

GROWTH HORMONE THERAPY IN CHRONIC KIDNEY DISEASE

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INTRODUCTION

In the last few years, there has been a shift in emphasis on the medical management of children with chronic kidney disease (CKD) from strategic attempts to preserve renal survival to optimizing global biological potential, and thereby maximizing quality of life. Early diagnosis and prompt treatment have become the cornerstones of modern care. Thus, in addition to measures like anemia

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From The Editor's Desk

This issue contains 9 printed and 8 e-abstracts of important papers in the field with editorial comments. Thus, we have doubled the content of *GGH* with the introduction of e-abstracts. This feature also allowed the publication of longer abstracts, data, and comments. Please take advantage of this added feature. I welcome your comments regarding the on-line and print aspects of the journal. Your feedback is important as we continue to grow and strive to serve your needs. The lead article by Drs. Bamgbola and Kaskel on Growth Hormone Therapy in Chronic Kidney Disease is a very comprehensive review of the pathophysiology of the disease as it pertains to growth hormone. It includes provocative ideas about possible future direction for treatment with growth hormone and insulin-like growth factor. I am sure you will enjoy it and save it as a reference source.

The expanded journal and all of its content is carefully prepared by the editorial board and all the lead articles are reviewed to comply with the high scientific standards of a peer review journal. *GGH* is also in compliance with the code of conduct for medical publishers on the internet (Health on the Net Foundation www.hon.ch).

Respectfully,
Fima Lifshitz, MD

control and improved nutritional intake, there is increasing use of recombinant human growth hormone (rhGH).

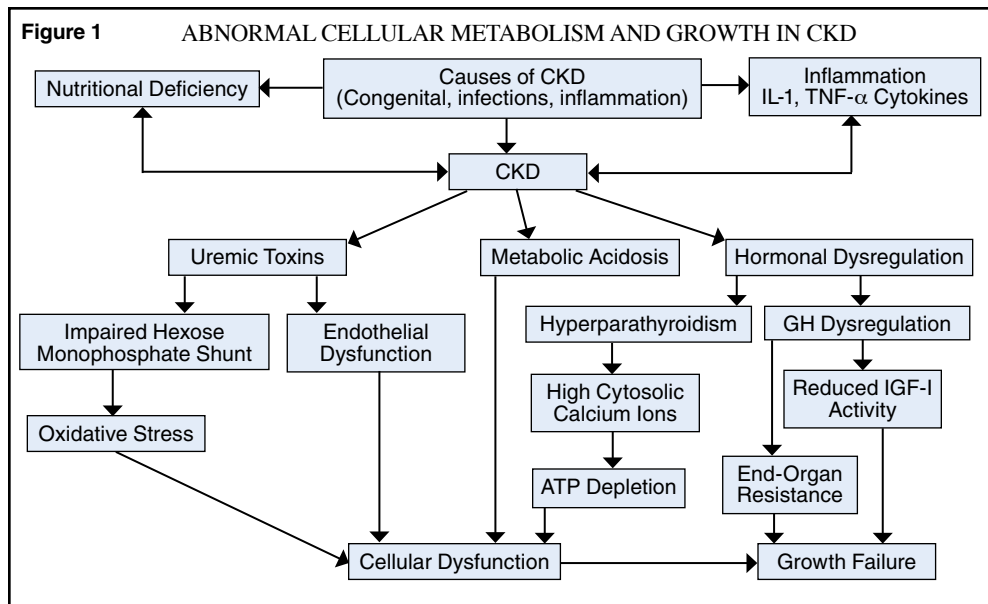
Although the FDA-approved indication for use of rhGH in CKD is growth failure, there are other clinically significant metabolic effects of the hormone. In this review, we shall highlight the potential benefits of rhGH therapy in CKD, including its positive impact on cellular growth and metabolism, immune regulation, and energy homeostasis. The roles of rhGH in modulation of psychosocial function, sleep physiology, and bone metabolism in children with CKD will also be discussed.

GROWTH FAILURE

More than 50% of adults with childhood-onset CKD attain final heights that are below the third percentile.¹ The burden of growth retardation in patients with renal disease is enormous, resulting not only in physical handicaps but also the potential for psychological and social distress.

