Growth, feeding, treatment of renal Fanconi Syndrome. Does early treatment with substrate depletion therapy prevent late complications?

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Interdisciplinary Cystinosis Clinic Traunstein

10/2010 - Interdisciplinary Cystinosis Clinic
Cooperation with the German Patient Organization

<u>children and adults</u>

3 times /year – in addition to regular medical care
3 hours as outpatient

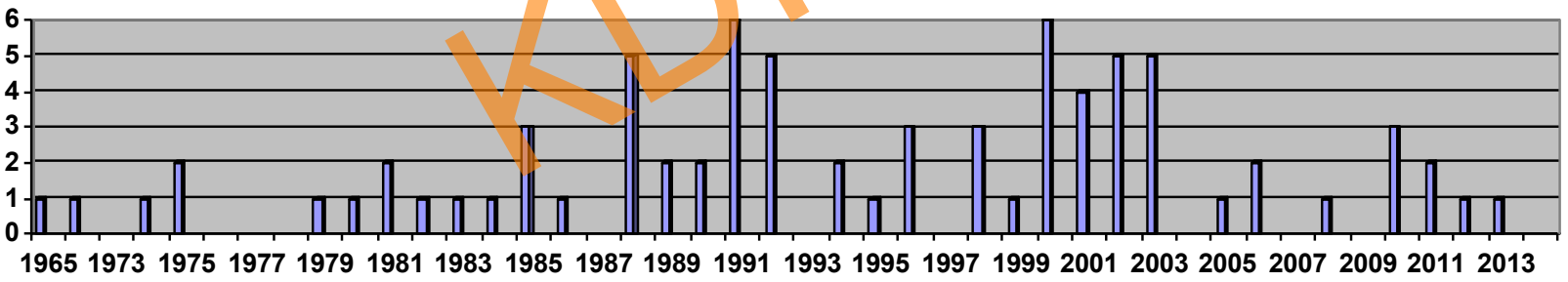
Prof. Harms
Nephrology (pediatrics, adult)
Orthopedics
Cardiology
Pulmonology
Ophthalmology
Gastroenterology
Endocrinology
Neurology
Internal Medicine
Dermatology
Dietician
Logopedics
Physiotherapist
Social worker
Prof. Marquardt

Interdisciplinary Cystinosis Clinic Traunstein

10/2010 – 10/2014

n = 92 patients / 7 clinics
56 individual patients

Contact with 77 patients



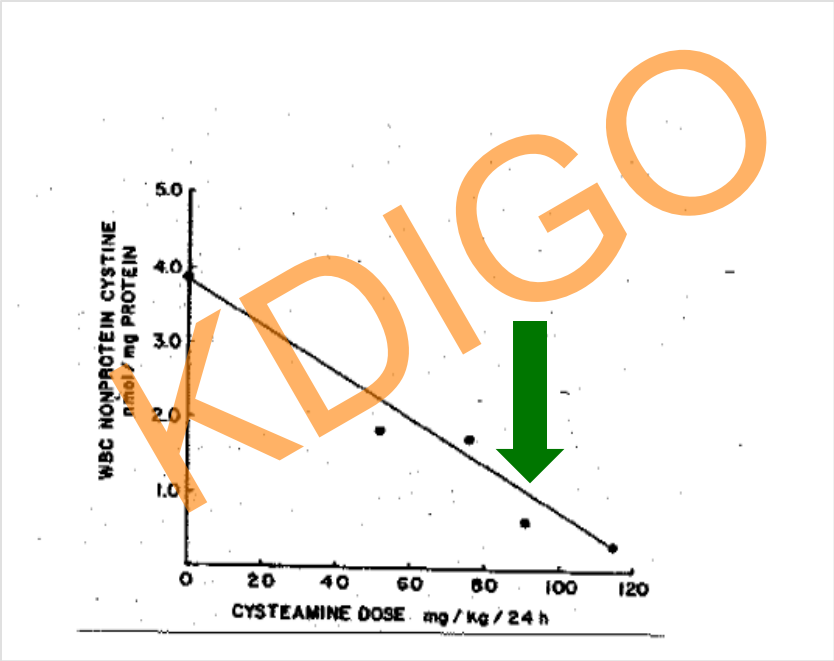
n = 35 < 18 y
n = 32 > 18 y

Treatment

What is the optimal Cysteamine dose ?

