Hypophosphatemic rickets:
growth and body proportions in a group of Czech patients conventionally treated

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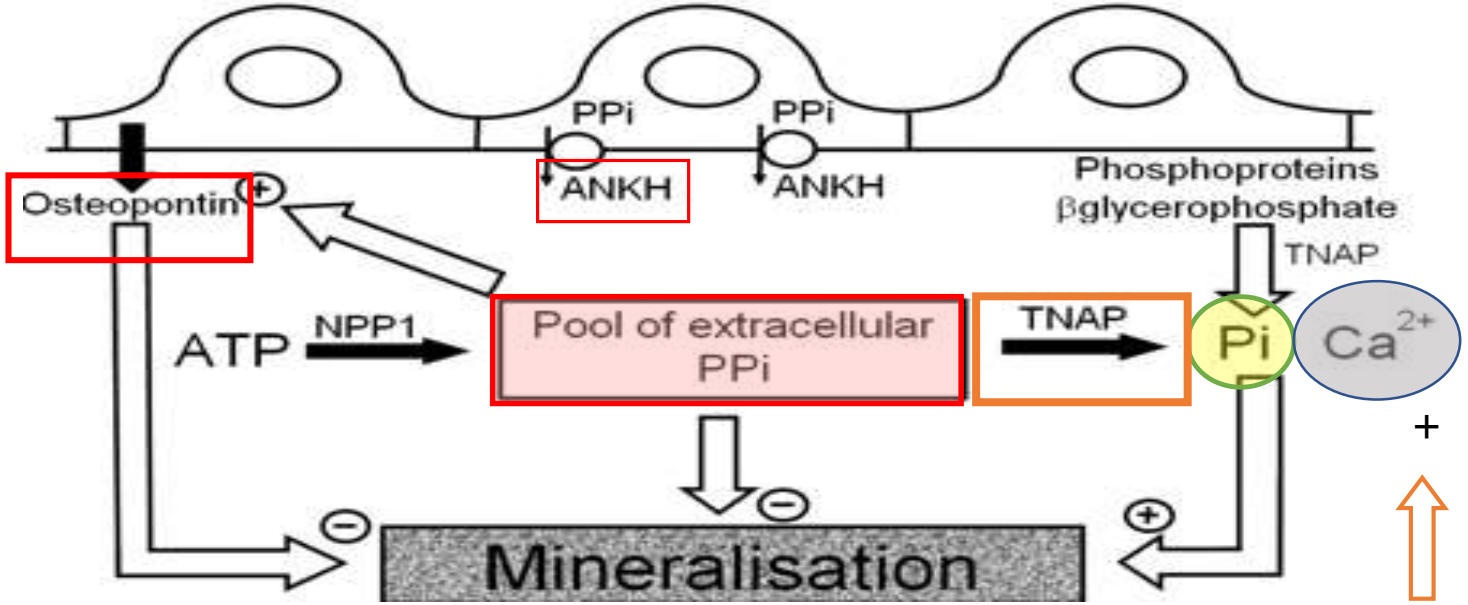
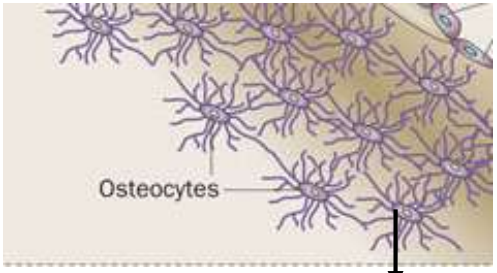
Introduction

- **Hypophosphatemic rickets** belong to rare diseases. In contrast to rickets caused by vitamin D deficiency, it is characterized by hypophosphatemia and normal serum levels of calcium.
- Characteristic clinical features include slow growth, bone pain and bone deformities.
- This group of diseases is caused by mutations in various genes involved in regulating renal phosphate reabsorption (*PHEX*, *FGF23*, *DMP1*, *ENPP1*).





