Bone disease in cystinosis including surgery

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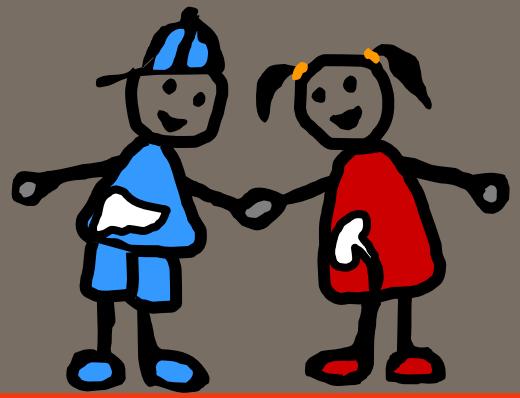

Medizinische Hochschule Hannover

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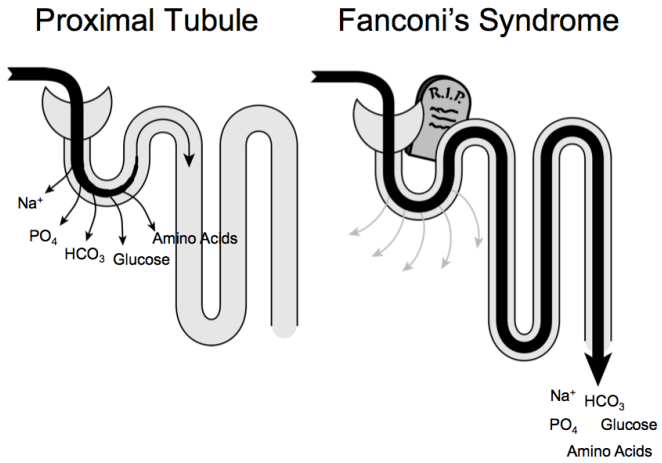
Leuven, Belgium

Disclosures

Speaker fees/consultancy: Amgen, Chiesi, Horizon, Kyowa Kirin, Pfizer

Research grants: Amgen, Chiesi, Horizon, Kyowa Kirin

Something is wrong.....



Growth deteriorates

The diapers are allways wet, a lot of thirst, likes salty things...

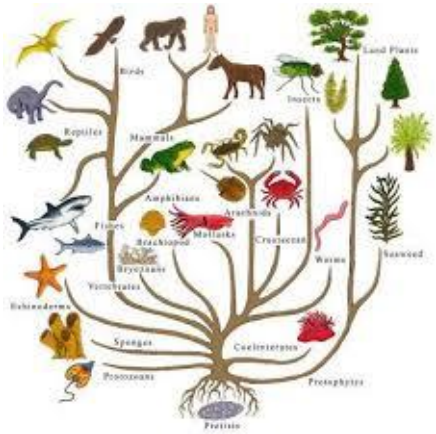
Does not start to walk, wants to be carried, ...waddling gait

Thick wrists, leg bowing

Vomiting, no appetite, fever, pain, weakness.....

Why do we have kidneys?

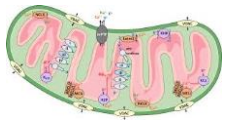
Our ancestors left the sea millions of years ago, and now we have to regulate our water and salt balance ourselves in order to survive.



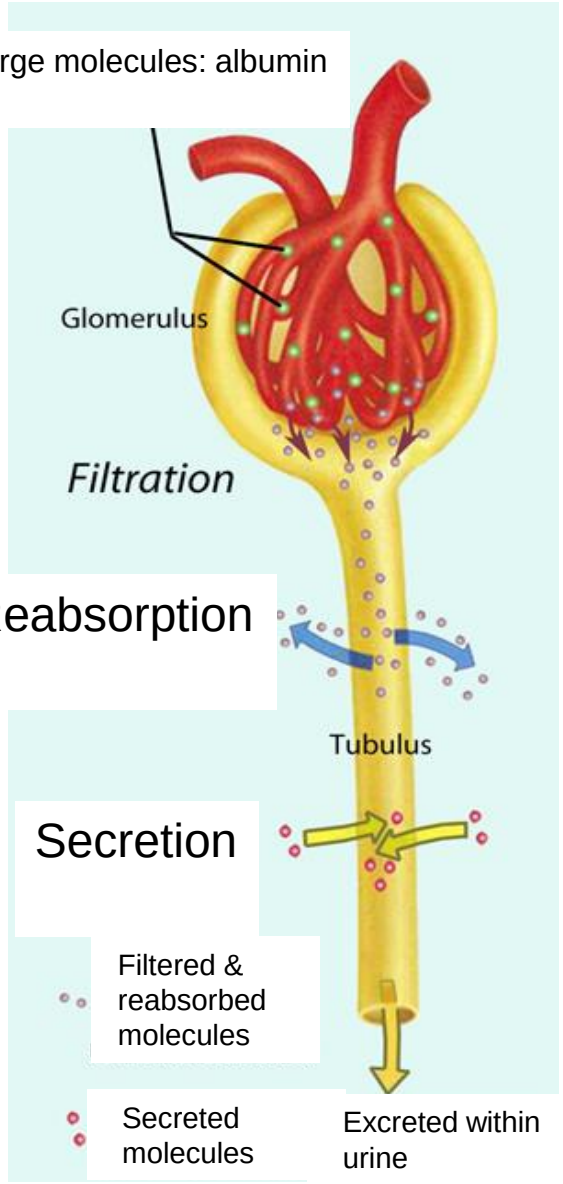
Every minute one liter of blood flows through the kidneys (adult)

Filter

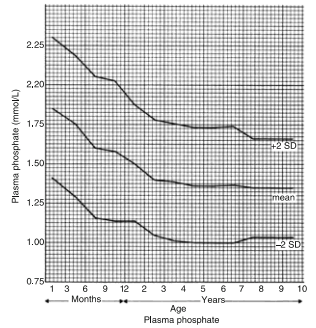
Pumps



Energy



- ✓ 2 million kidney units = nephrons; 1 mio per kidney
- ✓ Primary urine: 150-200 liter per day
  ca. 120 ml/min per 1.73m^2 = glomerular filtration rate (eGFR)
- ✓ „Cleans“ blood (metabolism)
- ✓ Balance of fluid, salt and minerals



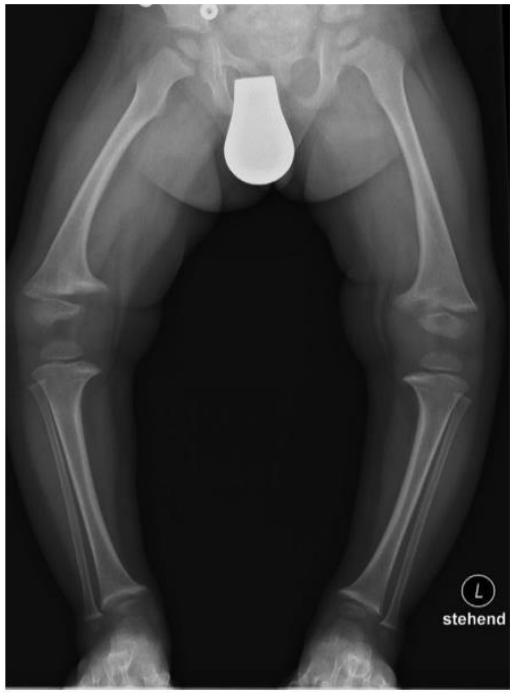
- ✓ Tubules: recovery from primary urine what is needed,
  e.g. water, salt, minerals, bicarbonate.....
- ✓ Secretion of bad things, e.g. acids
- ✓ Urine excretion: 0.2-3 liter depending on the amount of drinking and extrarenal losses (sweat, stool) of the body
- ✓ Synthesis: glucose, active vitamin D (calcitriol), erythropoietine, renin, klotho..

