Review

Role of Growth Hormone Deficiency and Treatment in Chronic Kidney Disease

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Key Words

Chronic kidney disease · Growth hormone · Hemodialysis · Inflammation · Malnutrition · Renal replacement

Abstract

Malnutrition and inflammation are strong predictors of mortality in advanced kidney disease, especially in patients on renal replacement therapy. The complex relationship between kidney disease, uremia, and malnutrition significantly contributes to the increased morbidity and mortality in this patient population potentially through a relative deficiency in growth hormone (GH). With an approximate 26 million Americans currently affected by some stage of chronic kidney disease and a predicted 750,000 people to be on dialysis by 2020, there is a need to develop innovative strategies aimed at reducing the high mortality seen in dialysis patients. We will review evidence on one such intervention with infusion of recombinant GH to improve the nutritional and inflammatory state, thereby expecting to improve the mortality and morbidity in this patient population.

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Introduction

Chronic kidney disease (CKD) is associated with high morbidity and mortality, largely due to cardiovascular disease (CVD). Patients on renal replacement therapy, especially hemodialysis, have mortality rates in excess of 20% in the United States. Greater than 40%

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of the deaths in CKD patients can be attributed to CVD events [1, 2]. In this context, there are several interventions that have been shown to reduce the burden of CVD in individuals with CKD, such as management of hypertension with inhibition of the renin-angiotensin system and glycemic control in those with diabetes. However, there has been intense interest in the remaining residual risk for CVD despite optimal control of blood pressure and glycemia.

Investigators have used several innovative strategies, such as the addition of anti-oxidants, and modification of dialysis dose to improve cardiovascular outcomes in patients with CKD on renal replacement therapy, with little or no benefit [2–5]. It is postulated that this residual risk is due to multiple factors unique to patients with CKD, of which inflammation/oxidant stress and malnutrition have gained prominence [6, 7]. Uremia in CKD contributes to a distinct milieu that consequently leads to malnutrition, through multiple mechanisms, with alterations in the growth hormone (GH)-insulin-like growth factor (IGF) axis creating a state of relative GH deficiency [8]. The advent of recombinant human GH (rhGH) therapy in this patient population, in addition to conventional therapies, has provided novel insights into potentially reducing the residual risk for kidney-related mortality. This review will focus on the role GH infusion has in improving the inflammatory and nutritional status of patients on renal replacement therapy.

Inflammation in CKD

Since the 1980s, patients with end-stage renal disease have been found to have a highly inflammatory/oxidant state [9]. Our understanding of the ‘uremic inflammatory state’ has grown over the last few decades and multiple elements have been implicated in this causality. For example, reduced clearance of cytokines, endotoxin, and advanced glycation end-products contribute to inappropriate activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system and alter the GH-IGF axis (table 1) [6, 10–13]. This state of inflammation has many consequences, including, but not limited to, accelerated atherosclerosis, cardiovascular death, anorexia, protein energy malnutrition, and relative GH deficiency. There has been a recent burgeoning interest in the use of GH infusion in CKD patients, especially individuals on hemodialysis, to improve nutritional status and the inflammatory milieu seen in this population (table 1).

Rationale for Use of GH

GH is produced by the anterior pituitary and is important for normal growth of children and adolescents. After attainment of adult stature, GH levels decline but continue to have important effects on body composition, lipids, protein and bone metabolism as well as cardiovascular function. GH exerts its effects predominantly via IGF-1 and -2, which are both produced by the liver and target organs, but also has direct action on target organs. In patients with uremia, the normal GH-IGF axis is altered. Despite a blunted pulsatile release of GH, the total amount of GH secreted per day is greater than normal [14–16]. However, there is a decreased synthesis of free IGF-1 and -2 in patients with uremia due to end-organ resistance (table 2) [17, 18].