CKD, whether caused by congenital anomalies, chronic infection, immune disorders, or connective tissue diseases, may be associated with nutritional deficiency and

growth retardation (Figure 1). Conversely, consequences of renal disease such as metabolic acidosis, endocrinopathy, chronic anemia, persistent micro-inflammation, recurrent infection, and cardiac dysfunction may also result in growth failure. Inadequate dietary intake (often less than 80% of RDA) and defective protein metabolism are common features of CKD. However, increased food intake does not necessarily translate into a healthy nutritional outcome, and it often leads to greater adiposity rather than musculo-skeletal growth.



Furthermore, metabolic acidosis, which is a common outcome of CKD, accelerates protein degradation by activation of the ubiquitin-proteasome pathway, stimulation of branched-chain keto-acid-dehydrogenase, and promotion of end-organ resistance to anabolic effects of GH.² In addition, steroid therapy, often used as an anti-inflammatory agent in some kidney diseases, or for immune suppression following renal transplantation, may not only impair GH release but also increase end-organ resistance. In this regard, there is a positive correlation between the cumulative dose of steroids and adult-height deficit in pediatric allograft recipients. Treatment with steroids may inhibit GH synthesis by stimulation of (hypothalamic) somatostatin production. Consequently, by acting on multiple receptor-sites of the pituitary gland, GH-releasing peptide-2 (a GH secretagogue) has the therapeutic potential of bypassing the inhibitory effect of somatostatin.³ Similarly, the use of rhGH alone or in combination with insulin-like growth factor (IGF)-I promotes musculo-skeletal growth, essentially by attenuating the inhibitory effect of steroids on protein synthesis.⁴

Whereas somatic growth at an early age is predominantly determined by factors such as birth size and adequate nutritional status, functional availability of GH is essential during childhood, and gonadotropin is a necessary adjunct for post-pubertal maturation.¹ Consequently, provisions of an optimal metabolic and nutritional milieu are often sufficient for growth in children with CKD who are less than 2 years of age, while use of rhGH is commonly required in older children.

GH/IGF AXIS

Although the pulsatile release of GH is blunted in uremia, the total amount of GH secretion from the pituitary gland is often increased.⁵ IGF-I and -II are derived from both hepatic cells and local tissues (of target organs) in response to a

primary activation of the GH receptor (GHR).^{6,7} Despite the higher plasma level of circulating GH,⁸ there is less synthesis of IGF-I due to end-organ resistance.⁹

Factors that contribute to GH tissue resistance in CKD include hyperparathyroidism, metabolic acidosis, and pro-inflammatory cytokines.⁹⁻¹² The mechanism of the end-organ resistance is inhibition of calcium-mediated intracellular signaling and impaired transcription of GHR-mRNA. Thus, GH activation of growth plates in uremic animals results in reduced local synthesis of IGF-I, impaired chondrocyte replication, and therefore retarded skeletal growth.¹³

The physiologic functions of GH are mediated by 2 different but complementary mechanisms: GH directly activates target organs while its indirect effects are mediated through IGF-I.⁷ While GH increases the hepatic production rate of glucose and glycerol (an index of lipolysis), IGF-I acts in concert with insulin to increase peripheral glucose uptake and to reduce protein breakdown.¹⁴

IGF-I is a small, single-chain peptide belonging to the same family of genes as IGF-II and pro-insulin,¹⁵ and its free bioactive form accounts for 1% of total plasma concentration.^{7,16} IGF-I has a very short half-life (20 minutes), rapidly losing its metabolic function in the absence of a carrier binding-protein (IGFBP).^{6,7} The most abundant of the 6 IGF-binding proteins (IGFBP-1 to -6) is IGFBP-3; it binds to circulating IGF-I and acid labile-sub-unit (ALS) as a 150 kDa ternary complex, thereby protecting it from premature degradation.^{7,16}

IGF-I receptors are heterotetramers comprised of 2 alpha and 2 beta sub-units attached by disulfide bridges. IGF-I ligand binds to the extracellular alpha sub-unit which in turn induces the transmembrane beta unit,

resulting in an autoactivation of tyrosine kinase and phosphorylation of an intracellular tyrosine residue.¹⁵ Interaction between insulin receptor substrates (IRS-1 and -2) and the receptor-tyrosine residue evokes a signal transduction thereby activating the downstream MAP-3 kinase (and protein kinase-B) pathways.¹⁵ The 2 pathways mediate protein synthesis, cellular growth, cell motility, and inhibition of apoptosis.

