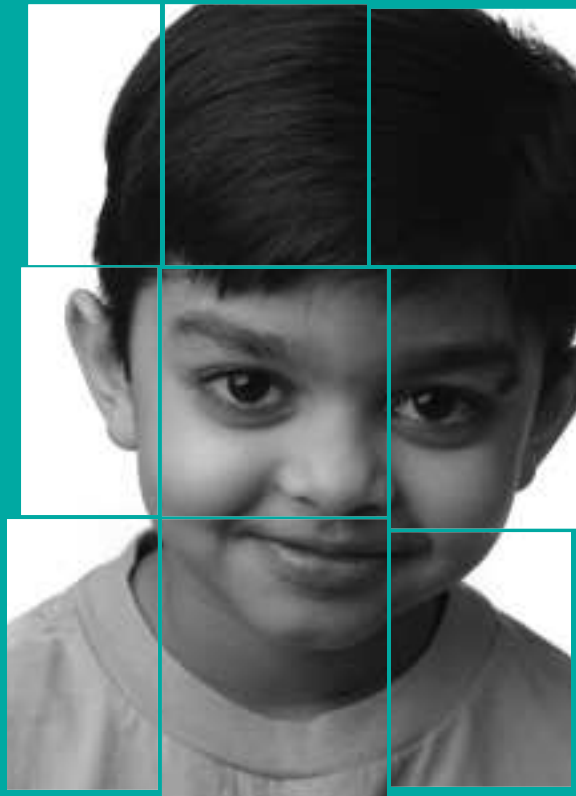


Chronic Renal Insufficiency



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Chronic Renal Insufficiency

Chronic renal insufficiency (CRI) in children describes a pathologic process affecting the kidneys.

A complex problem with no easy answers

Over a variable period of time, CRI leads to a decline in renal function resulting in total kidney failure or end-stage renal disease (ESRD). CRI is characterized by the destruction and progressive loss of nephrons. As a result, there is an increase in both the severity and frequency of symptoms including:

- Acidosis
- Renal osteodystrophy
- Hypertension
- Azotemia
- Growth failure
- Anemia
- Uremia

In children with CRI, the kidneys typically function between 25% and 75% of normal glomerular filtration rate. CRI is defined as $<75 \text{ mL/min/1.73 m}^2$ residual creatinine clearance.¹



Growth failure is common in children with CRI and it constitutes a serious problem in these children.²

Growth Failure in Children with CRI

Multiple interrelated factors, including malnutrition, bone disease, acidosis, and electrolyte and water imbalances contribute to growth failure in CRI. It must also be noted that anemia is one of the most common manifestations of progressive CRI and ESRD.³

The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis may be disturbed in several ways. Growth hormone (GH) levels are usually normal or even elevated in CRI patients. Yet despite normal or elevated GH levels, activity is low. Therefore, the problem is GH insensitivity rather than inadequate GH production. This GH insensitivity may be due to several factors including:

- The inability of GH to bind to receptors
- Low concentrations of receptors and associated binding protein
- IGF-1 and IGFBP disturbances⁴

Children with CRI have low GH-binding protein (GHBP) levels, which indicate there may be a decreased number of GH receptors.⁵ Levels of IGF-binding protein (IGFBP-3) in CRI patients may be increased.⁶ IGFBP-3 binds to IGF-1, reducing free IGF-1 levels, blocking its growth-stimulating effects.⁷

Additional hormonal imbalances found in CRI patients include disturbances of the hypothalamic-pituitary-gonadal-axis, which normally interacts with growth-plate cartilage to regulate growth. Hypothyroidism may occur, leading to abnormal skeletal ossification and deficient connective-tissue growth. Hyperparathyroidism contributes to growth failure by inhibiting bone growth.⁶

Malnutrition is a common problem in children with CRI. Patients are often anorexic, and low energy intake may have a direct inhibitory effect on growth-plate chondrocyte metabolism. Malnutrition may be exacerbated in children with CRI because protein-calorie intake requirements are often increased in the uremic state. Protein catabolism (the breakdown and loss of protein) occurs in CRI and further contributes to malnutrition and muscle wasting.^{8,9}

Bone disease is a serious complication of renal insufficiency and contributes to growth failure in children. Osteodystrophies that may be observed in these children include osteomalacia, osteofibrosis, and osteoporosis.⁹