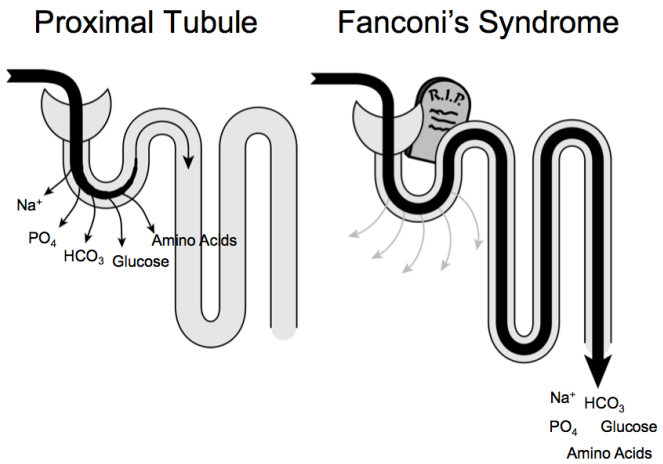
http://physiologie.cc/IX.1.htm

Holliday, Textbook: Pediatric Nephrology 1998
www.kidney.org/professionals/KDOQI/guidelines/

Bone disease in cystinosis

Hypophosphatemic rickets
(100%-15% of normal kidney function;
CKD stage 1-4)



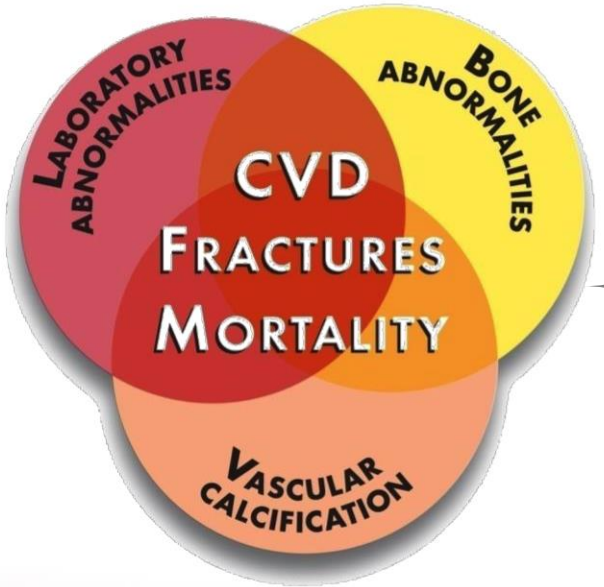


Low phosphate, acidosis.. =>

- Soft cartilage = Rickets
- Soft bone = Osteomalacia

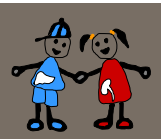
This happens despite normal glomerular kidney function (GFR)

Chronic kidney disease:
Mineral and bone disorder
(< 50% of kidney function; on dialysis, after transplantation; CKD stage 3-5D/T)



Hyperphosphatemia
High FGF23
Vitamin D deficiency
Hypocalcemia
High PTH
Acidosis
Inflammation
Sclerostin
„High bone turnover“
„Renal osteodystrophy“

CKD = chronic kidney disease



Cystinosis Metabolic Bone Disease (CMBD)

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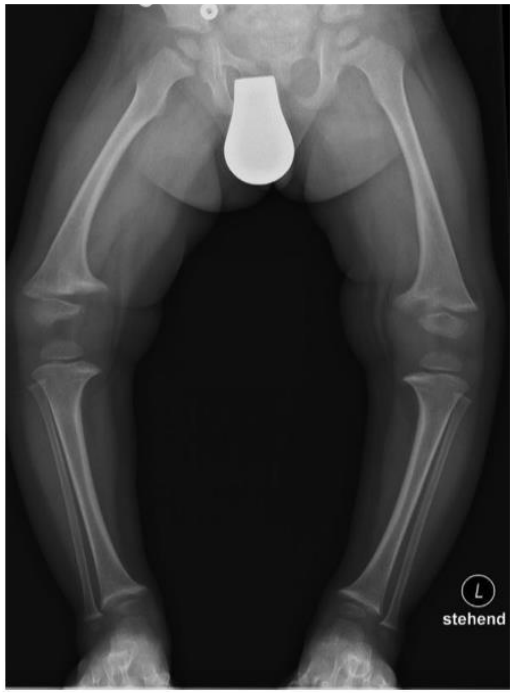

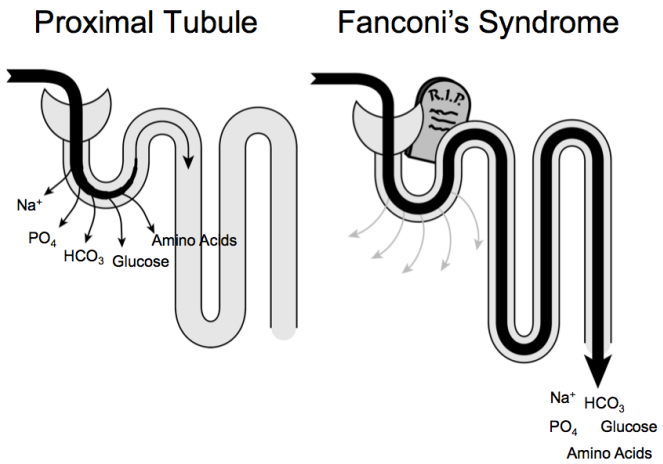

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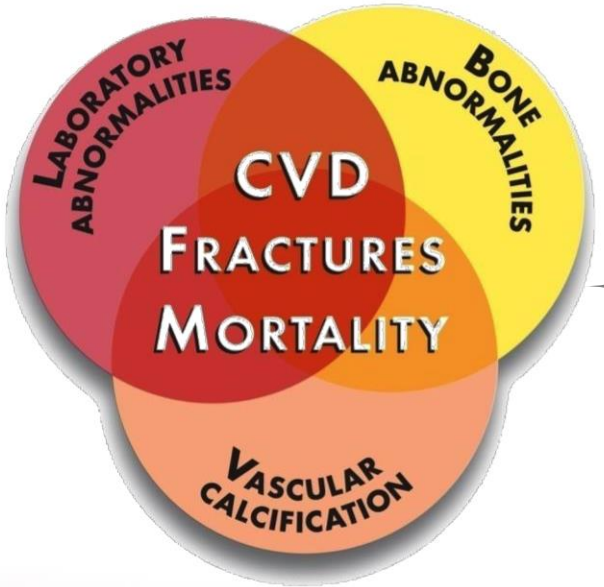

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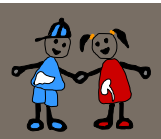


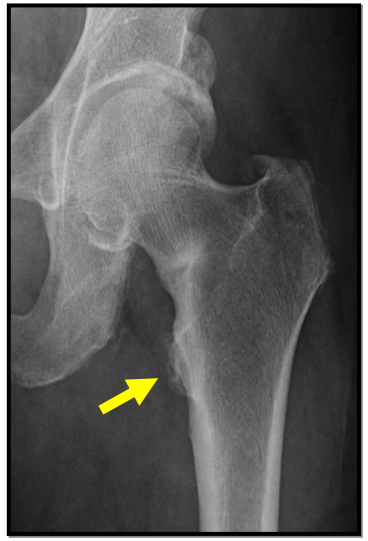
Clinical presentation

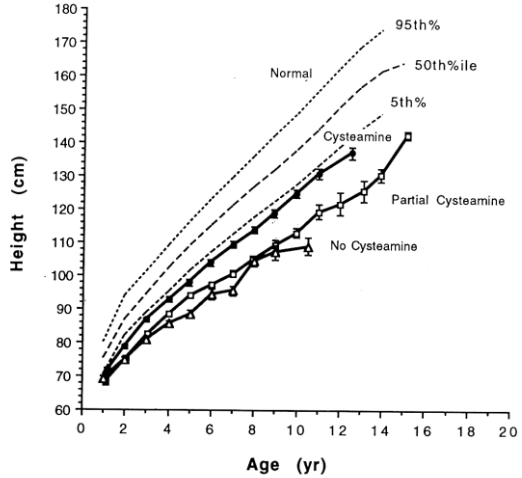
Cystinosis metabolic bone disease (CMBD)