IGFBP-3, by sharing a similar molecular structure, competitively inhibits IGF-I receptors.¹⁵ However, the receptor molecules have stronger affinity for the IGF-I ligand. Consequently, there is a regulated but slow release of the plasma IGF-I from its carrier proteins at the designated target tissue. In uremic plasma, IGFBP-3 peptides are more rapidly degraded into smaller fragments. The smaller molecules of IGFBP-3 have less avidity for IGF-I and are often poorly excreted by the diseased kidneys. The reduced renal clearance of the relatively inefficient IGFBP-3 fragments and retention of inhibitory binding proteins, including IGFBP-1, -2, -4, and -6, substantially reduce the bioavailability of IGF-I.^{16,17}

Future Directions for GH/IGF-I Treatment

Despite end-organ resistance to GH in uremia, exogenous administration of rhGH accelerates skeletal growth by increasing the molar ratio of IGF-I to IGFBP-3. However, CKD patients often require dose levels of rhGH 2 to 3 times higher than doses administered to GH-deficient subjects.⁷ In addition, combined therapy with rhGH and rhIGF-I results in a greater than additive effect, or synergistic interaction, in CKD patients.⁶

Given the prevalent organ resistance to GH in CKD, therapeutic approaches that increase functional availability of IGF-I may be more effective than the simple administration of rhGH as is currently practiced.^{6,7} These measures may include the use of exogenous IGFBP-3 to replace the inhibitory smaller fragments and IGF-I analogs to displace endogenous IGF-I from its binding proteins.^{6,7} While the binding protein may prolong the half-life of IGF-I, IGF-I analogs may increase the effective concentration of the bioactive free IGF-I. Therapeutic administration of combined IGF-I and IGFBP-3 complexes have been successfully used to enhance positive nitrogen balance in burn patients.⁶

Furthermore, synthetic GH-releasing peptide (GHRP) and its endogenous equivalent, ghrelin, may be available for oral administration in the near future.⁷ These GH secretagogues are more potent than the conventional GH releasing hormone (GHRH) in stimulating a pulsatile release of GH. They act on specific receptors of the anterior pituitary gland, thereby restoring its normal physiologic characteristics. These include capacity for feedback regulation and a greater than 6-fold increase in IGF-I synthesis.⁶ This therapeutic approach has been introduced into clinical practice with the combined use

of GHRP and thyroid-releasing hormone to reactivate pulsatile pituitary secretion of GH and thyroid-stimulating hormone, thereby preventing protein catabolism and muscle wasting in protracted critical illness.¹⁸

Delayed Puberty, Hypogonadism, and rhGH

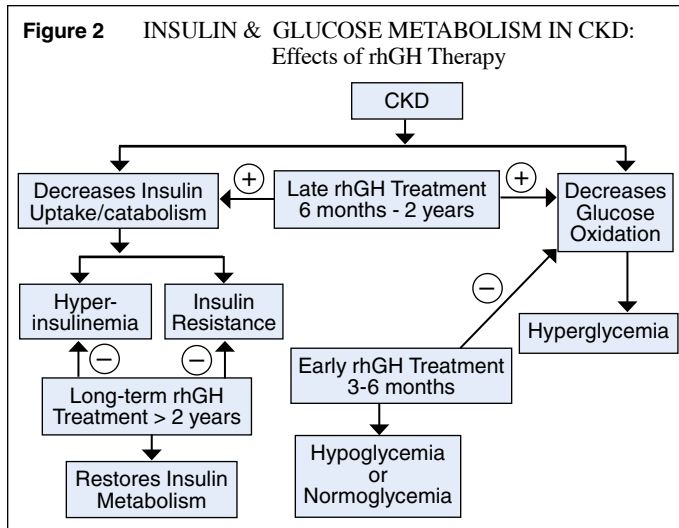
There is a complex interaction among GH, IGF-I, and sex steroids in maximizing growth potential and body composition and in promoting sexual and reproductive capacities in human subjects.¹⁹ Although the mechanism is unknown, the increase in pituitary GH synthesis during mid-puberty in boys is preceded by an increase in plasma testosterone. Similarly, the GH/IGF-I axis is activated by small increases in plasma estrogen in girls at the onset of puberty. GH and IGF-I influence reproductive function directly by modulation of gametogenesis and indirectly by enhancing steroidogenesis. Achievement of critical body weight is associated with pubertal onset, suggesting that somatic effects of rhGH treatment may play a role in the attainment of spontaneous puberty.^{20,21}