Treatment

Cumulative dose-response curve for orally administered cysteamine and peripheral leukocyte nonprotein cystine content at progressively increasing dose levels



At dosis over 80mg/kg/day: leukocyte nonprotein cystine level was in the range of asymptomatic heterozygotes

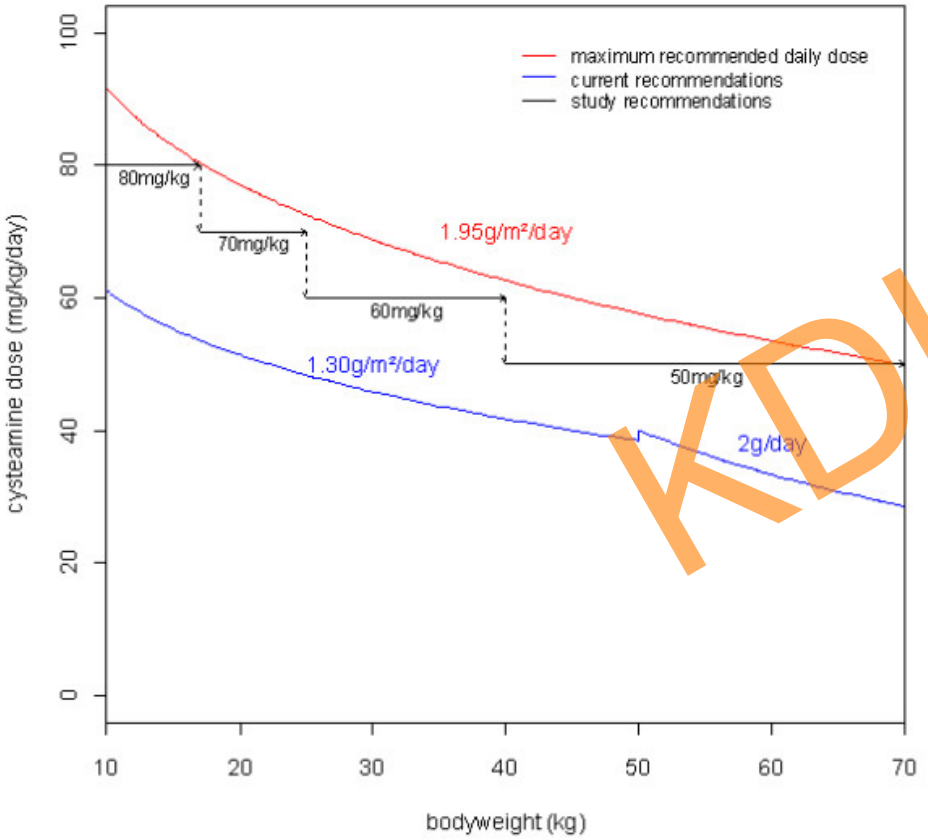
Thoene, et al, The Journal of Clinical Investigation 58 (7), 180-189,1976

Optimal dose of cysteamine

Kleta R. et al J Pediatr (2004); 145 :555-560	1 – 7 years:	80-90 mg/kg/day
	7 – 8 years:	70 mg/kg/day
	> 8 years:	60 mg/kg/day
	> 10 years :	40 mg/kg/day
Emma F. et al Nephrol Dial Transplant (2014); 29: iv87-iv94	≤ 12 years :	1,30g/m²/day
	> 12 years, > 50 kg:	2,00 gr/day
Bouazza N. et al Orphanet Journal of Rare Disease (2011); 6:86	10-17 kg:	80 mg/ kg /day
	17- 25 kg:	70 mg/ kg /day
	25- 40 kg:	60 mg/ kg /day
	40-70 kg:	50 mg /kg /day

Optimal dose of cysteamine

Pharmacokinetics and pharmacodynamic study



n= 69 nephropathic cystinosis patients
age: 0.4 – 36 years
bodyweight:7.6-83 kg
(mean cysteamine dose: 35.5 mg/kg/day)

Determination of cysteamine plasma concentration/
PMN cells cystine levels

Model linking cysteamine concentrations to
WBC cystine levels

Dosing scheme - not exceeding max.
recommended dose of
1.95 g/m²/day

Bouazza N. et al, Orphanet Journal of Rare Disease 2011,6:86

Optimal dose of cysteamine

Initiation of treatment as early as possible to preserve renal function:

Kleta R. et al*.: sibling 10 week of age
J Pediatr
(2004); 145 :555-560

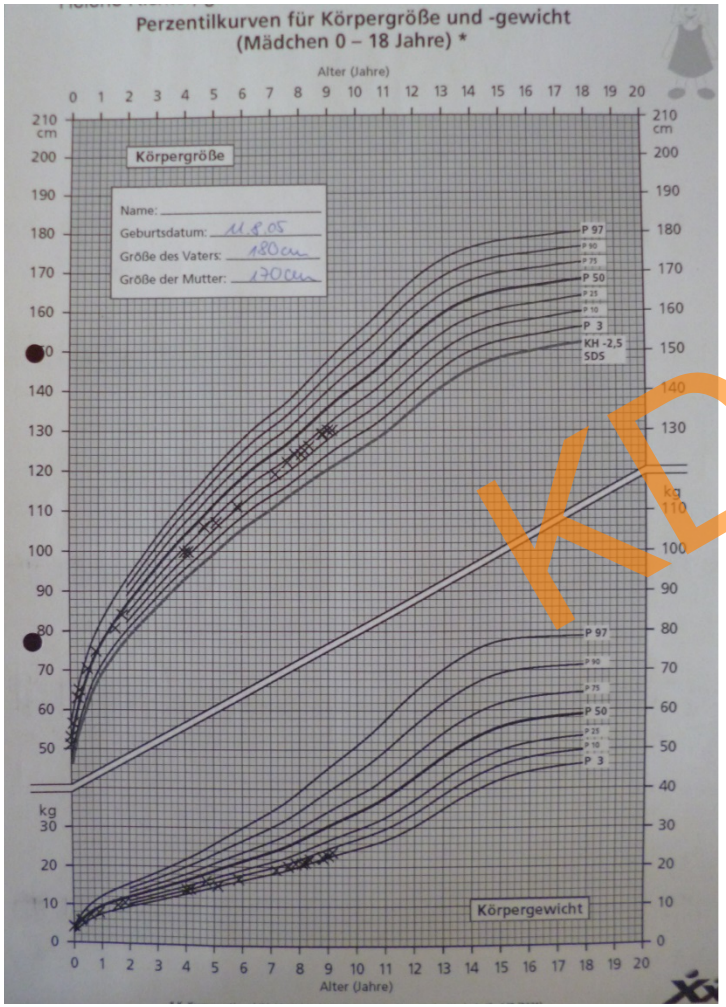
Harms E. et al*: as soon as possible

Angeborene Stoffwechselerkrankungen bei Erwachsenen
2014; 167-175

youngest patient: 5 days

*Initial therapy 10 mg/kg/day increasing weekly until (60)-90 mg/kg/day or 1300 g/m²

Optimal dose of cysteamine



Diagnosis at 5 days (11.08.2005)

Treatment with Cystagon:

14.11.05	80 mg/kg/day	
08.10.09	85 mg/kg/day	0,53 nmol cystine/mg protein
16.10.12	82 mg/kg/day	0,46 nmol cystine/mg protein
21.10.13	78 mg/kg/day	

06.10.2014:

Creatinine 0.35 mg/dl, Cystatin C 0.87 mg/dl,

Cystatin-C-GFR 128 ml/min/1.7m2

Urine:

Albumin 19.6 mg/l < 20mg/dl

Imunglobulin G 8.2 mg/l

α1-Mikroglobulin 50.6 mg/l

A2-Makroglobulin< 2.3 mg/l

Optimal dose of cysteamin

- cystine levels < 1nmol half-cystine/mg protein
- maximum recommended Dose:1.95 g/m²/day

At what age should treatment be started (siblings) ?

Prenatal diagnostic- postpartal cystine levels- postpartal genetics ?

Which dose regime should be used ?

Maximal dose in adults ?

Timing of PML cells cystine measurement after intake of medication ?