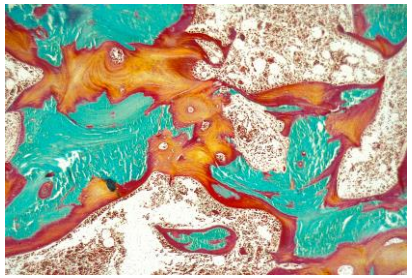
- Short stature
- Osteomalacia
- Bone deformities
- Bone pain
- Osteoporosis

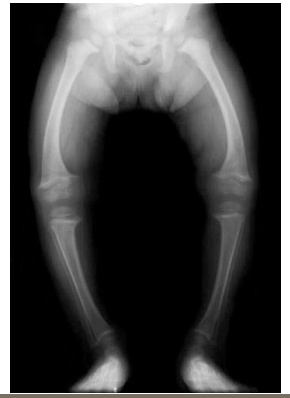
Children: - Rickets

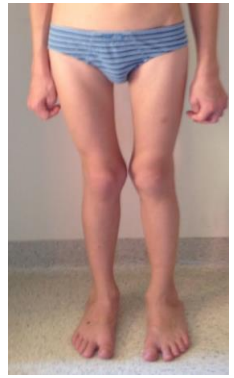
Adults:
- Long bone fractures
- Incidental vertebral fractures
- Scoliosis
- Low bone mass
- Cortical impairment





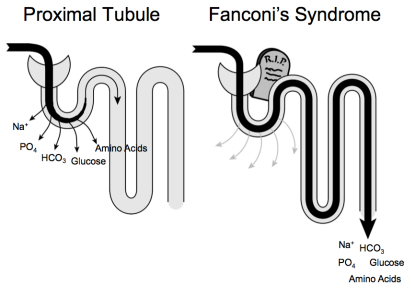






Pathophysiology

1- Renal Fanconi syndrome
resulting in rickets due to
- Hypophosphatemia
- Metabolic acidosis
- 1,25-D deficiency
- Hypocalcemia



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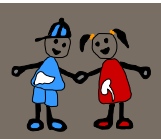
Hohenfellner K et al. J Inherit Metab Dis 2019



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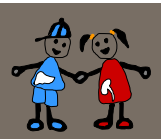

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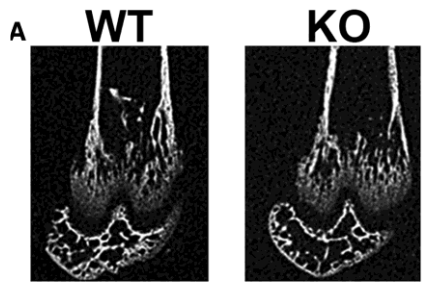
5- Intrinsic and treatment associated bone lesions
- Intrinsic osteoblast/ osteoclast defect due to *CTNS* mutation
- Cysteamine toxicity

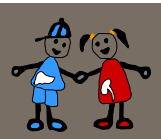
Table 4 Microarchitectural Parameters of Femurs from WT a

	1 Month	
Variable	WT	KO
BMD, mg HA/cm^3	189 ± 9	163 ± 8**
BV/TV, %	16.0 ± 0.1	12.7 ± 1.1**
Tb.N, 1/mm	4.50 ± 0.26	3.56 ± 0.42**
Tb.Th, µm	43.60 ± 0.55	41.00 ± 0.82***
Tb.Sp, µm	230 ± 10	300 ± 40**
Conn.D, 1/mm^3	293 ± 29.5	244 ± 27.7
SMI	1.86 ± 0.05	1.99 ± 0.14



Battafarano G et al. Am J Pathol 2019

Hohenfellner K et al. J Inherit Metab Dis 2019



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7- CKD-MBD post transplantation
- Glucocorticoid and CNI treatment
- Hypophosphatemia due to persistent Fanconi syndrome
- Mineral and bone disorders related to transplant dysfunction

Astrid Lindgreen rose in our garden

Cystinosis outcome in Germany and Austria 2016-2022

Growth and cognitive-motor abilities in children with cystinosis and CKD controls

Design: Prospective multicenter study

Setting: 12 hospital clinics in D and A

Patients:

54 children with nephropathic cystinosis

107 matched CKD controls (age, eGFR)

Outcome measures:

- Longitudinal growth
- Anthropometry (26 parameters)
- Musculo-skeletal health
- Bone marker panel
- Cognitive function

Miroslav Zvicnjack, PhD
Anthropometrist

Annika Ewert, M.D.
Pediatrician

Rika Kluck
PhD student

Sabine Wiedenhöft
Study nurse

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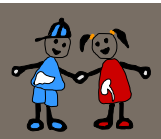
Patient characteristics and treatment at the time of evaluation

Characteristics	All patients			Patients pre-transplant			Patients post-transplant		
	NC (n=49)	Controls (n=80)	p value	NC (n=41)	Controls (n=44)	p value	NC (n=8)	Controls (n=36)	p value
Age (years)	11.4 (6.2-14.7)	10.3 (6.5-13.1)	0.24	10.0 (5.8-14.2)	10.0 (5.1-13.1)	0.64	**14.6 ± 2.2**	**10.3 ± 4.1**	**<0.01**
eGFR (mL/min/1.73 m²)	61 (39-96)	56 (41-77)	0.33	60 (25-105)	54 (30-76)	0.21	67 (58-75)	62 (44-86)	0.41
Phosphate, n (%)	**26 (56.5)**	**0 (0.0)**	**<0.01**	**26 (66.7)**	**0 (0.0)**	**<0.01**	0 (0.0)	0 (0.0)	n.a.
Potassium, n (%)	**35 (76.1)**	**0 (0.0)**	**<0.01**	**35 (89.7)**	**0 (0.0)**	**<0.01**	0 (0.0)	0 (0.0)	n.a.
Calcium, n (%)	**8 (17.4)**	**2 (2.5)**	**<0.01**	**8 (20.5)**	**0 (0.0)**	**<0.01**	0 (0.0)	2 (5.6)	0.70
Calcitriol, n (%)	17 (37.0)	24 (30.0)	0.42	17 (43.6)	19 (43.2)	0.97	0 (0.0)	5 (13.9)	0.39
Bicarbonate, n (%)	**32 (69.6)**	**32 (40.0)**	**<0.01**	**30 (76.9)**	**15 (34.1)**	**<0.01**	2 (25.0)	17 (47.2)	0.37
rhGH, n (%)	**27 (55.1)**	**7 (8.8)**	**<0.01**	**22 (53.7)**	**6 (13.6)**	**<0.01**	**5 (62.5)**	**1 (2.8)**	**<0.01**

Data are presented as mean±SD, median (IQR), or n (%). NC, nephropathic cystinosis; eGFR, estimated glomerular filtration rate; rhGH, recombinant human growth hormone; n.a., non applicable



Mineral metabolism in NC patients compared to controls

Characteristics	All patients			Patients pre-transplant			Patients post-transplant		
	NC (n=49)	Controls (n=80)	p value	NC (n=41)	Controls (n=44)	p value	NC (n=8)	Controls (n=36)	p value
Hypophosphatemia, n (%)	**12 (28.6)**	**8 (10.1)**	**0.01**	**12 (35.3)**	**4 (9.1)**	**0.01**	0 (0.0)	4 (11.4)	0.42
Hypocalcemia, n (%)	**19 (46.3)**	**18 (24.3)**	**0.02**	17 (51.5)	12 (30.8)	0.08	2 (25.0)	6 (17.1)	0.61
Acidosis, n (%)	18 (41.9)	20 (25.6)	0.07	**15 (42.9)**	**8 (18.6)**	**0.02**	3 (37.5)	12 (34.3)	0.87
Hypokalemia, n (%)	**11 (22.4)**	**1 (1.3)**	**<0.01**	**11 (26.8)**	**1 (2.3)**	**<0.01**	0 (0.0)	0 (0.0)	n.a.
iPTH below KDOQI target range, n (%)	**15 (38.5)**	**13 (18.6)**	**0.02**	12 (37.5)	8 (21.0)	0.12	3 (42.8)	5 (15.6)	0.11
VitD insufficiency, n (%)	11 (23.4)	28 (38.4)	0.09	**7 (17.9)**	**15 (40.5)**	**0.03**	4 (50.0)	13 (36.1)	0.47