The common findings of hypogonadism and delayed puberty in CKD are characterized by a loss of the normal pulsatile hypothalamic release of gonadotropin-releasing hormone (GnRH).²² Puberty may be delayed for up to 2 years, while peak height velocity is often less than 50% of normal in CKD patients. There is a low expression of GHR in a GHR gene knockout-mouse model, similar to the findings in human CKD subjects. These mice have delayed maturation of seminal vesicles, spermatids, and testes, with a poor testicular response to leutinizing hormone, supporting a role for rhGH in induction of pubertal maturation.²³ The use of rhGH/IGF-I administered with GnRH analog (experimental hypogonadism) in men has been shown to preserve protein synthesis and lipid oxidation compared with controls, indicating an independent effect of the combined regimen in the maintenance of fat-free mass.²⁴ Similarly, combined therapy with rhGH and testosterone synergistically promotes muscle IGF-I gene expression, whole body protein anabolism, bone turnover, physical performance, and sexual function.^{25,26}

METABOLIC CHANGES AND rhGH THERAPY

Insulin and Glucose Metabolism

Insulin and glucose metabolism in CKD (Figure 2) is characterized by reduced activity of glycolytic enzymes with a consequent decrease in glycolysis, glycogen synthesis, and storage. In uremic rats, there is 25% to 45% reduction in hepatic gluconeogenesis and glucose formation rate from fructose and pyruvates.⁹ Similarly, due to a defective intracellular (post-receptor) signaling there is impairment of hepatic insulin metabolism in uremic rats. In addition, although pancreatic insulin secretion is reduced, its renal degradation is substantially compromised in CKD. The resultant hyperinsulinemia stimulates plasminogen activator inhibitor,



reduces fibrinolysis and, therefore, promotes vascular thrombus formation.

rhGH Therapy and Glucose Metabolism

In the early phase of rhGH therapy, insulin-like effects (including hypoglycemia and protein synthesis) predominate and serve to overcome the uremic-induced insulin resistance (Figure 2). This effect is due to a cross-affinity of IGF-I with insulin receptors leading to an increased glucose uptake and cellular oxidation.²⁷ On the other hand, with long-term rhGH administration, there is impairment of insulin-mediated glucose uptake, increased lipid oxidation, and formation of insulin-resistant (glycolytic type II) muscle fibers.²⁸ Consequently, hyperglycemia ensues with an increase in glycosylated hemoglobin. In general, restoration of normal glucose tolerance has been shown to occur within 2 years of starting rhGH therapy.^{29,30} These paradoxical effects of rhGH may result from functional and structural diversities of its fragments. For example, GH fragment 1-15 is endowed with insulin-like effects, whereas GH fragment 177-191 possesses anti-insulin properties, and the 20K-GH variant promotes cellular growth.³¹

Protein Metabolism in CKD

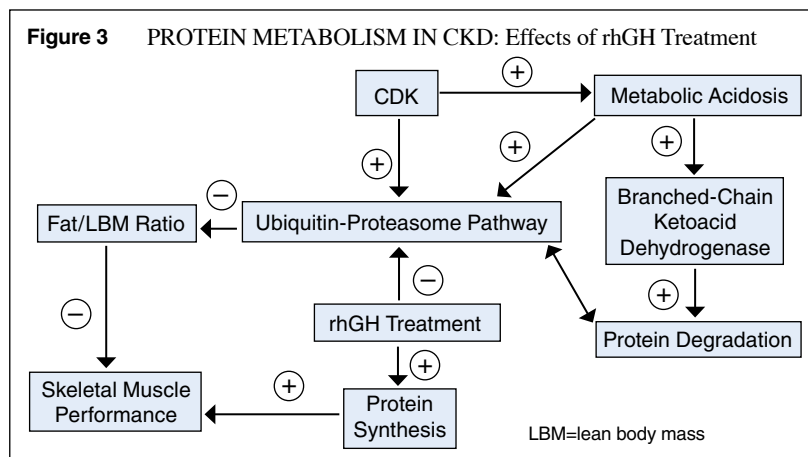
Although hepatic synthesis of total serum protein is often preserved in CKD subjects, production of specific proteins such as IGF-I and apolipoprotein A1 are commonly reduced.⁹ Similarly, there is a 30% to 40% reduction in enzymatic activity of the urea cycle, with a down-regulation of ureagenesis and accumulation of nitrogenous substances, including middle molecule toxins (poorly dialyzed, larger-sized uremic molecules) such as advanced glycation end products, and β 2-microglobulin.⁹