IGF-1 has a short half-life and is bound to IGF binding proteins (IGFBP). There are 6 IGFBP of which IGFBP-3 is the most abundant in extrauterine life. This binding of IGF-1 to these carrier proteins makes it less vulnerable to degradation. However, IGFBP has greater affinity to IGF-1 than IGF-1 has to its receptor [19]. In addition, IGFBP-3 and -5 share a sim-

Table 1. Causes of inflammation in end-stage renal disease

Infections due to <i>Chlamydia pneumoniae</i>
Periodontitis
Decreased clearance of cytokines
Blunted vagal response
Sympathetic overactivity
Advanced glycation end-products
Hemodialysis membranes
Impure dialysate solutions
Volume overload leading to gut translocation of endotoxin
Oxidative stress
Decreased levels of some antioxidants
Heparin

Table 2. Causes of GH resistance in CKD

Hyperparathyroidism
Metabolic acidosis
Inflammation
Impaired intracellular signaling following activation of GH receptor
Increased concentrations of IGFBP and metabolites

ilar molecular structure with IGF-1 and thus act as competitive inhibitors of IGF-1 [20]. In patients with uremia, there is decreased clearance of these IGFBP and retention of the metabolized by-products leading to an excess amount of circulating proteins which have a high affinity towards IGF-1 [19, 20]. Similar changes in circulating IGFBP concentrations can be seen in the extravascular space. These changes consequently lead to a decrease in the bioavailability of IGF-1 [19, 20]. The above factors hence lead to a functional deficiency in GH and IGF-1 in uremic patients, which can have deleterious effects [8, 21]. Epidemiological studies have demonstrated an increased incidence of mortality and morbidity in patients with GH deficiency due to cardiovascular causes like ischemic heart disease, congestive cardiac failure and cerebrovascular disease [8, 22–24]. This increase in CVD events may be due to reductions in bioavailable nitric oxide (NO) formation in patients with GH deficiency [25]. Studies looking at markers for atherosclerosis have demonstrated increased intimal thickness, atherosclerotic plaques, arterial stiffness, and endothelial dysfunction in GH-deficient patients [26, 27]. GH deficiency also furthers an inflammatory milieu leading to hyperhomocysteinemia, elevated C-reactive protein (CRP), elevated plasminogen activator inhibitor-1 and elevated fibrinogen [28–30]. Decreased left ventricular mass and ejection fraction have been observed in GH deficiency. These parameters, as well as left ventricular posterior wall thickness, intraventricular septal thickness, and end-diastolic diameter improve with GH treatment [31]. Epidemiological studies and placebo-controlled trials using GH receptor antagonists (e.g. pegvisomant) have shown that GH deficiency is associated with increases in abdominal fat, low-density lipoprotein (LDL) and triglyceride levels, and insulin resistance and a decrease in lean body mass (LBM) and associated hyperinsulinemia [32, 33]. Some of the aforementioned abnormalities were reversed to varying degrees following GH replacement [31, 34, 35]. Various therapeutic options for GH replacement are available. Therapies using rhGH alone or in combination with recombinant human IGF-1 infusion have been applied [36]. IGFBP-3 infusion has also been used in combination with IGF-1 to help improve IGF-1 availability [37, 38].

Table 3. Randomized trials investigating benefits of growth hormone in CKD patients