Data are presented as n (%); NC, nephropathic cystinosis; iPTH, intact parathyroid hormone; KDOQI, Kidney Disease Outcome Initiative

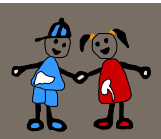
Skeletal findings in NC patients compared to CKD controls

Characteristics	All patients			Patients pre-transplant			Patients post-transplant		
	NC (n=49)	Controls (n=80)	p value	NC (n=41)	Controls (n=44)	p value	NC (n=8)	Controls (n=36)	p value
Height (z-score) -2.0 = lower limit of normal	**-1.9 ± 1.3**	**-0.8 ± 1.2**	**<0.01**	**-1.8 (-3.2 to -1.0)**	**-0.8 (-1.4-0.1)**	**<0.01**	-1.5 (-2.5 to -0.8)	-0.7 (-1.8 to -1.2)	1.00
Short stature, n (%)	**21 (42.9)**	**12 (15.0)**	**<0.01**	**18 (43.9)**	**4 (9.1)**	**<0.01**	3 (37.5)	8 (22.2)	0.37
Rickets, n (%)	**10 (20.4)**	**1 (1.3)**	**<0.01**	**9 (22.0)**	**0 (0.0)**	**<0.01**	1 (12.5)	1 (2.8)	0.24
Fractures, n (%)	3 (6.1)	3 (3.8)	0.55	3 (7.3)	2 (4.5)	0.59	0 (0.0)	1 (2.8)	0.33
Surgery, n (%)	**6 (12.2)**	**2 (2.5)**	**0.02**	5 (12.2)	1 (2.3)	0.08	1 (12.5)	1 (2.8)	0.24
Skeletal deformities, n (%)	**21 (42.9)**	**2 (2.5)**	**<0.01**	**18 (43.9)**	**0 (0.0)**	**<0.01**	**3 (37.5)**	**2 (5.6)**	**0.01**

- **NC associated with a 11-fold increased risk for development of short stature, bone deformities, and/or surgery** (OR 11.43, 95% CI 4.92-26.50, p<0.001)
- **rhGH treatment: Risk of short stature was reduced to 1/3** (OR 0.32, 95% CI 0.13-0.82, p<0.05)

Data are presented as mean±SD, median (IQR), or n (%)
NC, nephropathic cystinosis

Ewert et al. J Clin Endocrinol Metab 2020;105:1-15



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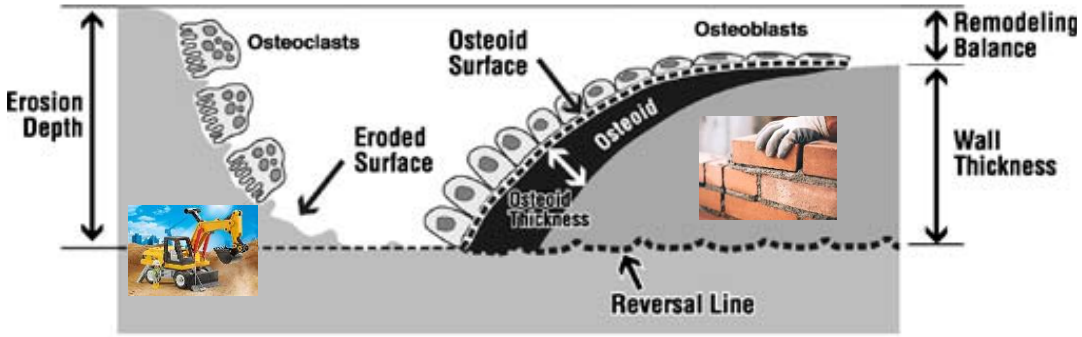
Bone modeling & remodeling

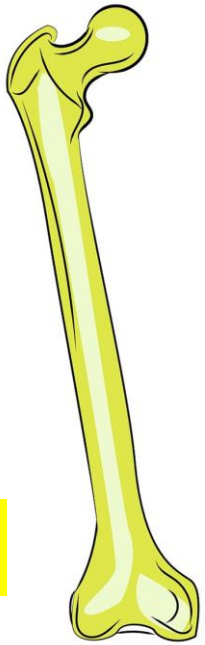


Sclerostin

OPG

RANKL

Osteoblasts



Osteoclasts

Bone alkaline phosphatase (BAP)