Feeding Problems

Common problems in patients with nephropathic cystinosis

at diagnosis

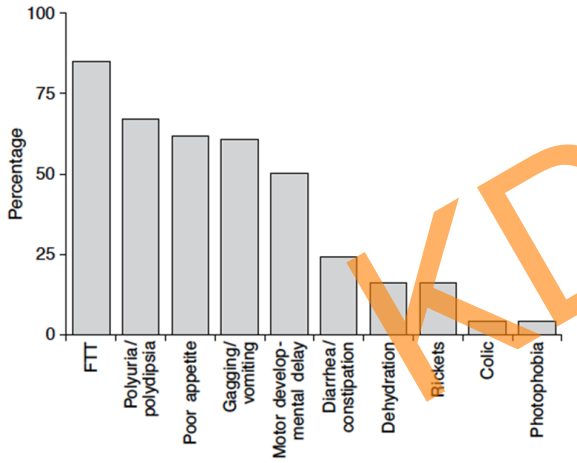


Fig. 1. Presenting symptoms in 70 cystinosis patients: 85% – failure to thrive (*FTT*), 67% – polyuria/polydipsia, 61% – poor appetite, 60% – gagging/vomiting, 50% – motor developmental delay, 24% – diarrhea/ constipation, 16% – dehydration, 16% – rickets, 4% – colic, 4% – photophobia

during course of disease

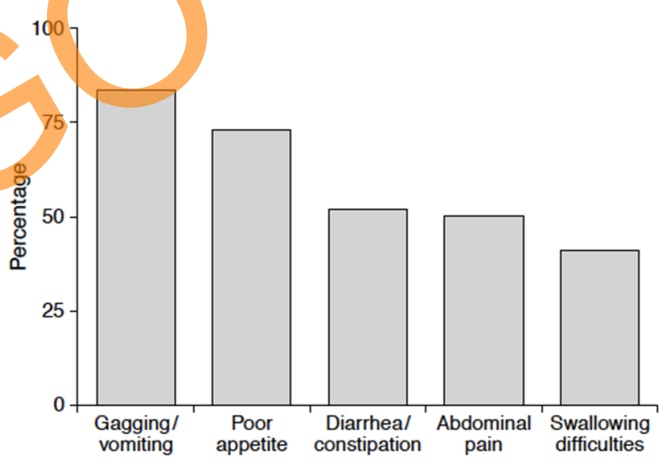


Fig. 2. Current gastrointestinal (GI) symptoms in the 70 cystinosis patients: 83% – gagging/vomiting, 71% – poor appetite, 57% – diarrhea/constipation, 50% – abdominal pain, 41% – swallowing difficulties

Elenberg E.et al, Pediatr Nephrol (1998) 12:365-370

Feeding Problems

45 patients (3,5 y - 33 y)

age at diagnosis	number of patients	PEG/Button
postpartal	2	1
0- 6 months	2	1
6- 12 months	15	8
12- 24 months	14	7
>24 months	12	5
	45	22

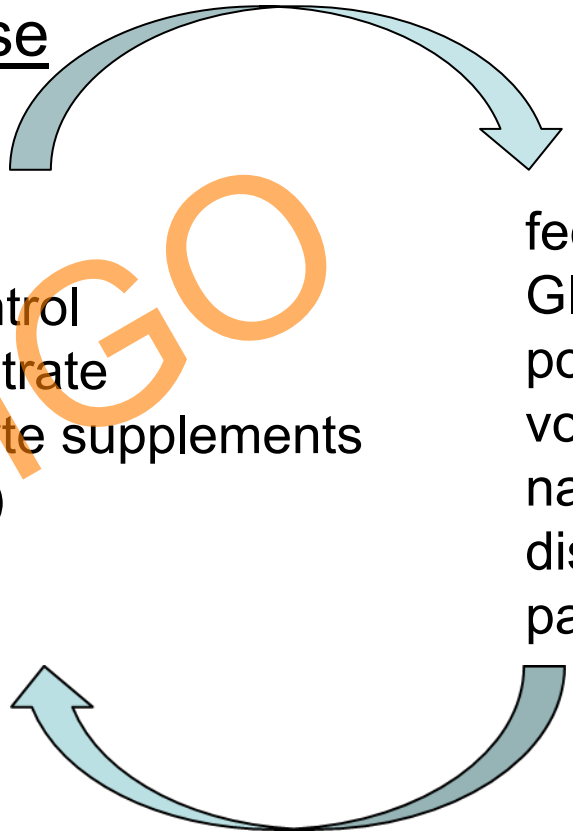
mean time of PEG/Button: 6.6 years

10 patients with swallowing difficulties – 3 patients > 25 years with additional severe diarrhea

Feeding Problems

Therapy to improve clinical course

- large volume of fluid
- polypharmacy for metabolic control
  (high dose) bicarbonate /citrate
  (large volume of) electrolyte supplements
  (K^+, Na^+, phosphate, Ca)
- Treatment with cysteamine
- several times a day



feeling unwell
GI discomfort
poor appetite
vomiting
nausea
distension
pain

Feeding Problems

Questions

- Small volumes of electrolyte supplements – more often /day
  Use of Amilorid ?

