of serum EPO, IGF-1 and hematocrit values
Małyszko J., et al. (2002)	Interventional study	Hemodialysis, CAPD and renal transplant patients	HD n= 79 CAPD n= 34 RT n= 46	rhEPO or no treatment
Xu S., et al. (2023)	Cross-sectional study	Hemodialysis patients	n=165	Measurement of serum IGF-1 and routine biochemistry

Abbreviations. FBS: Fetal bovine serum. SHPT: Secondary hyperparathyroidism; ESRD: End stage renal disease; rhEPO: Recombinant human erythropoietin; HD: Hemodialysis. CAPD: Continuous ambulatory peritoneal dialysis. RT: Renal transplant patients.

Table 6. Evidences for a role of IGF-1 in sarcopenia.

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention
Ding H., et al (1994)	Animal model	Male Sprague Dawley with ischemic acute renal failure	n=14 per group	rhIGF-1 (50µg/100g;s.c) three times daily
Ding H., et al. (1996)	Animal model	Male Sprague-Dawley	n= 10 to 35	5/6Nx and Sham rats
Wang H., et al. (2005)	Cross-sectional study	Hemodialysis patients and normal control participants	HD n= 51 Control n= 21	Skeletal muscle biopsy and IGF-1 expression analysis
Sun DF., et al. (2006)	Animal model	Male Sprague–Dawley rats	5/6Nx n= 14 Sham n= 11	5/6Nx and Sham rats and unilateral work overload of the plantaris muscle
Zhang L., et al. (2010)	<i>In vitro</i> and <i>in vivo</i> studies with animal models	Primary cultures of muscle cells and 5/6Nx mice (C57/BL6)	n= 3 to 5	Inducible IGF-1 receptor ablation in Estrogen Receptor-expressing cells
Delanaye P., et al (2019)	Observational multicenter prospective study	Hemodialysis patients	n= 204	Measurement of serum markers of muscle function an IGF-1

Abbreviations. WO: work overload; HD: Hemodialysis

Respuesta a revisores Manuscrito NEFRO-S-25-00010

Estimado Editor de la Revista NEFROLOGÍA,

En nombre de los coautores, me gustaría expresar nuestro sincero agradecimiento por todos los comentarios y recomendaciones constructivas sobre el manuscrito titulado “The multiple functions of Insulin-like Growth Factor 1 in kidney disease” (ID del manuscrito: NEFRO-S-25-00010). Agradecemos la ayuda y los consejos que nos han permitido mejorar nuestro manuscrito.

Más abajo, hemos proporcionado las respuestas a los comentarios del Revisores nº1, las cuales hemos desglosado para que su abordaje sea más claro. Además, hemos resaltado los cambios en el manuscrito en fuente roja.

Esperamos que esta nueva y mejorada versión de nuestro manuscrito revisado pueda ahora considerarse para su publicación en la revista NEFROLOGÍA. No obstante, estamos dispuestos por supuesto a revisarlo más a fondo de acuerdo con cualquier otra sugerencia o inquietud planteada por la Editorial y el Revisor.

Atentamente,

Juan Miguel Díaz-Tocados.

Autor de correspondencia.

Revisor nº1

Cuestión #1

Es una revisión muy interesante de un tema muy antiguo, como puede verse fácilmente al consultar la bibliografía. Está muy bien, no obstante, que se actualicen los conocimientos sobre temas que han sido y son objeto de investigación en nefrología. El manuscrito está bien escrito y se lee bien. No obstante, aporta muchísima información en campos muy diversos, por lo que su lectura abrumba a veces. Quizá un poco de trabajo de edición podría hacerlo más amable.

Respuesta #1

Agradecemos al Revisor nº1 que haya apreciado el valor de esta revisión enfocada a la descripción profunda del papel del factor de crecimiento similar a la insulina 1 (Insulin-like Growth Factor 1, IGF-1) en la fisiología renal y en la fisiopatología general que acompaña la enfermedad renal. Se trata de un tema que ha suscitado gran interés desde hace décadas y que, aunque su interés en el área de nefrología alcanzó un pico durante la década de los 90, actualmente sigue arrojando resultados con potencial traslación clínica. Por lo tanto, también consideramos que su revisión puede ayudar tanto a comprender su relevante papel en el campo de la nefrología como a estimular la realización de nuevos estudios en este sentido.