TRAP5b

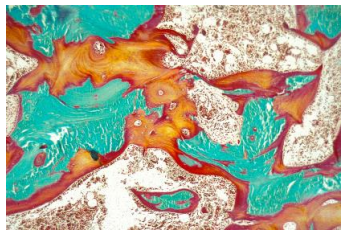
Inreseased: Rapid growth and rickets

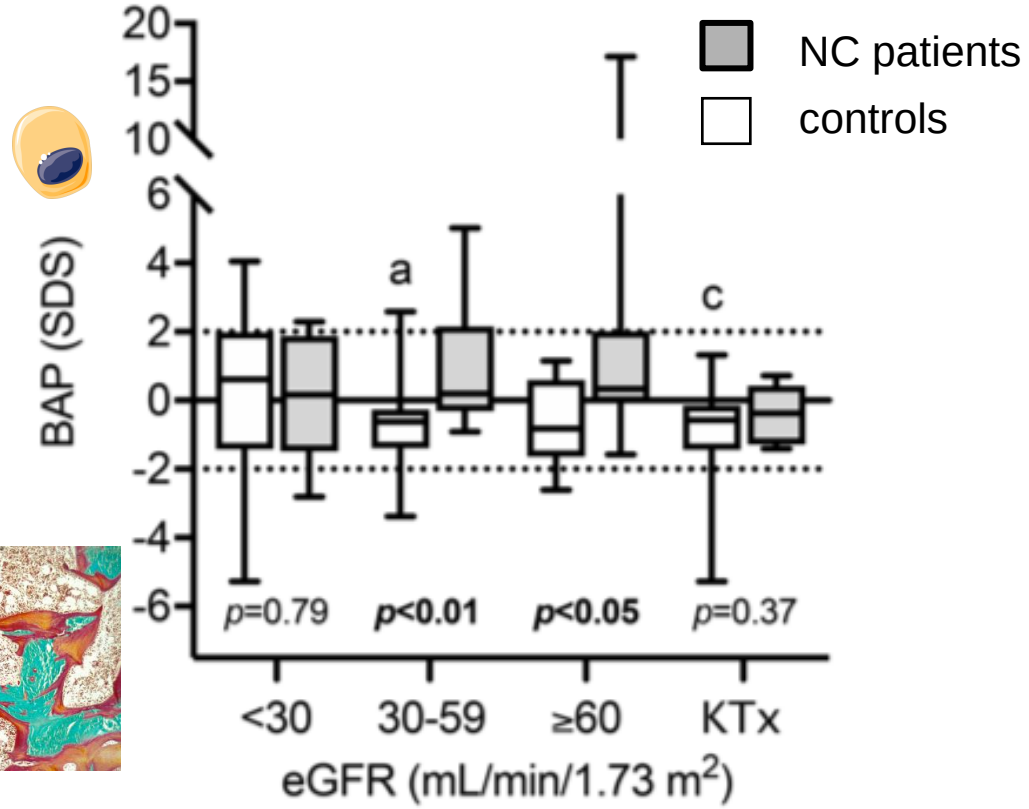
Inreseased: Bone resorption↑

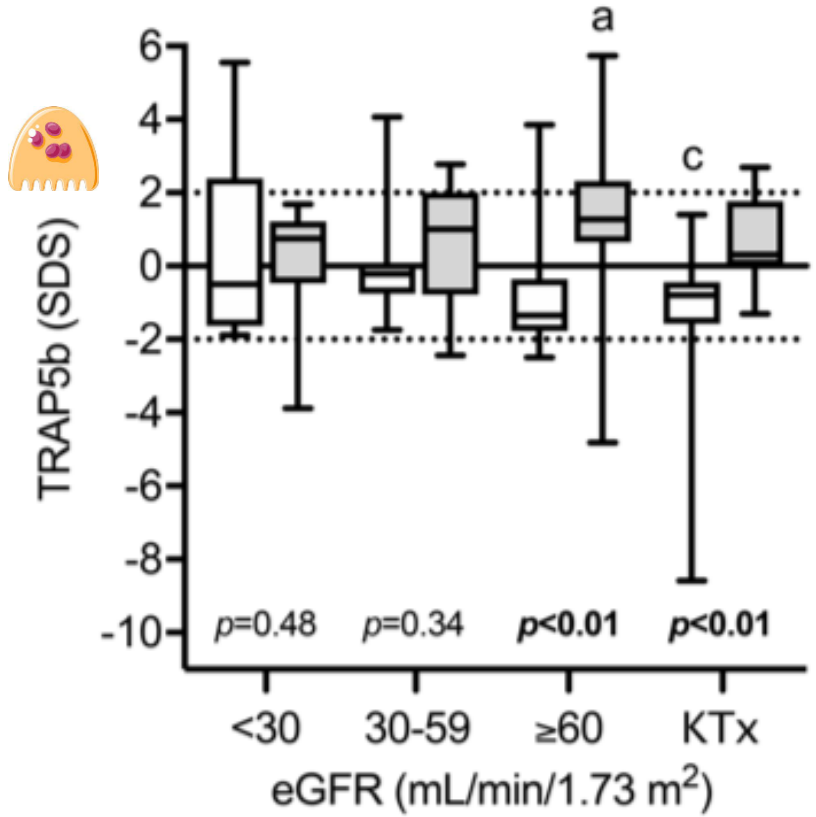
Adapted from Rauch F, Pediatr Nephrol 2006

- Osteoblast: https://www.wikiwand.com/de/Osteoblast
- Osteoclast: https://www.wikiwand.com/en/Osteoclast

Cystinosis patients show elevated bone alkaline phosphatase & TRAP5b levels suggesting impaired bone mineralization & increased osteoclast activity







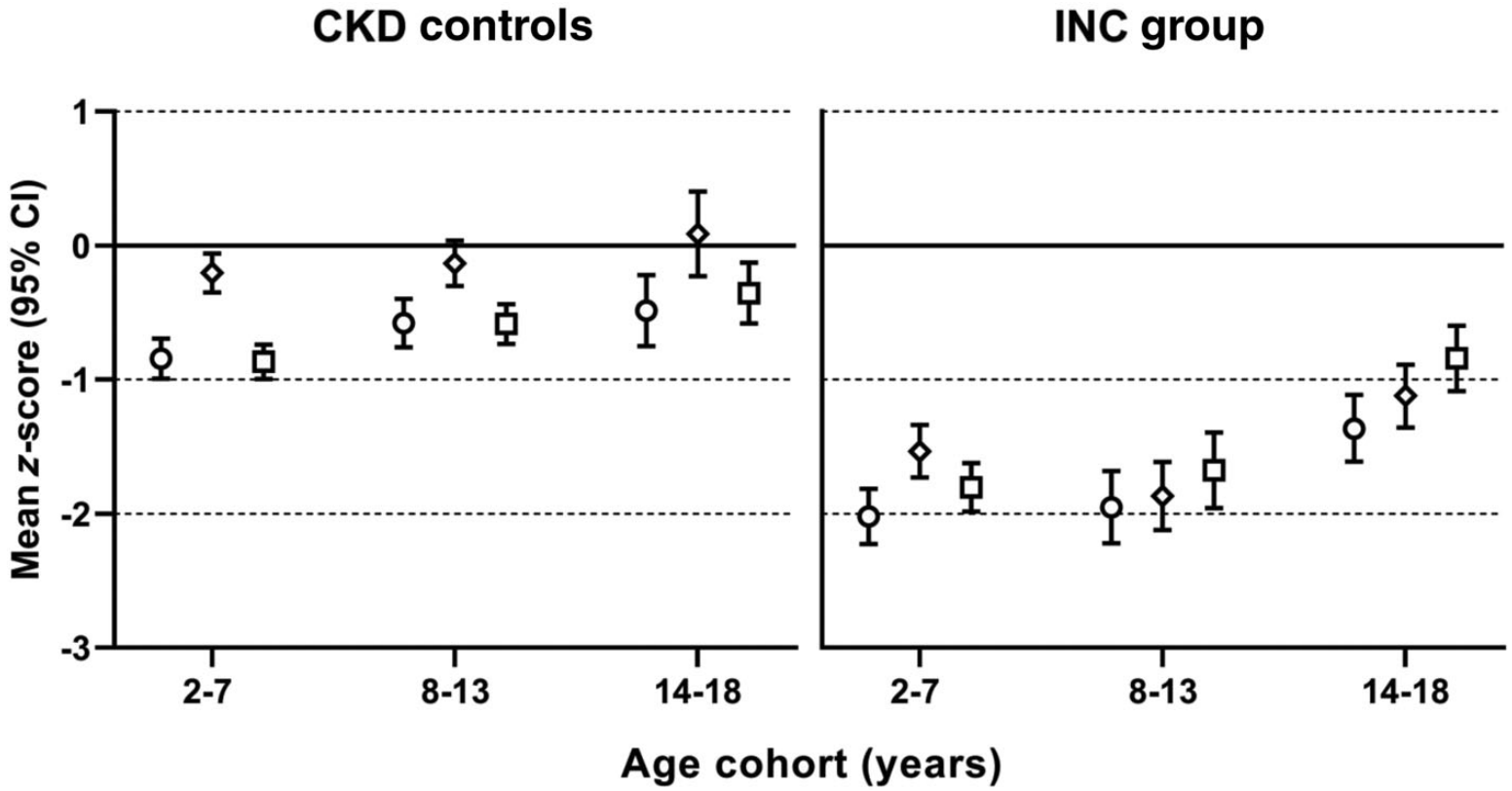
BAP was associated with phosphate dosage and diagnosis of NC (each $p<0.05$)

TRAP5b was associated with diagnosis of NC only ($p<0.05$)

KTX, kidney transplantation
a and c indicate p<0.05 and p<0.001 versus healthy children, respectively
… = upper and lower normal range

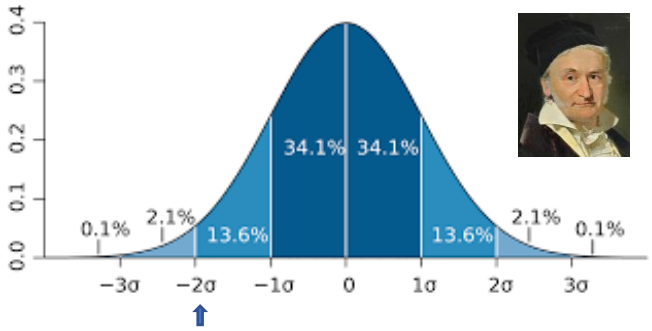
Ewert et al. J Clin Endocrinol Metab 2020;105:1-15

Height, sitting height and leg length in children with cystinosis compared to CKD controls