Study	Number of patients		Study design	Inclusion criteria	Follow-up period (mo)	Parameters		GH infusion		placebo		P value	
	GH infusion	placebo				parameters		baseline	end of study	change	baseline	end of study	change
Hansen et al. [46]	9	11	RCT	18–70 years hemodialysis >6 months	6	Body weight, kg		57.29 ± 3.7	57.1 ± 3.9	0.2 ± 0.06	60.7 ± 3.2	60.5 ± 2.9	0.3 ± 0.05
						IGF-1, µg/l		199 ± 19	527 ± 111	327 ± 104	285 ± 36	219 ± 35	66 ± 22
						PIIINP, µg/ml		7.86 ± 1.35	14.33 ± 2.12	6.48 ± 1.42	8.87 ± 1.41	8 ± 1.02	0.86 ± 1.03
Kotzmann et al. [47]	9	10	RCT	serum cholesterol and transferrin <200 mg/dl	3	Body weight, kg		60.5 ± 12	59.9 ± 13	no data	59.8 ± 11	60 ± 10	no data
						IGF-1, µg/l		169.2 ± 95.6	262.9 ± 144.4		no data	no data	
						total body fat, %		17.5 ± 10	16.7 ± 10		17.1 ± 9	16.9 ± 8	
Kober et al. [48]	37	34	RCT	non diabetics serum albumin <40 g/l age >18 years	6	Cholesterol, mg/dl		165.3 ± 32.1	158.6 ± 33.9		188.2 ± 39.4	180.2 ± 22	
						LBM		no data	no data	3.06 ± 0.49	no data	no data	0.39 ± 0.50
						IGF-1, µg/l		233.2 ± 161.7	no data	503.3 ± 339.6	no data	no data	213.4 ± 113.7
Johannsson et al. [49]	10	10	RCT	age >50 years survival >6 months	6	LDL		112 ± 37	90 ± 26	19 ± 33	106 ± 31	106 ± 31	3 ± 20
						Lp(a)		24.2 ± 20.2	31 ± 32.7	3.5 ± 16	40.6 ± 42.3	45.2 ± 43.2	0.9 ± 14.9
						left ventricular mass, g		208.2 ± 68.6	212.9 ± 63.0	2.3 ± 25.7	197.6 ± 60.9	218.7 ± 63.6	4.4 ± 47.0
Iglesias et al. [50]	8	9	RCT	serum albumin <40 g/l age >18 years >10% weight loss over last 6 months	3	Homocysteine, mg/l		no data	no data	0.53 ± 0.83	no data	no data	0.64 ± 2.42
						albumin, g/dl		3.79 ± 0.2	no data	0.13 ± 0.15	3.88 ± 0.27	0.13 ± 0.15	0.02 ± 0.26
						body mass index		25.4 ± 1.8	25.4 ± 1.6	no data	25.5 ± 1.5	25.3 ± 1.2	no data
Johannsson et al. [50]	8	9	RCT	serum albumin <40 g/l age >18 years >10% weight loss over last 6 months	3	IGF-1, µg/l		277 ± 29	415 ± 41	no data	322 ± 44	329 ± 35	no data
						Body weight, kg		64.3 ± 4.3	65.2 ± 5.5	no data	70.3 ± 6.3	69.8 ± 6.1	no data
						Transferrin, mg/dl		271.2 ± 16.3	291.7 ± 18.0		237.7 ± 16.3	233.6 ± 17.1	
Johannsson et al. [50]	8	9	RCT	serum albumin <40 g/l age >18 years >10% weight loss over last 6 months	3	IGF-1, µg/l		216.6 ± 42.5	251.5 ± 59.4		231.4 ± 43.6	244.3 ± 43.0	

RCT = Randomized control trial; IGF-1 = insulin-like growth factor; PIIINP = n-terminal propeptide type III procollagen; LBM = lean body mass; mo = months.

Fig. 1. Summary of causes and consequences of GH and IGF-1 deficiency in CKD patients. ApoB = Apolipoprotein B; HDL = high-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1; TG = triglycerides; VLDL = very-low-density lipoprotein; LBM = lean body mass.

Effects of rhGH Therapy

Infusion of rhGH helps reverse insulin resistance, endothelial function, and increases protein synthesis by increasing amino acid uptake and decreasing ATP-ubiquitin proteolytic pathways. Additionally, it decreases LDL and apolipoprotein B by inducing enzymes like lipoprotein lipase, which plays a key role in the metabolism of lipoproteins [39–41]. The anorexic hormones leptin and ghrelin, which accumulate in CKD patients, decrease following infusion of rhGH in GH-deficient adults and animal models of obesity [42, 43]. In patients with CKD and animal models of GH deficiency, increased endothelial NO synthase and NO production has been demonstrated, leading to improvement in endothelial dysfunction following short-term infusion of rhGH [44, 45].