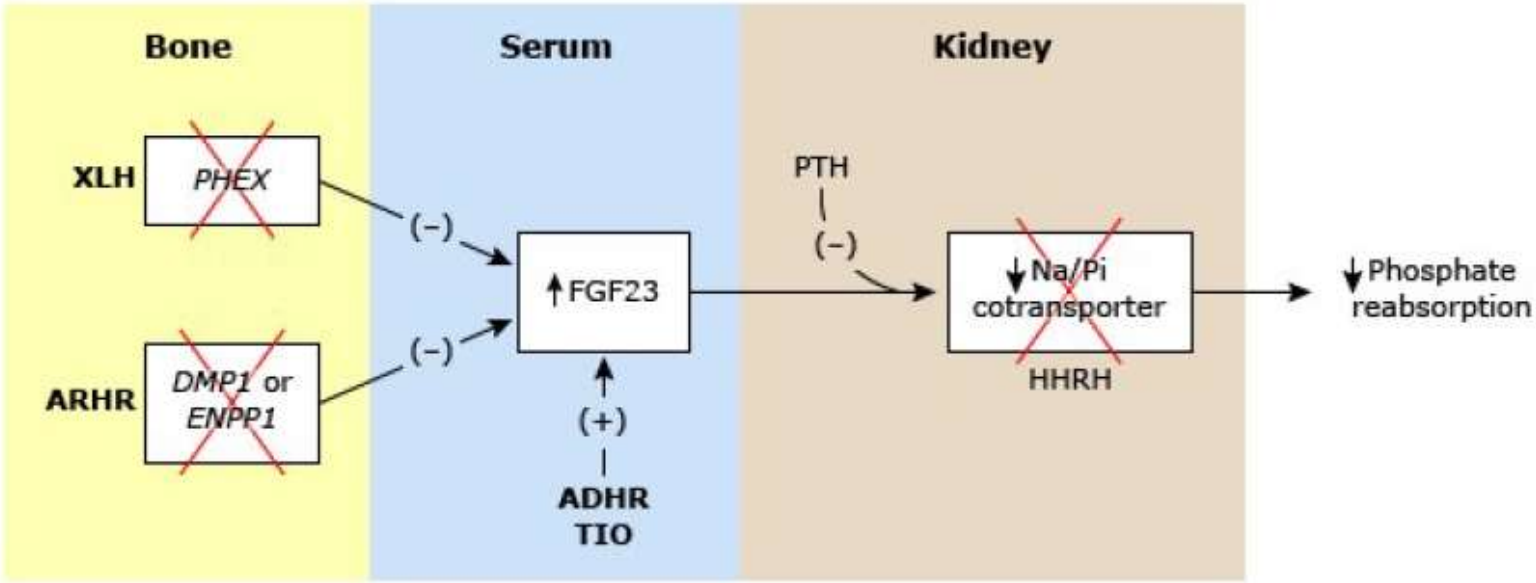
PTH 1,25(OH)2D3

PHEX
DMP1

FGF23

Phosphaturic factor

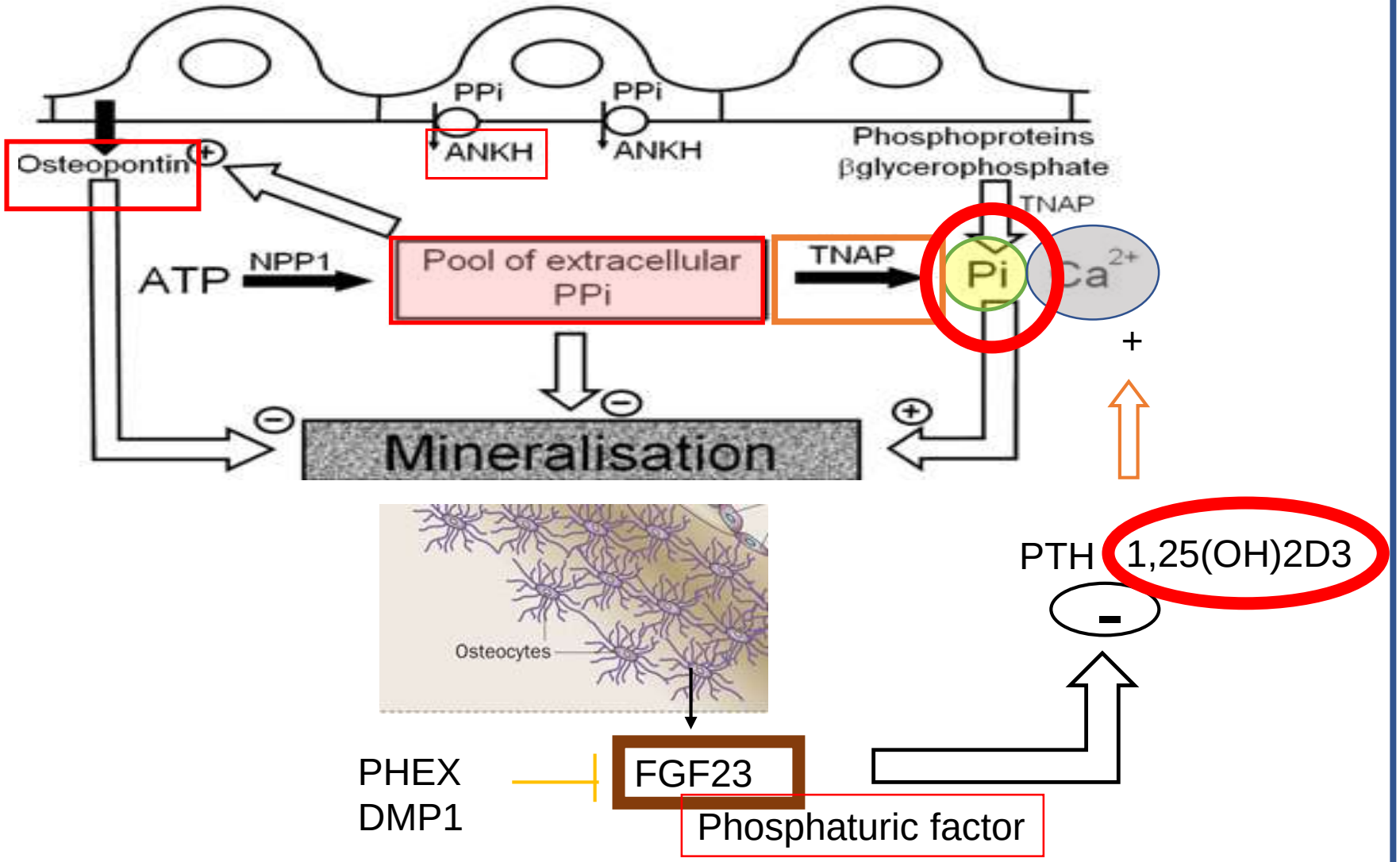
Pathways of renal phosphate wasting in hereditary hypophosphatemic rickets and tumor-induced osteomalacia