As previously stated, metabolic acidosis and uremic-induced inflammation cause protein degradation by activation of ubiquitin-proteasome pathway, induction of

branched-chain ketoacid dehydrogenase, and promotion of end-organ resistance to insulin and GH/IGF-I (Figure 3). The physiologic impact of activated uncoupling proteins (UCP polymorphism) on mitochondrial oxidative phosphorylation is substantial and may account for up to 20% of basal energy expenditure.³² Tumor-necrosis factor (TNF)- α cytokine, often elevated in CKD, promotes negative nitrogen balance by up-regulating UCP-2 and -3 genes in skeletal muscles of experimental rats.³³

rhGH Therapy on Protein Metabolism

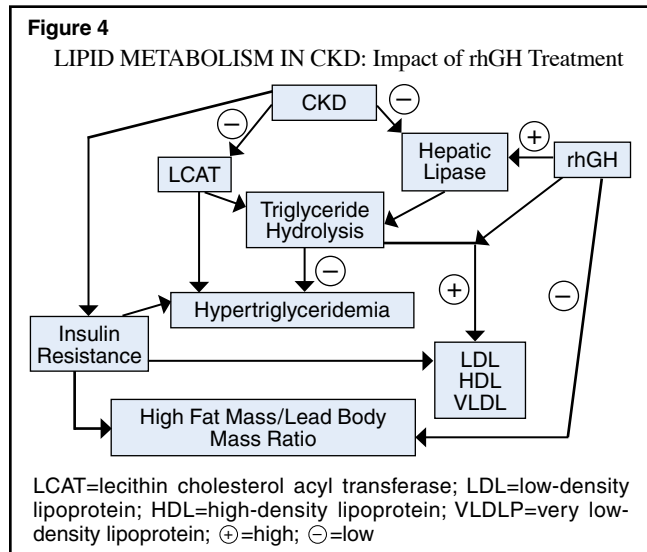
Treatment with rhGH increases protein synthesis, not only by stimulating uptake of amino acid, but also by promoting intracellular peptide assembly.³⁴ Protein degradation is prevented by inhibition of lysosomal and ATP-ubiquitin-proteasome pathways. Thus, the net effect of rhGH therapy in CKD is an efficient use of dietary branched-chain amino acids with improved skeletal muscle performance.^{35,36} Consequently, administration of rhGH therapy after long-term mechanical ventilation has been shown to result in improved respiratory muscular strength, reduction in ventilator settings, and successful extubation in post-surgical patients.³⁷ Similarly, combined use of GH/IGF-I as an adjunct to total parenteral nutrition results in a net positive protein balance in critically ill patients.³⁸ On the other hand, in a multi-institutional, randomized, controlled trial of critically ill adults, the use of high dose rhGH resulted in longer length of hospitalization and a higher mortality rate.³⁹



Lipid Metabolism in CKD

CKD subjects exhibit a reduction of lecithin-cholesterol acyl transferase (LCAT) enzyme, down-regulation of apo-A1 genes, and inhibition of hepatic lipase activity.⁹ (Figure 4) Consequently, there is impaired hydrolysis of triglycerides (TG) in high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL), resulting in hypertriglyceridemia. Plasma low-density lipoprotein (LDL) has been shown to be elevated due to a down-regulation of its receptor function.⁹ In addition, insulin resistance may promote dyslipidemia and pro-coagulant activity in CKD.⁴⁰ The pattern of lipid profiles in CKD patients are strikingly similar to findings

in metabolic syndrome. Both clinical syndromes share other characteristics such as hypertension, altered body composition, low-grade persistent inflammation, and hyperinsulinemia with a common outcome of premature cardiovascular (CV) disease.⁴¹



rhGH Therapy and Lipid Metabolism

In general, rhGH therapy improves lipid profiles by decreasing LDL and apo-B while increasing HDL.⁴⁰ By induction of lipoprotein lipase and stimulation of LDL receptor, rhGH attenuates the characteristic increase in VLDL-TG in CKD.⁴⁰ In addition, rhGH reduces visceral adiposity, increases lean body mass, and restores normal body composition in CKD.⁴² However, it is yet to be seen if these favorable metabolic and biological changes will translate into a better long-term CV outcome in CKD. On the other hand, GH therapy may increase lipoprotein (a), an independent CV disease risk factor.⁴⁰ While it shares a common lipid fraction with LDL, lipoprotein (a) clearance is not influenced by the GH-induction of LDL-receptor activity.⁴⁰ Nevertheless, the clinical significance of the modest yet notable increase in lipoprotein (a) during rhGH treatment on CV health is not known.