Igualmente, coincidimos con el Revisor nº1 en que la revisión contiene un gran volumen de información, que a la vez es muy diversa, lo cual podría conllevar al riesgo de dificultar su lectura y comprensión en esta versión inicial. Por lo tanto, coincidimos y apreciamos la sugerencia del Revisor nº1 de realizar una edición conveniente que ayude a una lectura más fluida y una más adecuada comprensión del tema.

Cuestión #2

Por ejemplo, podría ser dividido en dos partes, Efectos de IGF1 en la fisiología y la fisiopatología renal (esa parte ya se ha considerado) e Importancia de IGF1 en las complicaciones de la disfunción renal. En este último, se encuadrarían lo de la nutrición, lo de la sarcopenia, lo cardiovascular, etc.

Respuesta #2

Agradecemos al revisor por este constructivo comentario. En el artículo revisado hemos considerado las divisiones sugeridas y lo hemos resaltado.

On page 5, line 3, the next paragraph has been included:

“This review is structured into two main sections: the first one explores the effects of IGF-1 on renal physiology and pathophysiology and the second one highlights the key role of IGF-1 in systemic complications associated with renal dysfunction.”

Moreover, the article has been divided as suggested, and the second main section, starting in the page 12, line 9, now is entitled “Role of IGF-1 in renal dysfunction-associated complications”, comprising the subsections “IGF-1 and nutritional status”, “IGF-1 and CKD-MBD”, “IGF-1 and Cardiovascular Complications”, “IGF-1 and Erythropoiesis” and “Potential Actions of the IGF-1 in Skeletal Muscle Cells”.

Cuestión #3

La iconografía es muy escasa. La figura 1 está bien, pero la dos junta todo pero le falta detalle. No sé si la dejaría, porque más o menos los puntos claves vienen a decir lo mismo Pero poner tablas que resuman los diferentes epígrafes que se están tratando ayudaría mucho. Por ejemplo: Tabla X: mecanismos propuestos mediante los que el IGF1 puede condicionar la sarcopenia ó Tabla y: Estrategias terapéuticas en las que se ha utilizado IGF1 y sus resultados. Habría que pensarlo un poco: deben recoger información importante, sin ser enormes y conteniendo una cantidad suficiente de información racionalmente organizada. El lector podría sacar mucho provecho de esas tablas. Por lo demás, el artículo es adecuado para Nefrología

Respuesta #3

Coincidimos con el Revisor nº1 en que la iconografía no es suficiente. Como se sugiere hemos mantenido la Figura 1, y hemos considerado eliminar la Figura 2 para evitar redundancia. La nueva Figura 1 ahora muestra las interacciones de la vía IGF-1 en el riñón de manera más clara. La leyenda de la Figura 1 también ha sido revisada y adaptada.

In the page 18, line 30, the paragraph “Figure 2 summarizes the principal actions of IGF-1 on the complications associated with renal disease.” has been removed.

Hemos incluido 6 tablas, que resumen los principales puntos que se tratan en la revisión y se han citado adecuadamente en el texto principal. Las tablas incluidas al final del manuscrito están detalladas al final de este documento como se listan a continuación.

Tabla 1. Estudios en modelos animales sobre las acciones renales del IGF-1

Tabla 2. Estudios clínicos sobre los efectos del IGF-1 en la tasa de filtración glomerular y la supervivencia en pacientes con ERC

Tabla 3. Evidencia sobre la participación del IGF-1 en el metabolismo mineral y óseo

Tabla 4. Estudios que demuestran la participación del IGF-1 en enfermedades cardiovasculares

Table 5. Estudios que sugieren un papel clave de la deficiencia de IGF-1 en el desarrollo de la anemia

Tabla 6. Evidencias del papel del IGF-1 en la sarcopenia.