- Metabolic acidosis: exchange bicarbonate to citrate
  chemical compounds: Potassium- citrate or chloride
  instead of carbonate
  Magnesium organic compounds instead of
  anorganic compounds (Magnesiumoxid)
  Hydrochlorothiazide ?

Feeding Problems

- Indication for Indomethacin – duration of treatment – dosage ?
  Indomethacin : effective reducing levels of:
  urinary sodium, potassium, phosphate, uprate, glucose, bicarbonate secretion *
  but: renal functional deterioration, ulcerogenic potential

- Early logopedic treatment for chewing and swallowing difficulties

- Muscle status : early physiotherapy

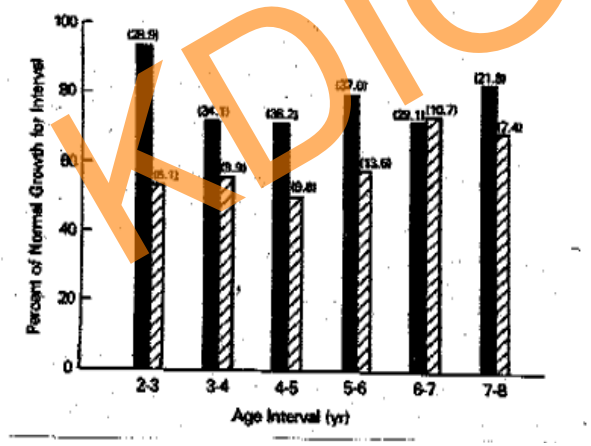
- Nutritional problems improve with age - training programs – for children/ adolescent
  similar to other patient groups with chronic illnesses as diabetes

*Haycock GB et al, Arch Dis Child 1982 57:934-939

Growth

Cysteamine –Treatment

- slows progression of renal insufficiency
- protects extrarenal organs
- accelerates growth



93 patients treated with cysteamine
55 historical controls

first year: 73.5%±3.4
of normal growth velocity
untreated:59±3.7

every succeeding year
76.4 and 97.9 %
of normal growth velocity

Percentage of normal Growth at different age intervals in Cysteamine-treated patients (solid bars) and Controls (hatched bars)

Gahl W et al, N Engl J Med 1987, Vol 316 (16);971-977

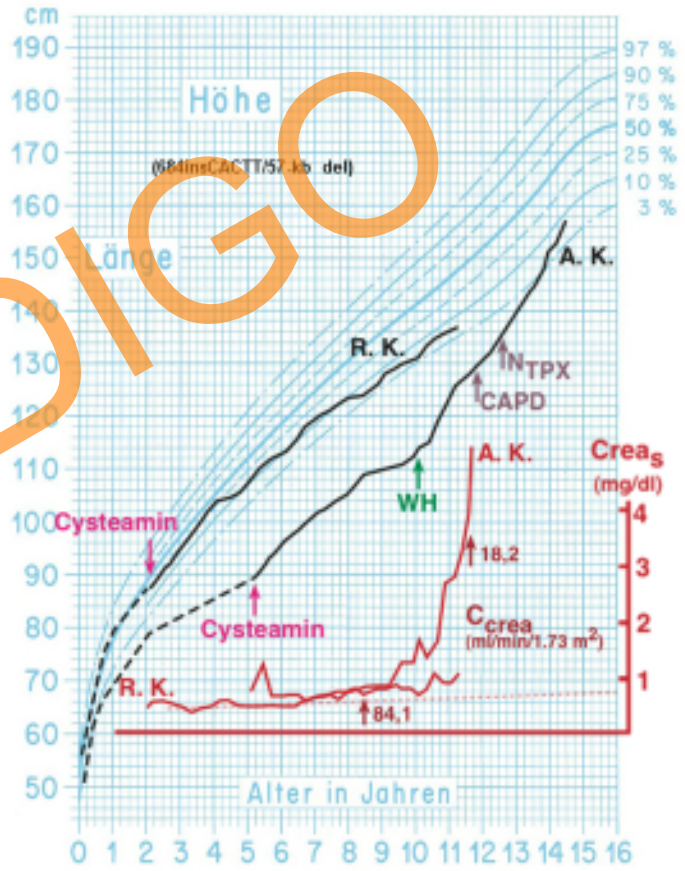
Growth

Improved renal function in children with cystinosis treated with cysteamine

Siblings

R.K.: Diagnose and initiation of treatment at age 24 months

Family history and examination of his brother A.K. lead to initiation of cysteamine treatment at age 5y