Electrolyte disturbances occur in CRI and may contribute to poor growth. These disturbances include chronic hypokalemia, dehydration, hyposthenuria, and metabolic acidosis. Severe metabolic acidosis leads to pronounced growth failure.⁹



Diagnosis

Early evaluation of the CRI patient for growth failure should include analysis of the patient's past growth patterns, genetic predisposition toward growth, and past laboratory evaluations including:

- Patient's age and sex
- Family heights
- Medical history
- Etiology of the primary renal disease
- Growth history determined from height measurements obtained for a period of at least one year
- Height, weight, and Tanner pubertal stage
- Laboratory results including hematology, blood chemistries, urinalysis, hormone/growth factor measurements, and renal function tests

Growth calculations that aid in this diagnosis include height SD scores, bone age, growth rate, and weight standardized for height.¹⁰

GH provocation testing is not required as a part of the diagnostic work-up for children who have growth failure associated with CRI.¹⁰



Growth Failure in CRI

Treatment of CRI is complex.¹¹ Whereas some treatment modalities are directed toward specific problems, others address more than one element of the disease.

This section will discuss those therapies that play a role in improving growth.

Nutritional therapy improves growth and weight gain. Specific attention must be paid to protein and caloric intake.¹² Alkali therapy is important in treating the metabolic acidosis that can contribute to anorexia.¹³

Hormonal imbalances require careful evaluation and frequent testing in order to ensure appropriate therapy. Treatment of hyperparathyroidism and its effects is important in restoring normal growth. This may be achieved by vitamin D therapy, calcium supplements, and a low-phosphorus diet. The GH imbalance associated with renal insufficiency contributes to growth failure.

Fine et al specified that patients were eligible for treatment with Nutropin AQ or Nutropin if they had CRI and height less than the third percentile.¹ CRI patients treated with Nutropin grow at an improved rate for a variety of reasons. Nutropin results in increased levels of GH, a several-fold increase in the level of IGF-1, and a slight increase in the level of IGFBP-3. Because GH levels are not deficient in CRI patients, the key is that high levels of GH are able to overcome the body's insensitivity to GH, resulting in improvement in growth rate of bone cells, muscle cells, and organ cells.

The Nutropin AQ Pen is available in the US by prescription only. Healthcare professionals should provide patient training prior to use.

Please see accompanying full prescribing information for Nutropin AQ and Nutropin for additional safety considerations.

Nutropin AQ Pen[®] 10
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Please see accompanying Nutropin AQ and Nutropin full prescribing information. Please see pages 12-13 for important safety information.

Efficacy of Nutropin AQ

Nutropin AQ® [somatropin (rDNA origin) injection] and Nutropin® [somatropin (rDNA origin) for injection] are indicated for the treatment of growth failure associated with chronic renal insufficiency (CRI) up to the time of renal transplantation. Nutropin AQ and Nutropin therapy should be used in conjunction with optimal management of CRI.

Two multicenter, randomized, controlled clinical trials were conducted to determine whether treatment with Nutropin prior to renal transplantation in children with CRI could improve their growth rates and height deficits. One study was a double-blind, placebo-controlled trial and the other was an open label, randomized trial. The dose of Nutropin in both controlled studies was 0.05 mg/kg/day (0.35 mg/kg/wk) administered daily by subcutaneous injection. Combining the data from those patients completing two years in the two controlled studies results in 62 children treated with Nutropin and 28 children in the control groups (either placebo-treated or untreated).

- The mean first-year growth rate was 10.8 cm/yr for the Nutropin-treated patients, compared with a mean growth rate of 6.5 cm/yr for placebo/untreated controls ($p < 0.00005$).
- The mean second-year growth rate was 7.8 cm/yr for the Nutropin-treated group, compared with 5.5 cm/yr for controls ($p < 0.00005$). There was a significant increase in mean height standard deviation score in the Nutropin group (-2.9 at baseline to -1.5 at Month 24, $n=62$), but no significant change in the controls (-2.8 at baseline to -2.9 at Month 24, $n=28$).
- The mean third-year growth rate of 7.6 cm/yr in the patients treated with Nutropin ($n=27$) suggests that Nutropin stimulates growth beyond two years; however, there are no control data for the third year because control patients crossed over to GH treatment after two years of participation. The gains in height were accompanied by appropriate advancement of skeletal age.¹⁴

Five years of treatment with Nutropin in 20 children with growth failure due to CRI produced a significant ($p < 0.00005$) improvement in standardized height (from -2.6 at baseline to -0.7 following 5 years of treatment).¹⁵

Please see accompanying Nutropin AQ and Nutropin full prescribing information. Please see pages 12-13 for important safety information.