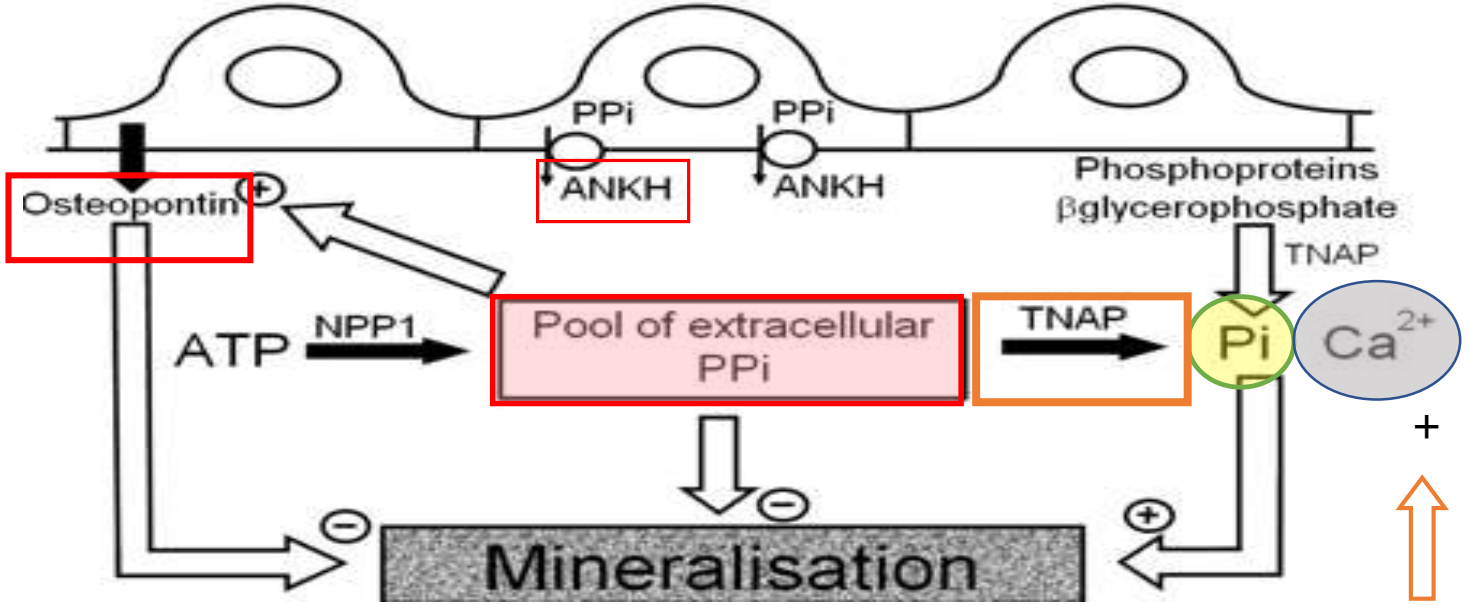


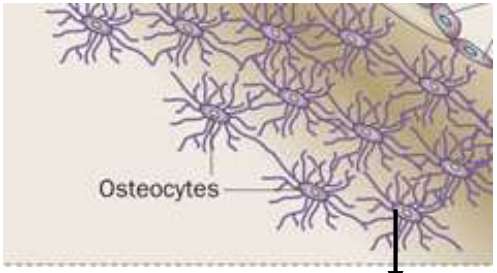
Levels of FGF23 are increased by inactivating mutations in *PHEX* (as in XLH) or *DMP1* (as in ARHR), by activating mutations in FGF23 (as in ADHR), or by tumor production of FGF23 (as in TIO). Each of these disorders leads to excessive activity of FGF23, which suppresses the Na/Pi cotransporter and causes renal phosphate-wasting. In HHRH the renal phosphate-wasting is caused by a mutation in the Na/Pi cotransporter itself.

Introduction

- Hypophosphatemic rickets is caused by mutations in various genes involved in regulating renal phosphate reabsorption (***PHEX***, *FGF23*, *DMP1*, *ENPP1*). The X-linked form is most common.
- For more than 30 years, **treatment** has consisted of the oral administration of phosphate and calcitriol. Contemporary fast technological development led to better understanding of the processes of bone mineralization and to development of new therapy.


PPi
PPi
ANKH
ANKH
Osteopontin
Phosphoproteins
βglycerophosphate
TNAP
ATP
NPP1
Pool of extracellular PPi
TNAP
Pi
Ca2+
+
Mineralisation
Osteocytes
PTH
1,25(OH)2D3
-
PHEX
DMP1
FGF23
Phosphaturic factor





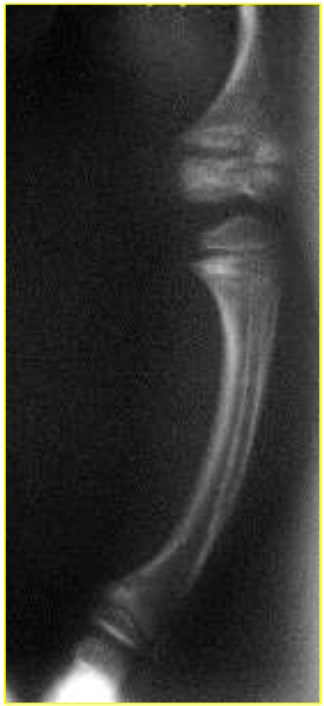
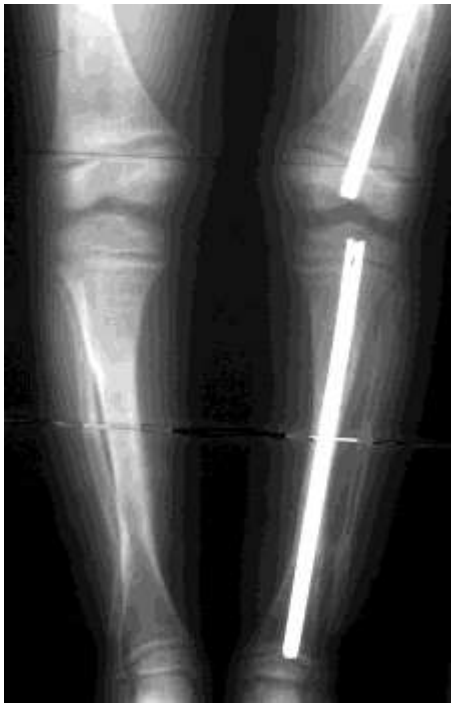
PTH 1,25(OH)2D3