Height
Sitting height
Leg length

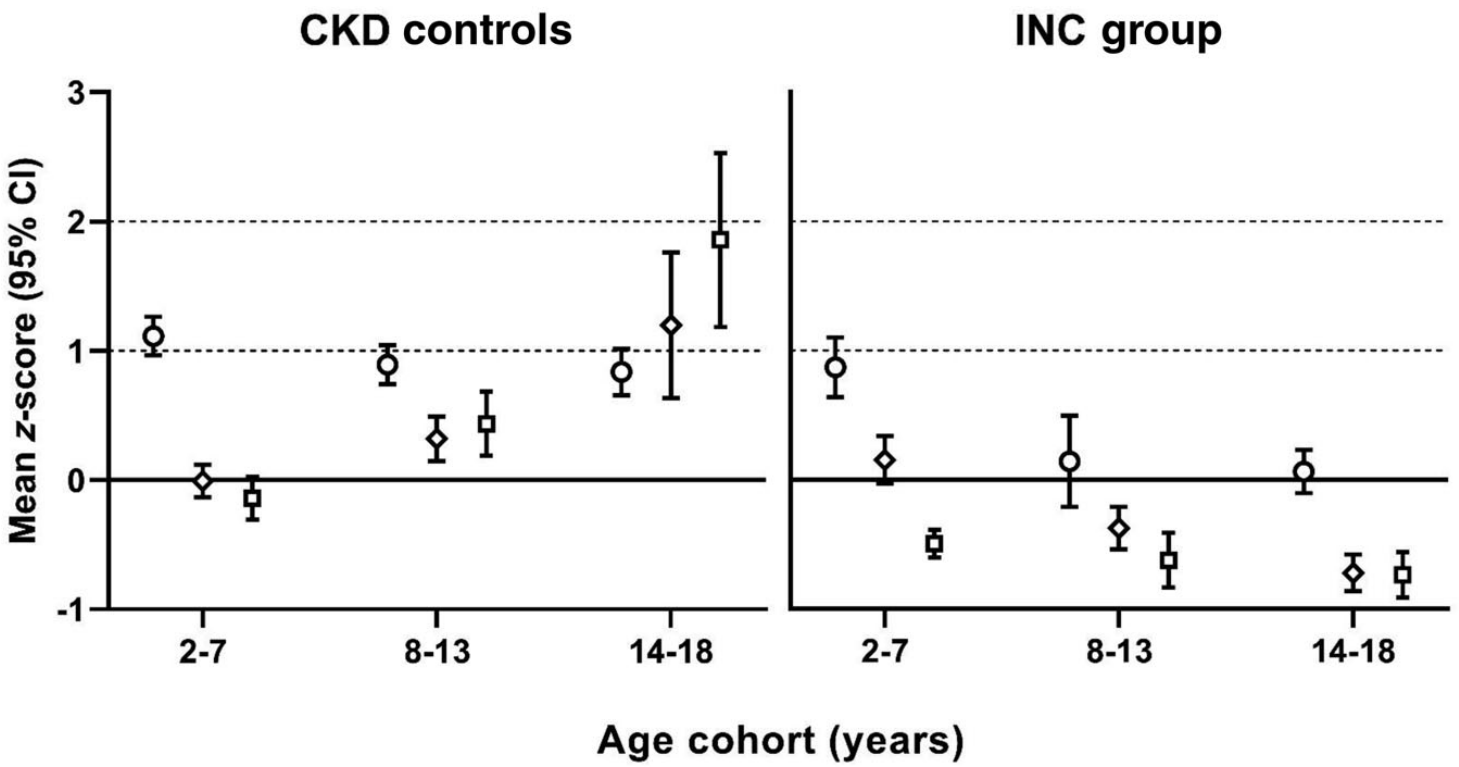
Gaussian or „normal“ distribution



2.2% of healthy children are below
– 2 standard deviations (z-score)

FIGURE 1 Height (circle), sitting height (rhombus) and leg length (square) *z*-scores in 43 INC patients and 49 CKD controls in the three age cohorts (2-7, 8-13, and 14-18 years) with CKD stages 1 to 5. Error bars represent 95% confidence intervals

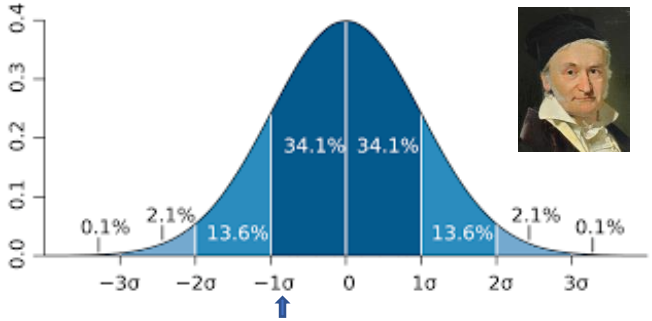
Sitting height index, body mass index and upper arm fat area in children with cystinosis compared to CKD controls



SHI: Ratio between sitting height (trunk) and body height

- Sitting height index
- BMI
- Upper arm fat area

Gaussian or „normal“ distribution



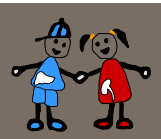
15.9% of healthy children are below – 1 standard deviation (z-score)

Birth parameters, parental height and age at menarche in children with cystinosis compared to CKD controls

TABLE 2 Clinical and biochemical characteristics of children with infantile nephropathic cystinosis with CKD stages 1-5 and CKD controls

	CKD controls			INC			
Non-repeated measurements[a]	**Mean ± SD/ median (IQR)**	**Min. – Max.**	**No. of patients/ measurements**	**Mean (±SD)/ median (IQR)**	**Min. – Max.**	**No. of patients/ measurements**	***P* value**
Birth length, cm	51.0 (49.0-54.0)	37.0 – 56.0	39 of 49	52.0 (50.0-53.3)	46.0 – 56.0	30 of 43	.21
Genetic target height, z-score	0.33 (±0.90)	−1.50 – 2.45	48 of 49	−0.14 (±0.86)	−2.28 – 1.69	40 of 43	.01
Mother height, cm	169.0 (164.25-173.75)	153.0 – 183.0	48 of 49	163.0 (162.0-170.0)	150.0 – 181.0	41 of 43	.03
Father height, cm	182.2 (±7.6)	169.0 – 199.0	48 of 49	179.0 (±6.39)	163.0 – 190.0	40 of 43	.04
Menarche, age	12.22 (±1.23)	10.94 – 13.75	5 of 16	13.67 (±1.01)	12.04 – 15.01	7 of 19	.049

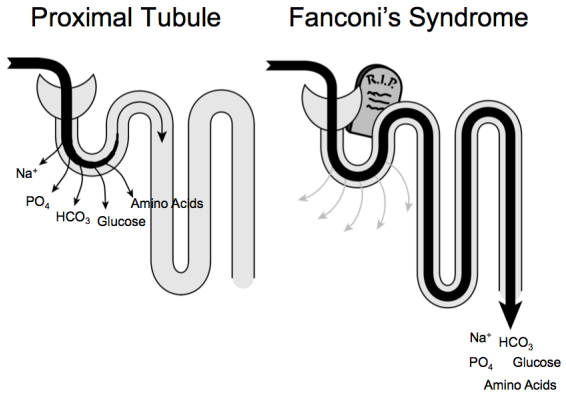
=> Menarche is delayed by approximately 1.4 years in female cystinosis patients compared to their CKD peers

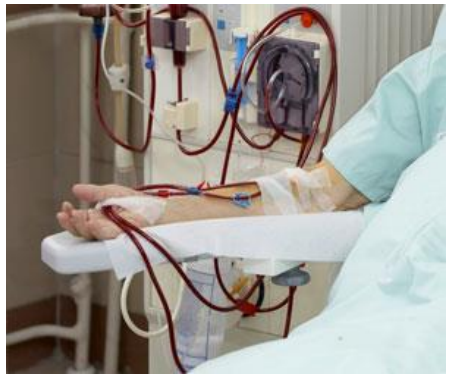


Another Astrid Lindgreen rose in our garden

What are the 10 most important measures for healthy bone in cystinosis?