FOOD INTAKE AND ENERGY HOMEOSTASIS

Uremia promotes excessive transport of tryptophan across the blood-brain barrier and consequently increases neuronal synthesis of serotonin, an endogenous anorectic compound.⁴³ Adequate food intake may be further compromised in uremic patients by an accumulation of cholecystokinin, TNF- α , interleukin (IL)-1, leptin, and middle molecule toxins (eg, beta (2)-microglobulin, advanced glycation end products).

Ghrelin and rhGH in CKD

Ghrelin, an endogenous ligand for GH secretagogue-receptor, is principally secreted by pancreatic alpha-like cells (designated Gr cells) from the stomach fundus, in

response to changes in nutritional status.⁴⁴ In addition to a potent pituitary stimulation for GH secretion, ghrelin increases food intake by activating agouti-related peptides and neuropeptide Y within the hypothalamus.⁴⁵ Experimental use of ghrelin in human subjects was shown to increase food intake, energy consumption, and visual analog scores for appetite.⁴⁶ Although the physiological consequence is unknown, there is often accumulation of biologically active (acylated polypeptide) and inactive (desacyl) ghrelin in CKD subjects because of impaired renal clearance. It may be speculated that ghrelin retention constitutes an adaptive mechanism to promote caloric intake in chronic uremia. Perhaps ghrelin's failure to correct the calorie deficiency state arises from the prevailing end-organ resistance to its orexigenic (appetite-stimulating) effects. Similarly, its role in promoting appetite may be physiologically counteracted by the anorexic forces from excessive accumulation of leptin, serotonin, and cytokines in CKD. It has yet to be determined whether the use of ghrelin as an adjunct to rhGH might be beneficial in overcoming anorexia in chronic uremia.⁴⁵

It has been suggested that there may be a negative feedback control of ghrelin by the GH/IGF-I axis. Thus, a short-term rhGH induction of IGF-I causes a proportionate reduction in ghrelin with no alteration in plasma adiponectin.⁴⁷ On the other hand, a reduction in body fat mass from long-term use of rhGH may contribute to an increase in circulating levels of ghrelin and adiponectin.⁴⁷ The confounding effect of impaired filtration and/or catabolism of ghrelin in renal failure on the purported ghrelin-GH/IGF-I feedback axis is not known.

Leptin and rhGH in CKD

Hyperleptinemia is a common finding in renal failure, and may result from decreased renal clearance, increased secretion from adipose tissue, and hyperinsulinemia. Leptin is a potent endogenous anorexic agent; its effect may be modulated by rhGH therapy. Thus, administration of rhGH in the Zucker obese rat (which is characterized by leptin and insulin resistance) induces lipolysis and down-regulates leptin gene expression in visceral fat mass.⁴⁸ However, as previously stated, the appetite-promoting effect of rhGH may be overcome by persistent hyperleptinemia in CKD subjects. Recent discovery of leptin receptor isoforms in multiple organs suggests that leptin is an important mediator of other unknown biological functions.⁴⁹ Therefore, further studies are required in defining the roles of leptin in the modulation of metabolic and nutritional derangements in uremic syndrome.

SLEEP DEFECTS AND rhGH

About 50% to 70% of adults with end-stage kidney disease suffer from sleep apnea, insomnia, daytime somnolence, and restless leg syndrome.⁵⁰ In CKD the

high prevalence of sleep disorders may be confounded by co-morbidities of obesity and depression. However, there is often a strong positive correlation between blood urea nitrogen and indices of sleep dysfunction in patients with kidney failure.⁵⁰ Potential complications of sleep defects in uremia may include resistant hypertension, autonomic dysfunctions, and left ventricular hypertrophy.⁵¹ Corroborating the role of uremic burden in sleep dysfunction is the remarkable improvement in symptoms with the administration of daily nocturnal hemodialysis. To date, there are no studies in humans on the therapeutic role of rhGH on sleep defects in CKD, although rapid eye movement (REM) sleep is restored by rhGH, and non-REM sleep is modulated by GHRH in GH-deficient (transgenic) animal models.⁵² Similarly, use of ghrelin, a GH secretagogue, results in a preponderance of the more physiological pattern of slow and delta waves that occur during sleep.