PHEX
DMP1

FGF23

Phosphaturic factor

Burosumab


The aim of our study was to evaluate the growth of body height and individual body segments of Czech patients with hypophosphatemic rickets treated by conventional methods (oral administration of phosphate and calcitriol).

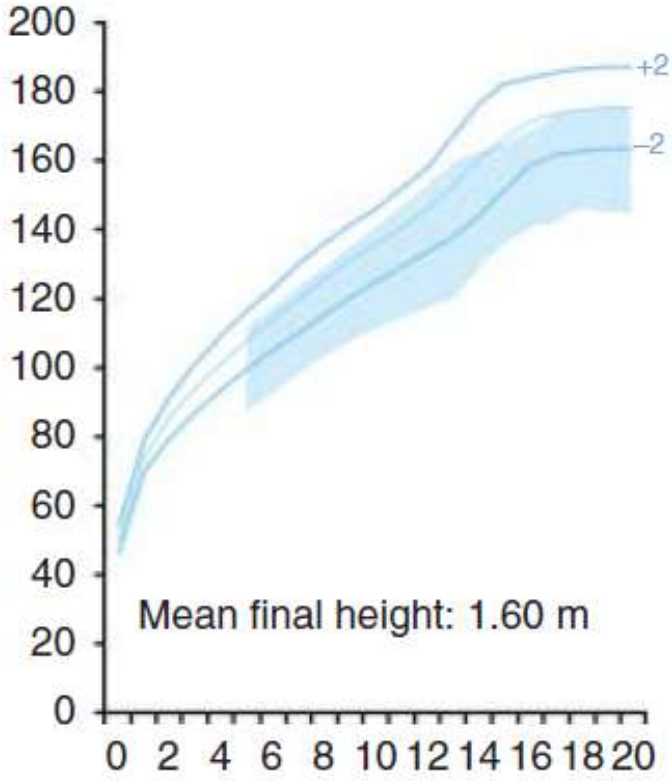
Methods

- We evaluated available anthropometric parameters in a group of Czech patients born 1940 – 2007 and examined during 1988 – 2018 in Ambulant centre for defects of locomotor apparatus or in University Hospital Motol.
- **29 patients** (20 women, 9 men) with clinical-radiological diagnosis **hypophosphatemic rickets**
- In **20 patients** the final height is known, **15** patients were longitudinally followed up and treated (phosphates, vitamin D3) during the growth period. 14 patients underwent surgery.
- Body height, weight, BMI, sitting height and subischial leg length were compared to norm by means of SD score.