- Early diagnosis
- Early start of cysteamine
- Good adhearance to cysteamine treatment
- Regular check of cystine levels (1-2 per year)
- Cysteamine treatment
- Cysteamine treatment
- Physical activity
- Adequate nutrition
- Substitution of losses, e.g. phosphate, bicarbonate,..
- Vitamin D……..





Management of CMBD: Fanconi syndrome

- ✓ **Free access to water and toilet** (up-to 8 l/day)
- ✓ **Nutrition:** ≥ 100% of the amounts recommended in healthy children, e.g. by nasogastral tube & gastrostomy (PEG)
- ✓ Advice by a **dietician**: Including intake of **calories, protein, calcium** (dairy products), **phosphate** (dairy products, cereals, meat), e.g. no appetitie in case of many sweet drinks

Table 7 Summary of SDI (suggested dietary intake) for calcium and phosphate in children with CKD2-5D

Age (years)	SDI calcium (mg)	SDI phosphate (mg)
0–< 4 months	220	120
4–< 12 months	330–540	275–420
1–3 years	450–700	250–500
4–10 years	700–1000	440–800
11–17 years	900–1300	640–1250

SDI = suggested dietary intake in healthy children

Emma F et al. NDT 2012; Hohenfellner K et al. J Inherit Metab Dis 2019; McAlister et al. Pediatr Nephrol 2021

Management of CMBD: Fanconi syndrome

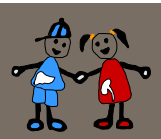
- ✓ **Supplementation of electrolyte losses**
  - **Salty food & sodium chloride** (2-4 mmol/kg per day)
    - Target: serum Na & Cl in the normal range (vomiting!)
  - **Potassium** (2-6 mmol/kg per day) QID
    - Target: serum K > 3 mmol/L
- ✓ **Severe polyuria: Indomethacin:** 1-3 mg/kg per day TID

SDI = suggested dietary intake in healthy children

Emma F et al. NDT 2012; Hohenfellner K et al. J Inherit Metab Dis 2019; McAlister et al. Pediatr Nephrol 2021

Management of CMBD

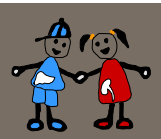
Treatment	Dosing
Phosphate	▪ Starting dose of 30–40 mg/kg/day based on elemental phosphorus in 3–5 doses equally spaced throughout the day ▪ Treatment needs to be individualized in order to control rickets and a wider range of 20–80 mg/kg/day may be used. Minimal effective dosage should be used ▪ Dosage should be adjusted to the stage of CKD
Citrate/bicarbonate	▪ Treat acidosis with alkali (citrate or bicarbonate) administered 3–4 times daily ▪ Aim to return bicarbonate levels to normal levels (22–25 mEq/L); levels >20 mEq/L may not be achieved in all patients



Management of CMBD

Treatment	Dosing
Calcium/active and native vitamin D	▪ Starting dose of calcitriol or alfacalcidol 0.1–0.75 µg depending on patient size and severity of rickets ▪ Maintain at lowest possible dose to successfully treat rickets and keep PTH in the CKD stage dependent target range (see below) ▪ Supplementation with native vitamin D (e.g., cholecalciferol) if 25 OH vitamin D levels are reduced ▪ Oral calcium supplements in case of persistent hypocalcemia based on albumin corrected calcium levels

Rationale for active vitamin D: To counter calcitriol deficiency, prevent secondary hyperparathyroidism, and increase phosphate reabsorption from the gut



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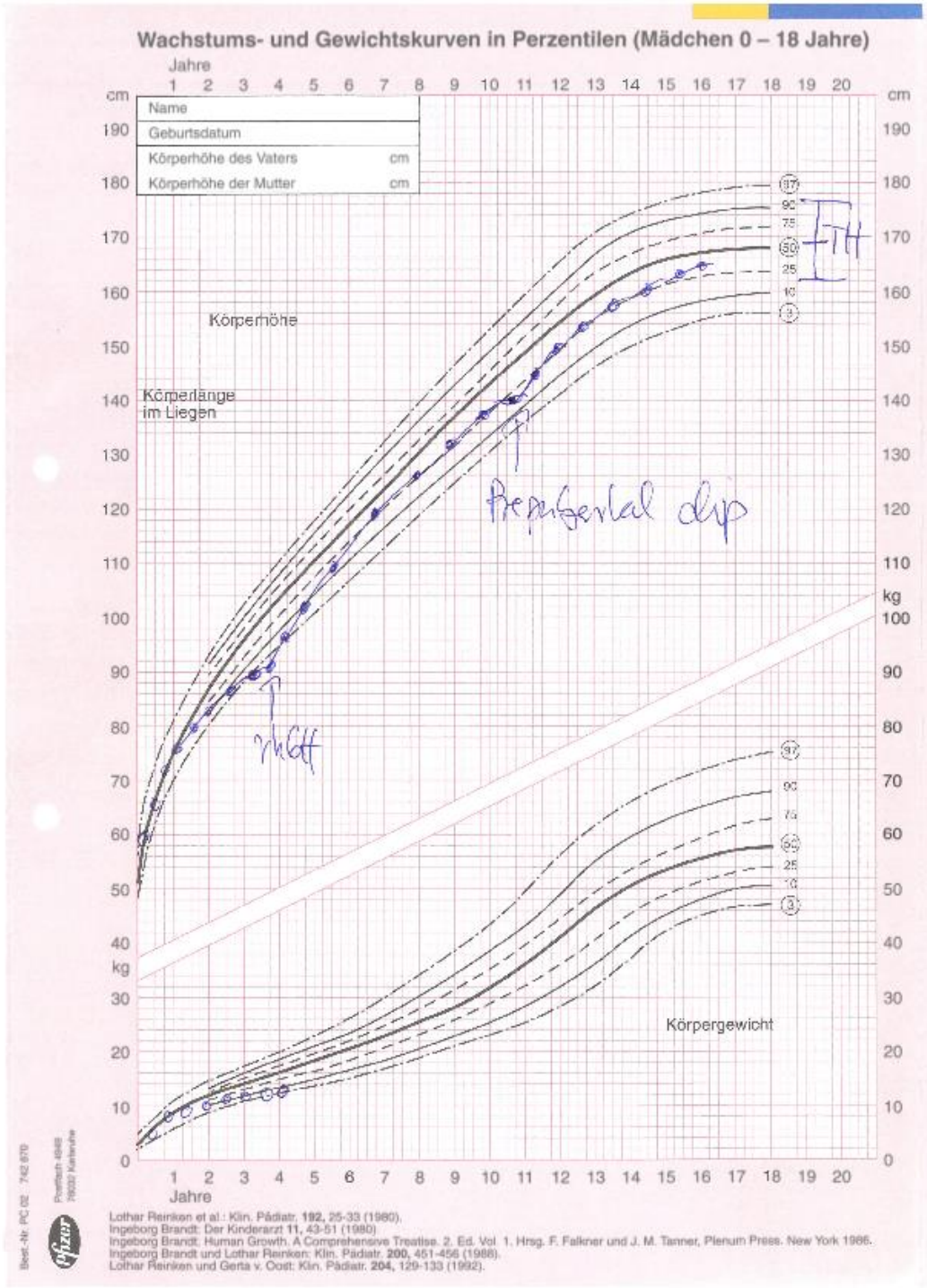
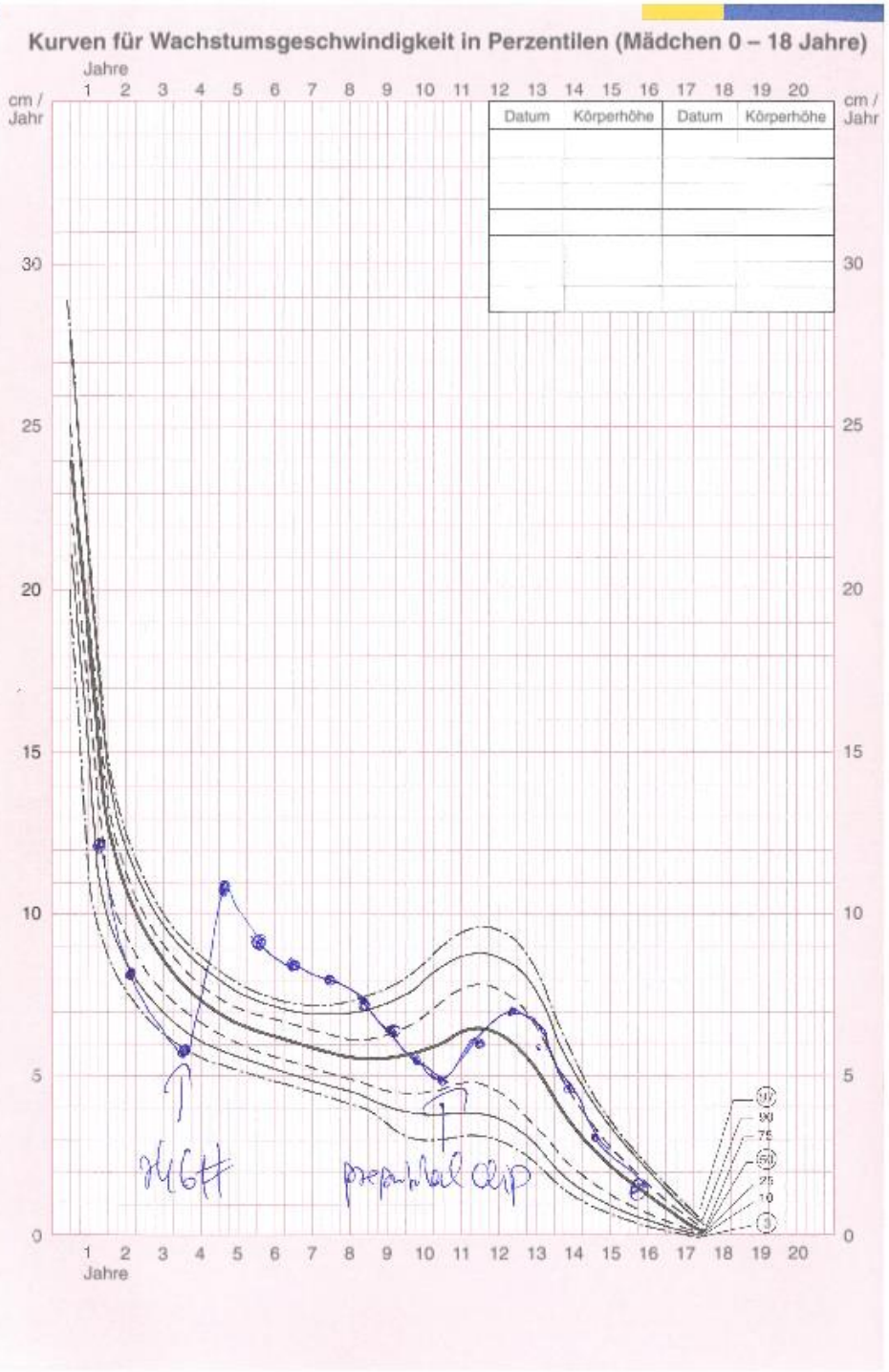