Particularmente, tras revisar los detalles en la Tabla 2. (*Estudios clínicos sobre los efectos del IGF-1 en la tasa de filtración glomerular y la supervivencia en pacientes con ERC*), hemos notado que los beneficios que se aprecian en los pacientes con ERC no se observan en los ensayos clínicos con un número de pacientes suficientemente elevado, probablemente debido a la heterogeneidad de la población estudiada. Es posible, que la mejora del filtrado glomerular observada en los estudios con un reducido número de pacientes se deba a las características de estos, por lo que podría haber un perfil concreto de pacientes renales en los que la administración de IGF-1 tenga un efecto significativo sobre el incremento del filtrado glomerular. Para remarcar esta observación, el siguiente párrafo se ha incluido en el texto principal:

On page 12, line 1. “Clinical trials investigating the renal effects of recombinant human IGF-1 are shown in Table 2. It is important to highlight that numerous studies in small groups of patients with kidney disease have demonstrated significant improvements in GFR following recombinant IGF-1 administration; however, these benefits are not observed in clinical studies with larger numbers of kidney patients. Since this discrepancy could be due, at least in part, to the heterogeneity of kidney patients in larger studies, there is a possibility that a particular profile of kidney patients may benefit from IGF-1 treatment.”

Comments to the Editor

- Hemos considerado pertinente la inclusión de dos estudios adicionales en la tabla correspondiente al apartado “*Potential Actions of the IGF-1 in Skeletal Muscle Cells*”, y un estudio en el apartado “*IGF-1 and CKD-MBD*”, los cuales podrían ser de relevancia. En este sentido, los siguientes párrafos refiriendo a estos estudios se han incluido en el texto principal.

On page 19, line 9, the next paragraph has been included:

“Studies in animal models of renal insufficiency have demonstrated that GH or work overload-induced upregulation of IGF-1 expression in the skeletal muscle is partially reduced in animals with renal insufficiency.¹³⁸ In the same way, a complementary study in patients undergoing hemodialysis has shown that IGF-1, IGF-2 and IGF-1 receptor gene expressions are reduced in skeletal muscle from hemodialysis patients as compare with normal control participant; however, at protein level, the amounts of IGF-1, IGF-2 and TNF- α in the skeletal muscle of hemodialysis patients were found elevated in

comparison to the control group,¹³⁹ which may suggest impaired IGF-1 signaling activation as observed in animal models of renal insufficiency,¹³⁷ considering the decreased muscle strength in the hemodialysis patient group. In Table 6 are presented principal studies showing evidences for a role of IGF-1 signaling in sarcopenia.”

In the section “*IGF-1 and CKD-MBD*”, we have included a paragraph referring a study that is also cited in the section “*Potential Actions of IGF-1 in Skeletal Muscle Cells*”, as we have noticed that the study also demonstrates an effect of IGF-1 in CKD-MBD.

On page 15, line 4, the following paragraph a cite has been added:

“In the same way, intensive treadmill exercise improves linear bone growth in a rat model of renal insufficiency (5/6Nx). This effect was associated with increased expression IGF-1 and VEGF in the primary ossification zone.¹⁰³”

- Hemos realizado una revisión del inglés en el texto principal. Las palabras que han sido corregidas se han resaltado en rojo.