Although there are case reports of sudden deaths from obstructive sleep apnea attributed to the use of rhGH in patients with Prader-Willi syndrome, scientific analysis has failed to confirm these assumptions.⁵³⁻⁵⁵ On the contrary, there is potential for beneficial effects on respiratory physiology because of the favorable effects of rhGH on inspiratory drives, ventilatory muscle functions, respiratory quotients and resting energy expenditure.⁵⁶⁻⁵⁸

IMMUNE FUNCTION

CKD is characterized by a persistent micro-inflammatory state with increased circulating levels of IL-1, IL-6, and TNF- α cytokines. Negative nitrogen balance may result from the reduced hepatic syntheses of albumin and apolipoprotein; however, increased release of fibrinogen and amyloid precursors by the liver may enhance vascular thrombogenicity.⁹

Immune deficiency in CKD results from a direct inhibition of uremic toxins and/or altered metabolic activities of immunological cells, including neutrophils, lymphocytes, and macrophages. One subset of T-helper cells, Th-1, is the effector of cell-mediated immunity and recruits new Th-1 cells by producing interferon-gamma while inhibiting Th-2 induced cellular differentiation.⁵⁹ The other subset of T-helper cells, Th-2, secretes inhibitory IL-4 and IL-10 cytokines and consequently attenuates the self-perpetuation of Th-1 cells. Uremia shifts the delicate regulatory balance between Th-1 and Th-2 cellular pathways in favor of the latter, thereby causing a depression of cell-mediated immunity.⁵⁹ In addition, the impaired expression of B7-2 (co-stimulatory) molecules on the surface of antigen-presenting cells may weaken activation of effector T cells.⁶⁰

The capacity for B-cell antibody production and superoxide generation by polymorphonuclear leukocytes

are also reduced in a uremic milieu.⁹ The defect may be due to elevated cytosolic Ca²⁺ resulting in poor ATP generation (impaired mitochondrial oxidative phosphorylation) and may be reversed by calcium-channel blockers.⁹ Increase in neutrophil apoptosis is in part mediated by the Fas-Fas-L pathway in CKD; there is a positive correlation between Fas-mediated apoptosis and creatinine clearance in plasma obtained from uremic subjects.⁶¹

rhGH Impact on Immune Dysfunction

GH stimulates T-cell cytotoxicity and releases superoxide anion from inflammatory cells. CD4 and NK-cell activities were shown to be restored in GH-deficient adults treated with rhGH, while phagocytic function was normalized.⁶² In addition, rhGH was shown to prevent apoptosis of immunologic cells by inactivating the pro-apoptotic Fas-FADD pathway and increasing the anti-apoptotic expression of Bcl-2. The overall physiological impact was a down-regulation of Caspase 3, an intracellular effector of apoptosis.⁶³

GH is a member of the cytokine super-family and has a similar structure to granulocyte colony-stimulating factor.⁶⁴ GHRs, which bind to GH, are found on a number of immunological cell surfaces. Use of rhGH in severe sepsis may exacerbate the ongoing inflammatory process by cross-activation with other cytokine-receptors and, thereby result in a higher fatality rate.⁶⁵ In a rat model of bacterial sepsis, increased expression of suppressors of cytokine signaling (SOCS)-1 and -3 inhibited intracellular signaling of GHR, resulting in a poor generation of IGF-I.⁶⁶ Thus, a relative IGF-I deficiency may contribute to the impairment of glomerular filtration rate that may result from septicemia. Although in normal circumstances IGF-I increases renal perfusion, its administration in a rat model of ischemic renal failure results in higher mortality, apparently by evoking adverse inflammatory processes.⁶⁷

The pro-inflammatory activity of rhGH was initially postulated to be a potential cause of allograft rejection. However, clinical evidence suggests otherwise, and the safety and efficacy of rhGH was recently demonstrated in renal transplantation.⁶⁸ In pediatric renal allograft recipients, rhGH has also been shown to prevent steroid-induced protein catabolism, maintain skeletal mass, and improve linear growth rate. In addition, postoperative administration of rhGH in rats with small bowel transplant restores morphology of allograft mucosa and promotes a net positive nitrogen balance.⁶⁹ Furthermore, the perioperative use of rhGH in immunocompromised rats enhances surgical wound healing.⁷⁰ Given that post-transplant use of the immunosuppressant sirolimus may cause a delay in wound healing because of its antifibrotic property, a study of the role of rhGH in this regard may provide useful information.