Clinical Practice Recommendations for treatment with growth hormone (GH) in children with chronic kidney disease (CKD)

Indications for GH treatment

Recommendations:

In children who have received a **kidney transplant** and fulfill the above growth criteria we recommend GH therapy **one year post-transplant**, if spontaneous catch-up growth does not occur and **steroid-free immunosuppressio**n is not a feasible option.

grade B, moderate recommendation

Management of CMBD

Treatment	Dosing
Sex hormone replacement therapy	▪ Per pediatric endocrinologist, for *pubertas tarda* and hypergonadotropic hypogonadism ▪ Testosterone patch or intramuscular
L-Thyroxine	▪ In case of hypothyroidism to normalize free T_4 and TSH
Cysteamine	▪ Ensure optimal dose adjustment and control of cystinosis

CKD, chronic kidney disease; GH, growth hormone; HbA1c, glycated hemoglobin; PTH, parathyroid hormone; TSH, thyroid stimulating hormone

Orthopedic management

- Check for leg bowing and scoliosis by physical examination and/or radiographs.
- DXA studies are not recommended, since the results are influenced by bone size and body height, do not distinguish between a mineralization defect (osteomalacia) and loss of bone tissue (osteoporosis), and have poor predictive value for fractures.
- Orthopedic surgery (temporary hemiepiphysiodesis or osteotomy) may be required to correct persistent leg bowing.
  Point of no return = mechanical axis deviation Zone 2 or greater.
- Surgery during puberty is preferred, with metabolic control optimized prior to surgery to prevent recurrence of leg bowing.
- Active vitamin D may be paused during prolonged immobilization to prevent hypercalcemia.

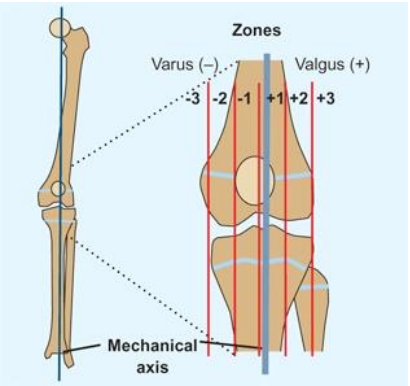
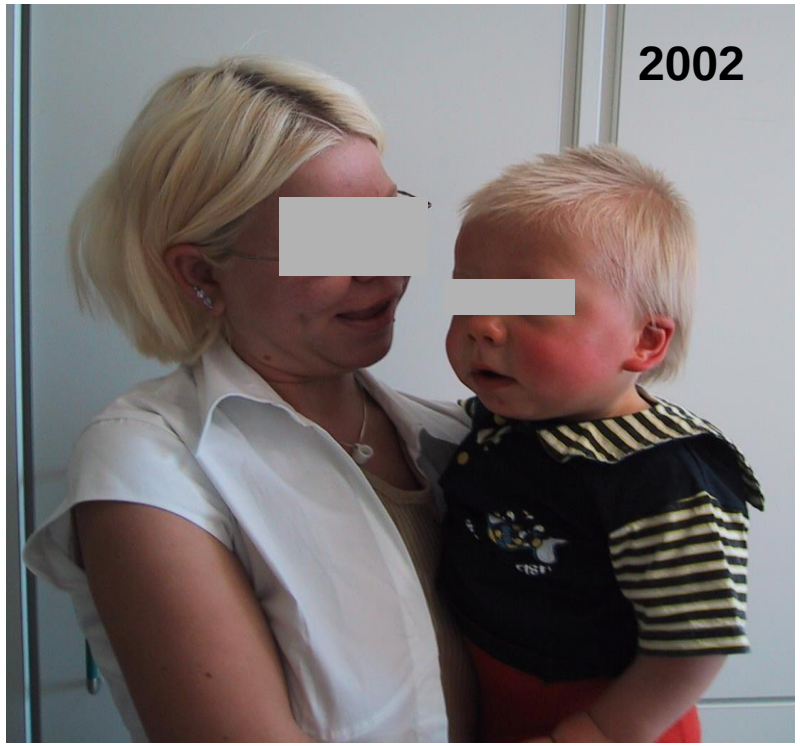


Image: https://musculoskeletalkey.com/lower-limb-4/

Cystinosis - CMBD - outcome in 2002 versus 2022

History: 2002



Age 23 yrs., hemodialysis,
start of cysteamine treatment at 11 yrs.
height 148 cm, osteotomies

Nowadays: 2022

Age 8 months
1st symptoms

Age 29, eGFR 19 ml/min/1.73m^2, 174 cm, straight legs
Master of business administration
Family planing => sperm cryoconservation✓

Medication: fluids 6l/day, adequate nutrition, bicarbonate, cysteamine (p.o./eye drops), native and active vitamin D

There is still room for improvement!

Thank you for your attention!

Medizinische Hochschule Hannover