Table 1. Studies in animal models on the renal actions of IGF-1

Study (year)	Animal model	Study design	Sample size	Type of intervention	Key findings
Hirschberg R., et al (1989)	Male Sprague-Dawley and Wistar rats	~3d fasting	n=6-8	rhIGF-1 (25µg/kg;i.v.)	- ↑ renal plasma flow, GFR and ↓ renal vascular resistance in IGF-1 treated animals - rhIGF-1 effects are mediated by eicosanoids
Hirschberg R., et al (1991)	Male Wistar rats	1) 12h fasting 2) ~3d fasting	n=6-8 per group	1) rhIGF-1 (75µg/kg;i.v) and continuous rhIGF-1 infusion (250µg/kg/h) 2) rhIGF-1 (25µg/kg/i.v) and continuous rhIGF-1 (75µg/kg/h)	- ↑ serum IGF-1 levels and GFR - ↑ single nephron GFR, renal blood and plasma flow rate - rhIGF-1 administration partially prevents fasting-induced single nephron GFR reduction.
Hirschberg R., et al (1992)	Male Wistar rats	N/A	n= 7 per group	Continuous infusion of rhIGF-1 (125µg/24h;s.c) or GH antagonist.	- rhIGF-1 infusion ↑ kidney/total body weight, GFR, glomerular volume, single nephron plasma flow and ↓ renal vascular resistance - treatment with GH antagonist ↓ GFR, but not kidney weight
Doi T., et al (1988); Doi T., et al (1990)	Transgenic mice over-expressing GH and IGF-1	N/A	n= 2-36	N/A	- Both GH and IGF-1 mice ↑ glomerular volume, with the latter having a lesser effect - GH mice had severe glomerulosclerosis - IGF-1 mice had no sclerotic lesions
Miller SB., et al (1990)	Male Sprague-Dawley rats	Normal renal mass and 5/6Nx	n= 3-8 per group	Continuous infusion of 200 µg/day of rhIGF-1 or rbGH or vehicle for 10 or 17 days	- rhIGF-1 or rbGH administration ↑ GFR in rats without reduction of renal mass - Treatment with rbGH nor rhIGF-1 do not modify inulin clearance in 5/6Nx rats
Miller SB., et al (1992)	Male Sprague-Dawley rats	Ischemic acute tubular necrosis	n= 7-9 per group	Continuous infusion of rhIGF-1 (100µg/day), rbGH, rhEGF or vehicle	- ↑ GFR and preserved renal function in rhIGF-1 treated rats - ↓ weight lost, renal injury and mortality
Rogers SA., et al (1993)	Male Sprague-Dawley rats	Uni-Nx and partial unilateral infarction	n= 4-8	Measure of IGF-1 in the tissue infarcted	- ↑ renal IGF-1 expression in the remnant kidney of Uni-Nx rats (peak at 3 days) - Partial unilateral infarction ↑ IGF-1 expression in the non-infarcted kidney

Ding H., et al (1994)	Male Sprague Dawley	Ischemic acute renal failure	n=14 per group	rhIGF-1 (50µg/100g;s.c) three times daily	- rhIGF-1 ↑ recovery of renal function at 3 days (GFR, renal plasma flow) - ↑ formation of new renal tubular cells
Haylor JL., et al. (JASN 2000)	Male Wistar rats	Uni-Nx and streptozotocin-induced diabetes		IGF-1 R inhibition (JB3, 10µg/kg/day) for 4 or 11 days	- JB3 prevents renal hypertrophy in Uni-Nx and diabetic rats.
Haylor JL., et al. (NDT 2000)	Male Wistar rats	Uni-Nx	n= 4-8 per group	IGF-1 neutralizing antibody	- ↓ renal hyperfiltration
Chevalier RL., et al (2000)	Sprague-Dawley neonatal rats	UUO	n= 21-24 per group	rhIGF-1 (2mg/kg/d; s.c.) for 3 or 7 days	- ↓ renal tubular atrophy, tubular cell apoptosis and interstitial fibrosis
Wu Z., et al. (2016)	C57BL/6 mice	UUO	n= 10 per group	rhIGF-1 (daily/i.p.; dose non-reported)	- Treatment with IGF-1 reduces renal fibrosis and apoptosis of renal epithelial cells (↑Bcl2)
Dong R., et al (2019)	Male C57BL/6J mice	Streptozotocin-induced diabetic kidney disease	n= 8-10 per group	IGF-1 R inhibition (GSK4529, 30 mg/kg/day; i.p.)	- IGF-1 R inhibition ↓ albuminuria, diabetes-induced kidney growth, glomerulomegaly, inflammatory infiltration and tubulointerstitial fibrosis

Abbreviations. rhIGF-1: Recombinant human IGF-1. Uni-Nx: Unilateral nephrectomy. GFR: glomerular filtration rate. GH: growth hormone; bGH: recombinant bovine growth hormone. EGF: epidermal growth factor. GH-rh: growth hormone-releasing hormone. UUO: Unilateral ureteral obstruction. IGF-1 R: IGF-1 receptor

Table 2. Clinical studies on the effects of IGF-1 on glomerular filtration rate and survival in CKD patients