Nutropin AQ and Nutropin are bioequivalent

The efficacy and safety of Nutropin AQ for the treatment of growth failure associated with CRI has been established through the efficacy and safety of lyophilized Nutropin. Studies have demonstrated that Nutropin AQ is bioequivalent to lyophilized Nutropin, which has been shown to significantly improve growth in children with CRI.

To optimize therapy with Nutropin AQ, correction of anemia, control of acidosis, appropriate nutrition, and prompt recognition of and treatment of osteodystrophy should be addressed before the introduction of GH therapy.^{8,9,14,16}

Dosage and Administration With CRI

A weekly dosage of up to 0.35 mg/kg of body weight divided into daily subcutaneous injections is recommended. Nutropin AQ and Nutropin therapy may be continued up to the time of renal transplantation.

In order to optimize therapy for patients who require dialysis, the following guidelines for the injection schedule are recommended:

- Hemodialysis patients should receive their injection at night just prior to going to sleep or at least 3-4 hours after their hemodialysis to prevent hematoma formation due to the heparin
- Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in the morning after they have completed dialysis
- Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection in the evening at the time of the overnight exchange

Important Safety Information

Indication

Nutropin AQ and Nutropin are indicated for the treatment of growth failure associated with chronic renal insufficiency (CRI) up to the time of renal transplantation. Nutropin AQ and Nutropin therapy should be used in conjunction with optimal management of CRI.

Contraindications

GH should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure.

Nutropin AQ and Nutropin should not be used for growth promotion in patients with closed epiphyses.

Nutropin AQ and Nutropin should not be used in patients with active neoplasia. GH therapy should be discontinued if evidence of neoplasia develops.

GH is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see **WARNINGS** in full prescribing information). Unless patients with Prader-Willi syndrome also have a diagnosis of GH deficiency, Nutropin AQ and Nutropin are not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Precautions

General

Nutropin AQ and Nutropin should be prescribed by physicians experienced in the diagnosis and management of patients with GH deficiency, Turner syndrome, or chronic renal insufficiency.

Because GH may reduce insulin sensitivity, patients should be monitored for signs of glucose intolerance. For patient with diabetes mellitus, insulin dosage may require adjustment when GH therapy is instituted.

Patients with a history of an intracranial lesion should be examined frequently for progression or recurrence of the lesion.

Patients with growth failure secondary to CRI should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy, and it is uncertain whether these problems are affected by GH therapy. X rays of the hips should be obtained prior to initiating therapy for CRI patients.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders or in patients undergoing rapid growth.

Because GH increases growth rate, patients with a history of scoliosis who are treated with GH should be monitored for progression of scoliosis. GH has not been shown to increase the incidence of scoliosis.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a smaller number of patients treated with GH products. Symptoms usually occurred within the first 8 weeks of the initiation of GH therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the GH dose. Fundoscopic examination of patients is recommended at the initiation and periodically during the course of GH therapy. Patients with CRI may be at increased risk for development of IH.

The use of Nutropin AQ or Nutropin in patients with CRI receiving glucocorticoid therapy has not been evaluated. Concomitant glucocorticoid therapy may inhibit the growth-promoting effect of Nutropin AQ or Nutropin. If glucocorticoid replacement is required, the glucocorticoid dose should be carefully adjusted.

There was no evidence of controlled studies of GH's interaction with drugs commonly used in chronic renal insufficiency patients. Limited published data indicate that GH treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that GH administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g. corticosteroids, sex steroids, anticonvulsants, cyclosporin). Careful monitoring is advisable when GH is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

As with any protein, local or systemic allergic reactions may occur. Prompt medical attention should be sought if allergic reactions occur.

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With SPOC, Genentech offers:

- Help for individuals and families seeking insurance reimbursement for GH therapy
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- Convenient service with a single, toll-free phone call at 1-800-545-0498 or on the Web at www.SPOCOnline.com

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