Growth

Growth retardation in patients with cystinosis is multifactorial

▪ renal Fanconi Syndrome	metabolic acidosis loss of sodium / potassium calcium/phosphate imbalance
▪ poor metabolic status	
▪ decreased renal function	impaired axis GH-IGF-1
▪ extrarenal complications	hypothyroidisms primary hypogonadisms (males) diabetes
▪ bone disease	rickets cystine accumulation in bones

Cysteamine therapy does not lead to catch-up growth*

* Gahl W., Eur J Pediatr (2003) 162: S38-S41

Growth

Fanconi-Syndrome

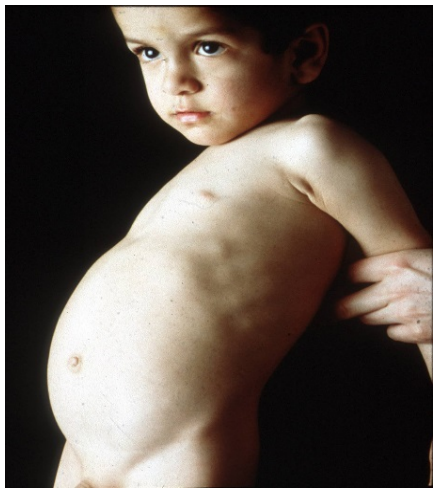
elevated urinary excretion

PTH
GH
IgF-1*

rickets

metabolic acidosis
elevated excretion of Vitamin D binding protein**

3 9/12 J, 88 cm



adequate therapy:

- 625µgr/day ergocalciferol no elevation of 1,25 Dihydroxycholecalciferol serum level
- substitution with 1,25 Dihydroxycholecalciferol
- supplement of calcium/ phosphate cave: nephrocalcinosis

⇒ linear growth

*Norden AG etal, Kidney Int 2001;60:185-1892;**Wilmer MJ, Am J Kidney Dis (2008);51:893-903
***Steinherz R et al, J Pediatr 1983;102:592-594.

Growth

Determination of Osteopenia

Osteopenia:	deposition of crystals hypothyroidism diabetes mellitus primary hypogonadism urinary phosphate wasting chronic renal failure
11 transplanted children	5 male / 4 female 3/5 males primary testicular failure 7/9 patients – normal BMD
Correlation of BMD with growth parameters Correlation of areal BMD	comparing to height, weight, pubertal stage growth
BMD measurement by DEXA:	predictive value for bone fragility is poor in patients with nephropathic cystinosis cannot be used to assess fracture risk

*Zimkas et al, Pediatr Nephrol (2003) 18 :384-390

Growth

Endocrine Functions

positive influence of cysteamine treatment *:

- on thyroid function – without treatment: thyroid atrophy
  Hypothyroidism: adequately treated: 56% vs. 87%
- on Diabetes mellitus: adequately 4% vs.50%

no influence of cysteamine treatment:

- primary hypogonadisms (males) due to testis fibrosis and atrophy*** (low testosterone, LH↑, FSH↑,)
- delayed puberty

*Gahl W et al, Ann Intern Med 2007 (147):242-250; ** Chick CL et al , Ann Intern Med 1993; 119; 568-575

Growth

Cysteamine-Treatment

Animal models: Effect of cysteamine on GH-IGF1 axis

Rats: GH • cysteamine is causing depletion of somatostatin
• increase ghrelin plasma levels*

carpe fish : increase of GH, thyroxin, T3 and growth**
chicken: enhanced growth and body weight***

Humans: positive effect on GH
cystine depleting effect in bone particular in epiphysis**

*Szabo et al, Endocrinology 1981;109:2255-2257, **Fukuhara S etal, Am J Physiol Gastrointest Liver Physiol 2005;289: G138-G145,Yang CM et al ,*** Poult Sci 2006;85 :1912-1916