Study (year)	Study design	Sample size	CKD stage of participants	Type of intervention	Key findings	Potential side effects
O'Shea MH., et al (1993)	Longitudinal study	n=4	Moderate chronic renal insufficiency (CrCl 25-60mL/min)	rhIGF-1 (100µg/kg; 12h; s.c.) for 4 d	- ↑ Circulating IGF1 - ↑ Inulin clearance - ↑ Kidney size	- Tachycardia
Miller SB., et al (1994)	Longitudinal study	n=9	CrCl less than 20 mL/min/1.73 m ²	rhIGF-1 (100µg/kg; 12h; s.c.) for 4 d (short-term) and for 13-27 d (long-term)	- ↑ GFR - ↓ Plasma creatinine and BUN levels - ↑ Inulin clearance during short-term administration	- Pericardial Rub - Nasal Congestion - Jaw pain
Fouque D., et al (1995)	Longitudinal study	n=18	Stage 5	rhIGF-1 (50 or 100 µg/kg; s.c.; twice)	Dose-dependent effects: - ↓ Plasma levels of insulin - ↓ serum C-peptide, amino acids and glucose levels - Partial resistance to IGF-1 in advanced CKD	Not reported
Hirschberg R., et al (1999)	Multicenter clinical trial, randomized, double-blind, placebo-controlled	n=72	Acute renal failure, CKD stage 5	rhIGF-1 (100 µg/12h; s.c.)	rhIGF-1 did not improve renal outcomes in patients with acute renal failure	Not reported
Vijayan A., et al (1999)	a) prospective open-labeled trial; b) randomized, double-blinded, placebo-controlled trial	a) n=5 b) n=10	End-stage renal disease	rhIGF-1 (50µg/kg; 24h; s.c.) for a) 24 d or b) 31 d	- ↑ GFR during the 3rd and 4 th week in both studies	- Peripheral edema - Local irritation at the site of drug injection
Frystyk J., et al (1999)	Cross-sectional case-control study	n=38	CrCl: 3-59 and 89 to 148 mL/min/1.73 m ²	Overnight fasting serum samples	- ↑ Production of IGFBPs - Low serum levels of IGF-1	Not reported
Hladunewich MA., et al (2003)	A randomized, placebo-controlled trial	n=47	Acute renal failure with GFR less than 20 mL/min	rhIGF-1 (100µg/kg; 12h; s.c.) for 6 d	Treatment failed to improve renal function compared to placebo	Not reported

Jia T., et al (2014)	Cohort study	n=365	CKD stage 5	Measurement of serum IGF-1 and other biochemical markers	- ↓ serum IGF-1 levels are associated with body composition and CKD-MBD parameters - serum IGF-1 levels predict increased mortality risk.	Not reported
Nilsson E., et al (2016)	Cohort study	n=265	CKD stage 5	Analysis of serum biochemistry and IGF-1 levels	- ↓ serum IGF-1 levels associate with increased mortality in HD patients	Not reported

Abbreviations. rhIGF-1: Recombinant human IGF-1. CrCl: Creatinine clearance. GFR: glomerular filtration rate. ESRD: End-stage renal disease. HD: Hemodialysis.

Table 3. Evidence on the involvement of IGF-1 in mineral and bone metabolism

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention	Key findings
Caverzasio J., et al. (1990)	Animal models	Hypophysectomized and tyroparathyroidectomized male Sprague Dawley rats	5 to 8 animals	rhIGF-1 continuous infusion (10 µg/h) for 6 days	- ↑ max. TRPi, 1,25-(OH) ₂ D ₃ and GFR - ↓ Urinary Na excretion
Coen G., et al. (1991)	Cross-sectional study	Non-dialysis CKD patients	n=28	Serum IGF-1 quantification	- Inverse association between serum IGF-1 and MAR
Nesbitt T., et al. (1993)	Animal models	C57BL/6J mice	Not reported	rhIGF-1 continuous infusion (0.1 to 10 µg/h) for 24h	- ↑ renal 1-α-hydroxylase
Condamine L., et al (1994)	<i>In vitro</i> study	Kidney cells	5 to 10 replicates	rhIGF-1 (25ng/ml)	- ↑ renal 1-α-hydroxylase
Ghiron LJ., et al. (1995)	Prospective interventional study	Healthy elderly women	n= 16	rhIGF-1 (15 or 50 µg/kg/12h; s.c) or GH for 28 days	- ↑ markers of bone turnover - ↑ urinary Ca excretion - ↓ urinary P excretion
Mak RH., et al. (1996)	<i>In vitro</i> study	Chondrocytes from 5/6Nx male Sprague-Dawley rats	n= 6	rhIGF-1 (1 to 100 ng/ml) for 3 days	- ↓ growth response to rhIGF-1 in chondrocytes from 5/6Nx rats
Johansson AG., et al (1996)	Randomized, crossover study	Idiopathic osteoporosis men	n= 12	rhIGF-1 (80µ/kg;s.c) for 1 week	- ↑ markers of bone turnover
Bianda T., et al. (1997)	Randomized, crossover study	Healthy young adults	n= 7	rhIGF-1 continuous infusion (8 µg/kg/h) for 2 weeks.	- ↑ markers of bone turnover - ↑ urinary Ca excretion - ↑ calcitriol (Free)
Bianda T., et al. (1998)	Randomized, crossover study	GH deficient adults	n= 8	Continuous infusion of rhIGF-1 (5 µg/kg/h)	- ↑ markers of bone turnover - ↑ 1,25-(OH) ₂ D ₃ - ↓ serum creatinine
Miyakoshi N., et al. (2001)	Animal models	IGF-1 deficient mice	n= 5 to 6	rhPTH (1-34) (160µ/kg;s.c) for 10 days	- Lack of IGF-1 blocks PTH osteoanabolic effects
Karava V., et al. (2021)	Cross-sectional study	CKD children and adolescent patients	n= 46 patients	Serum IGF-1 quantification	- Association between serum IGF-1 and lumbar BMD