Evidence for the Use of GH in CKD

There have been several randomized, clinical trials to investigate the benefits of GH replacement in CKD patients (table 3). One group looked at the short- and long-term effects of GH infusion (4 IU/m² per day) on LBM and markers of connective tissue synthesis, e.g. N-terminal propeptide type III procollagen (PIIINP) [46]. At the end of 6 months, there was a significant increase in serum levels of IGF-1, LBM, and PIIINP, with a decrease in truncal fat mass (which has shown to be an important cardiovascular risk factor). A similar decrease in

percent total body fat and increase in PIIINP was reported in a similar study [47]. In this study, there was also a significant increase in IGF-1 3 months after the infusion of rhGH (0.125 IU/kg three times a week for the first 4 weeks and 0.25 IU/kg thereafter) with a slight change in IGFBP-3 levels. In addition, there was an increase in the measured marker of bone turnover: procollagen I carboxyterminal peptide with no changes in other markers such as serum osteocalcin and collagen I carboxyterminal telopeptide at the end of 3 months. The increases in the phagocytic activity of polymorphonuclear leukocytes in the rhGH group could be of clinical relevance. However, there were no changes seen in the serum levels of cholesterol, transferrin and albumin.

Several other groups [48–50] have also investigated changes in markers of nutrition as protein calorie malnutrition, which remains one of the most important predictors of mortality in CKD patients, whether they are dialysis dependent or not [51]. A few studies have reported a possibility of reversing this morbidity and mortality following improvement of the malnutrition state [52–54]. To study this effect, investigators infused rhGH at varying doses with primary end points being change in body composition, LBM and other nutritional markers like serum albumin. Secondary end points of muscle performance and changes in inflammatory markers were also measured. At the end of 6 months, investigators reported an increase in whole body protein metabolism with decreases in catabolism and urea generation [49]. They also found an increase in serum IGF-1, IGFBP-3, serum albumin and fat-free mass. Another group looked at changes after 4 weeks of rhGH (0.2 IU/kg after dialysis) and reported an increase in serum transferrin, body weight and IGF-1 concentration, with a decrease in urea generation at the end of the study period [50]. However, there were no changes in nutritional indices. To investigate the impact on LBM, investigators [48] randomized 139 patients to receive three different doses of GH infusion or placebo. GH doses included 0.02, 0.035 and 0.050 mg/kg/day for 6 months after dialysis. The end results were an increase in the LBM, IGF-1 and IGFBP-3 in the three groups compared to placebo. A pooled analysis showed an improvement in serum high-density lipoprotein with a trend towards decreases in LDL and lipoprotein(a) in comparison to placebo. However, a caveat to note is that an improvement in lipid profile in this patient population may not equate to reductions in cardiovascular mortality [5, 55, 56]. Other end results included an increase in serum transferrin and albumin levels with a decrease in the elevated homocysteine levels. Changes in the inflammatory markers included a trend towards a decrease in tumor necrosis factor (TNF)- α with no changes in the serum CRP and interleukin (IL)-6 levels.

In summary, these studies demonstrate increases in serum IGF-1 levels, LBM, bone turnover, and phagocytic activity of polymorphonuclear leukocytes, and an overall decrease in the body fat mass following GH infusion in dialysis patients. Varying results for changes in serum albumin and other nutritional markers have been observed. Furthermore, there was a trend towards improvement in the lipid profile, with significant changes in serum transferrin levels. Studies failed to show an improvement in CRP and IL-6 levels; however, there was normalization of elevated homocysteine levels and a trend towards improvement in TNF- α . Consequently, these changes support improvements in the malnutrition state implicated as a key contributor to the development of inflammation, and the atherosclerosis syndrome in CKD [57].

Adverse effects reported with infusion of GH in these studies included minor complaints from headaches, arthralgia, edema, nausea/vomiting, and paresthesia to more serious adverse effects with a few reports of congestive heart failure and skin malignancies. Notably, there was no significant increase in incidence rates of diabetes, left ventricular hypertrophy, or hypertension.

Conclusion

CKD is considered a leading cardiovascular risk factor, with cardiovascular death being the major cause of mortality in CKD patients. Multiple strategies have been evaluated to help reduce CVD mortality and morbidity in this unique patient population. Longer-term studies demonstrating improvement in hard CVD outcomes are needed before the infusion of GH can be considered as a potential therapy to counteract the complex interplay of malnutrition, atherosclerosis, and inflammation in CKD patients.

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