BONE MINERAL CONTENT AND rhGH

Within a few weeks of initiation of rhGH therapy, the molecule interacts with the bone-forming unit by increasing the biochemical markers of bone formation and resorption. In general, short-term (3–6 months) rhGH therapy may reduce or maintain bone mineral density, while treatment of GH-deficient adults for 2 years results in a sustained increase in mineralization.⁷¹ On the other hand, the common use of high-dose calcium and calcitriol in CKD subjects for the treatment of hyperphosphatemia may result in suboptimal skeletal response to rhGH. Calcium-containing phosphate binders and vitamin D inhibit chondrocyte proliferation and delay mineralization, thereby causing adynamic bone disease.⁷² Resistance to GH effects is manifested by low expression of IGF-I protein and decreased bone morphogenetic protein-7 staining, despite an increase in GH concentration and higher density of GHR.⁷² It may therefore be prudent to avoid calcium-containing phosphate-binders and ensure appropriate vitamin D doses in CKD subjects receiving rhGH.⁷³

There is evidence to suggest that GH may play a modulatory role in the musculo-skeletal effects of parathyroid hormone. Administration of rhGH to GH-deficient subjects improves end-organ responsiveness with a decrease in urinary calcium excretion, increased tubular phosphate reabsorption, and increased markers of bone turnover (type I collagen C-telopeptide and pro-collagen type I amino-terminal propeptide).⁷⁴

QUALITY OF LIFE

Psychometric analysis and physical assessment of renal patients reveals a high prevalence of reactive depression, reduced physical performance, and cognitive deficits. However, psychosocial support, physical exercise, and anemia control may ameliorate many of these deficits. Administration of rhGH may also play a positive role as replacement therapy in GH-deficient adults; rhGH has been shown to improve quality-of-life indices.⁷⁵ Similarly, rhGH improves linear growth and physical agility, and reduces psychosocial burden in children with Prader-Willi syndrome.^{76,77} Confounding variables such as anemia in CKD make studying the psychosocial impact of rhGH a difficult exercise.

CONCLUSIONS & SPECULATION

This review describes and highlights the potential therapeutic impact of rhGH in CKD patients. In the absence of kidney transplantation, it is important to restore the profound metabolic and physiological defects arising from renal insufficiency. In many instances, studies in GH-deficient models have demonstrated the beneficial effects of rhGH therapy beyond the longitudinal

skeletal growth for which rhGH is commonly indicated. Additional problems in CKD patients for whom rhGH may play a significant role include modulation of nutritional inadequacies, altered body composition, immune dysregulation, and impaired sexual development and/or reproductive capacity. However, given the differences in their pathogenesis, it may be overly simplistic to project similar benefits of rhGH therapy to all the clinical settings of growth failure in CKD.

The multifaceted physiological effects of rhGH should still be taken into consideration in future studies of renal patients. Efforts must be made to broaden the scope of outcome measures to include cellular growth, cellular metabolism and function, neurocognitive development, psychosocial impact, sleep physiology, energy homeostasis, and anemia control. The beneficial role of rhGH in uremic cardiomyopathy, bone disease, anemia management, body composition, hospitalization requirements, and vascular diseases should also be examined. Co-morbidities are common in CKD and, therefore, multiple pharmacological agents are often needed to treat the disease. The physiological outcome of the combined use of erythropoietin, steroids, vitamin D, carnitine supplements, and other nutritional supplements with rhGH requires further study. Experimental studies in animals suggest a favorable role for rhGH in surgical wound healing; studies are therefore needed to examine the role of rhGH in ameliorating delayed wound-healing that may characterize the use of sirolimus after surgical transplantation.

Furthermore, the role of ghrelin (a recently discovered endogenous GH secretagogue) in CKD requires critical evaluation. Relevant questions for future studies are numerous. What is the role of ghrelin in food intake behavior in CKD patients? What are the metabolic effects of uremia on the capacity of Gr cells to produce ghrelin? What is the effect of uremia on the pituitary GH secretagogue receptor? What is the therapeutic impact of oral administration of ghrelin as a sole agent and/or combined therapy with rhGH/rhIGF-I, GH releasing peptides, exogenous IGFBP-3, and IGF-I analogs? What are the relationships between ghrelin, leptin, cytokines, and UCP polymorphism in the regulation of food intake, energy balance, and body composition in CKD?

Finally, the essence of this review is to inform the scientific community of the need for operational research endeavors concerning the metabolic impacts of rhGH therapy. Therefore, efforts must be made to critically assess the risk and benefit of the continued use of rhGH beyond the traditional end-point of linear skeletal growth in children with CKD. Hopefully, an improved understanding of the roles of rhGH in restoring physiological disturbances in CKD will provide added value to the treatment of such patients throughout their lives.

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