Abbreviations: rhIGF-1: Recombinant human IGF-1. Max TRPi: maximal tubular reabsorption of phosphate; GFR: Glomerular filtration rate; BMD: bone mineral density. MAR: mineral apposition rate.

Table 4. Studies demonstrating an involvement of IGF-1 in cardiovascular diseases

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention	Key findings
Haylor J., et al. (1991)	Animal models	Male Wistar rats	n= 11 to 13	rhIGF-1 (50µg/kg;i.v)	- ↑ Renal blood flow - ↓ Blood pressure and renal vascular resistance
Wåhlander H., et al. (1992)	Animal models	Male Wistar rats	n= 10	Renal artery occlusion-induced hypertension	- ↑ Left ventricular IGF-1 expression after renal artery occlusion, in association with LVH.
Schini VB., et al. (1994)	<i>In vitro</i> study	Rat vascular smooth muscle cells		rhIGF-1 (1 - 100 ng/ml)	- ↓ IL1β and TNF-induced production of nitrate and citrulline formation
Tsukahara H., et al. (1994)	<i>In vitro</i> study	Endothelial cells	n= 4 to 14	rhIGF-1 (1 - 20 ng/ml)	- ↑ Nitric oxide production
Guron G., et al. (1996)	Animal models	Male Wistar rats	n= 5 to 8	Renal artery occlusion-induced hypertension	- ↑ IGF-1 expression in the left ventricle of hypertensive rats with LVH in comparison with Sham.
Huang CY., et al. (2003)	Animal models	Male Sprague-Dawley rats	n= 4	Abdominal aorta occlusion- induced hypertension	- ↑ IGF-1 expression in the left ventricle of hypertensive rats precedes LVH
Prelevic V., et al. (2020)	Multicentric cohort study	Hemodialysis patients	n= 102	Measurement of serum IGF-1	- Serum IGF-1 levels associate directly with left-ventricular EF and inversely with LVMI
Nakaya R., et al. (2022)	Cross-sectional cohort study	Hemodialysis patients	n= 506	Measurement of serum IGF-1	- Low serum IGF-1 levels are associated with all-cause and CVD mortality. - No association among serum IGF-1 and new CVD events or hospitalization

Abbreviations. rhIGF-1: Recombinant human IGF-1. IL1β: Interleukin-1β; TNF: Tumor necrosis factor; LVH: Left ventricular hypertrophy; EF: ejection fraction; LVMI: Left ventricular mass index.