Growth

Growth hormone secretion in cystinosis patients:

- 4/9 nocturnal GH measurements:
  normal mean GH level >3 ng/ml
  normal number of peaks during 7 h of measurement
  no difference to case control

  4/9 glucagon test
  Glucagon-Test: 3/4 normal peak levels
  1/4 GH deficiency
  2/4 patients with abnormal peaktiming

  before rhGH treatment exclusion of GH-deficiency with IGF-1

*Besouw et al, Pediatrt Nephrol (2012) 27:2123-2127

Growth

„Long-term treatment with growth hormone in short children with nephroathic cystinosis“

Safety of growth hormone treatment
74 /children (3-18 years) men period 3.1 years

52 patients conservative (mean age 7.1y)
7 Patients on dialysis (12.5 y)
15 renal transplant (14.8 y)

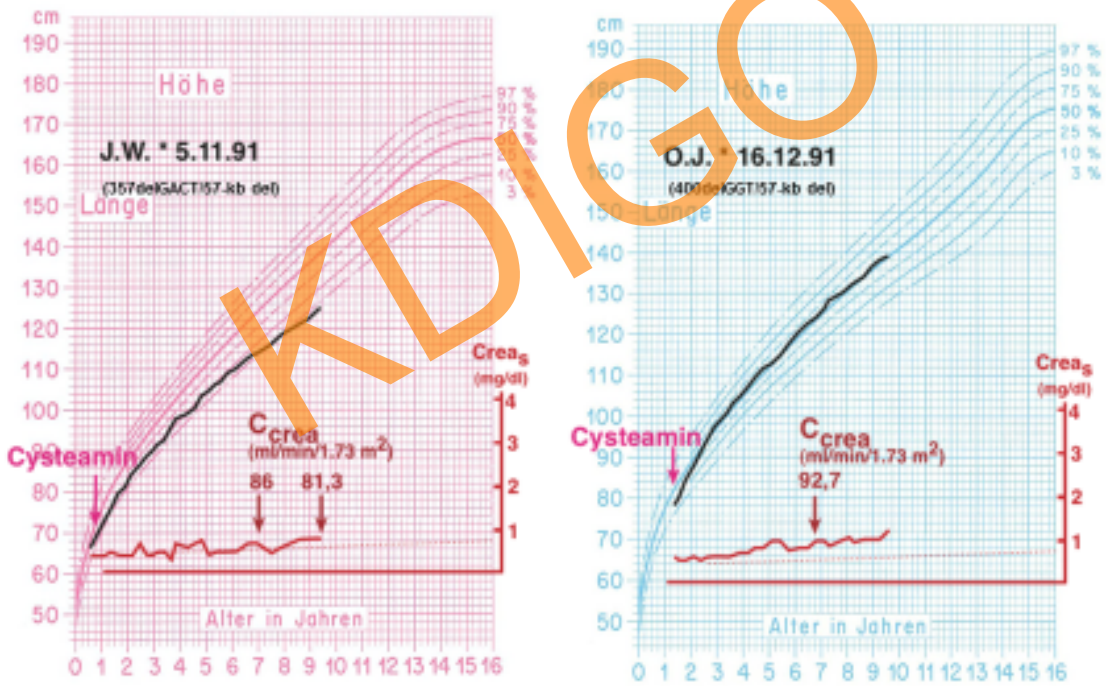
1.	**SD -4.0±1.2**	**4.3±1.6 cm/y**
2.	SD -4.4±1.2	2.5±2.1 cm/y
3.	SD -4.9±1.1	3.7±2.4 cm/y

no faster deterioration in renal function
no major side effects
Insulin fasting levels elevated – no significant change in glucose levels

Wühl, E et al, J Pediatrics, 138, 6, 2001, 880-887

Growth

Early oral cysteamine therapy



Growth

Optimal growth

- Management of rickets
- Vitamin D and 1,25 dihydrocholecalciferol treatment
- Supplement of phosphate and Calcium
- Parameters to start enteral feeding
- Hormonal treatment with rhGH
  - Exclusion of GH deficiency IGF1 measurements
  - IgF1 low – glucagon test
- Hormonal treatment with thyroxin
  normal values – healthy children ?
- Hormonal treatment of primary hypogonadisms in males
- Bone structure