Table 5. Studies suggesting a key role of IGF-1 deficiency in the development of anemia

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention	Key findings
Kurtz A., et al. (1985)	<i>In vitro</i> study	Fetal mouse liver cells	n= 21	Administration of FBS, rat or human serum and IGF-1 antiserum	- ↑ erythroid colonies formation in cells treated with IGF-1-containing serum
Ureña P., et al. (1992)	Cross-sectional study	Hemodialysis patients with severe SHPT	n= 17	Measurement of serum EPO, IGF-1 and hematocrit values	- Positive association between Serum IGF-1 levels and hematocrit
Geffriaud-Ricouard C., et al (1993)	Cross-sectional study	Non-dialysis patients with CKD	n= 12	Analysis of serum IGF-1 levels and anemia parameters	- Inverse association between serum IGF-1 and hematocrit
Brox AG., et al. (1998)	Cross-sectional study	Renal transplant recipients with/out erythrocytosis	RT-E n=18 RT-nE n=23 Control n=15	Measurement of serum EPO, IGF-1, IGFBP1, and IGFBP3	- ↑ IGFBP1 and IGFBP3 levels in CKD patients with erythrocytosis
Shih LY., et al. (1999)	Cross-sectional study	ESRD patients with erythrocytosis	n=8	Measurement of serum EPO, IGF-1 and hematocrit values	- No correlation between serum EPO and hematocrit - ↑ IGF-1 and ↓EPO serum in ESRD patients with erythrocytosis - ↑ <i>in vitro</i> erythropoietic effects of serum from ESRD patients with erythrocytosis.
Małyszko J., et al. (2002)	Interventional study	Hemodialysis, CAPD and renal transplant patients	HD n= 79 CAPD n= 34 RT n= 46	rhEPO or no treatment	- ↑ serum IGF-1 and IGFBP3 levels in rhEPO-treated patients - Association of serum IGF-1 and IGFBP3 with serum Crosslaps
Xu S., et al. (2023)	Cross-sectional study	Hemodialysis patients	n=165	Measurement of serum IGF-1 and routine biochemistry	- ↓ Serum IGF-1 levels are associated with anemia

Abbreviations. FBS: Fetal bovine serum. SHPT: Secondary hyperparathyroidism; ESRD: End stage renal disease; rhEPO: Recombinant human erythropoietin; HD: Hemodialysis. CAPD: Continuous ambulatory peritoneal dialysis. RT: Renal transplant patients.

Table 6. Evidences for a role of IGF-1 in sarcopenia.

Study (year)	Study design	Characteristics of participants	Sample size	Type of intervention	Key findings
Ding H., et al (1994)	Animal model	Male Sprague Dawley with ischemic acute renal failure	n=14 per group	rhIGF-1 (50µg/100g;s.c) three times daily	- ↑ synthesis and ↓ degradation of skeletal muscle protein
Ding H., et al. (1996)	Animal model	Male Sprague-Dawley	n= 10 to 35	5/6Nx and Sham rats	- ↓ serum and skeletal muscle IGF-1 levels in rats with renal insufficiency. - ↑ IGF-1 receptor expression in skeletal muscle, but impaired IGF-1 signaling in rats with renal failure.
Wang H., et al. (2005)	Cross-sectional study	Hemodialysis patients and normal control participants	HD n= 51 Control n= 21	Skeletal muscle biopsy and IGF-1 expression analysis	- ↓ IGF-1, IGF-2 and IGF-1 Receptor mRNA expression in skeletal muscle of HD patients vs controls. - ↑ serum levels of IGF-2 and TNF-α in HD patients vs control.
Sun DF., et al. (2006)	Animal model	Male Sprague–Dawley rats	5/6Nx n= 14 Sham n= 11	5/6Nx and Sham rats and unilateral work overload of the plantaris muscle	- ↑ skeletal muscle IGF-1 production in rats subjected to WO. - ↓ skeletal muscle IGF-1 production in response to WO in CKD rats.
Zhang L., et al. (2010)	<i>In vitro</i> and <i>in vivo</i> studies with animal models	Primary cultures of muscle cells and 5/6Nx mice (C57/BL6)	n= 3 to 5	Inducible IGF-1 receptor ablation in Estrogen Receptor-expressing cells	- IGF-1 increases myogenesis, while inhibition of the IGF-1 signaling impairs satellite cell function.
Delanaye P., et al (2019)	Observational multicenter prospective study	Hemodialysis patients	n= 204	Measurement of serum markers of muscle function and IGF-1	- Serum IGF-1 levels associate with muscle strength and muscle mass.

Abbreviations. WO: work overload; HD: Hemodialysis