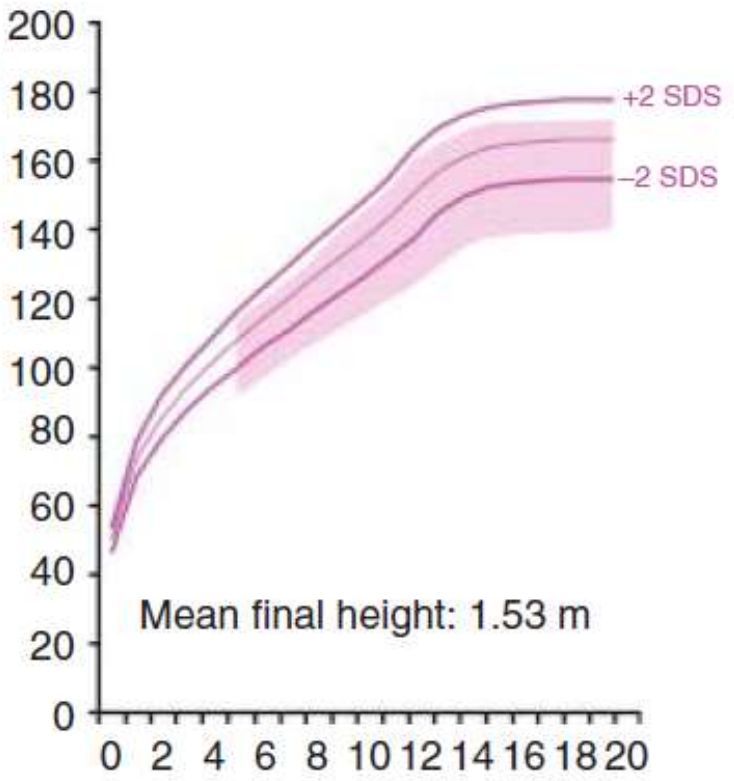
Results
Final height

- Final height of Czech patients differs significantly from the norm (-3,2 SD). Males achieved on average **155.7** +/- 10 cm and females **148.1**+/- 9.7 cm, i.e. -3.5 SD and -3 SD, resp.
- The difference between males and females SDS was not statistically significant.
- Final height of patients born before 1980 was **-3.7** +/- 1.5 SD, after 1980 **-2.71** +/- 1.4 SD (n.s.)

Comparison with available foreign data *Linglart 2014*



Our group **155.7** +/- 10 cm
Ns.

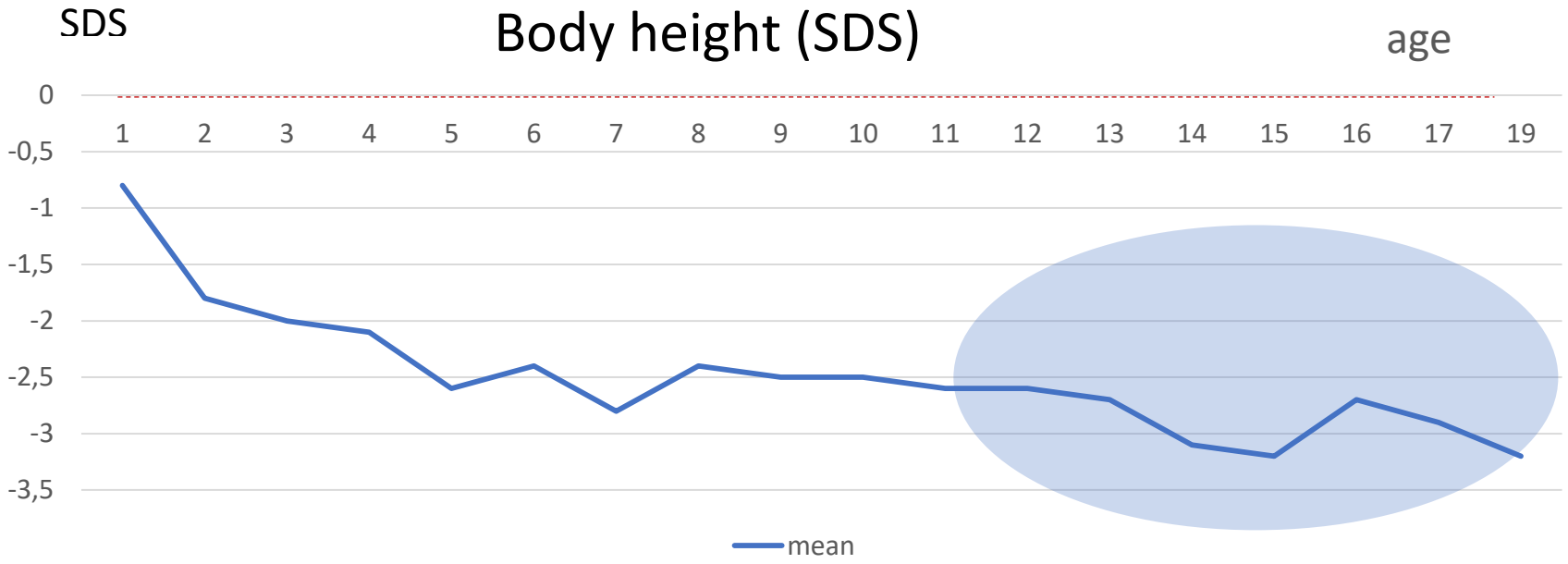


Our group **148.2** +/- 9.7 cm
P<0.05

In our group (examined mostly in orthopaedic ambulance) the patients have more severe course of the disease required surgical treatment and were born earlier.

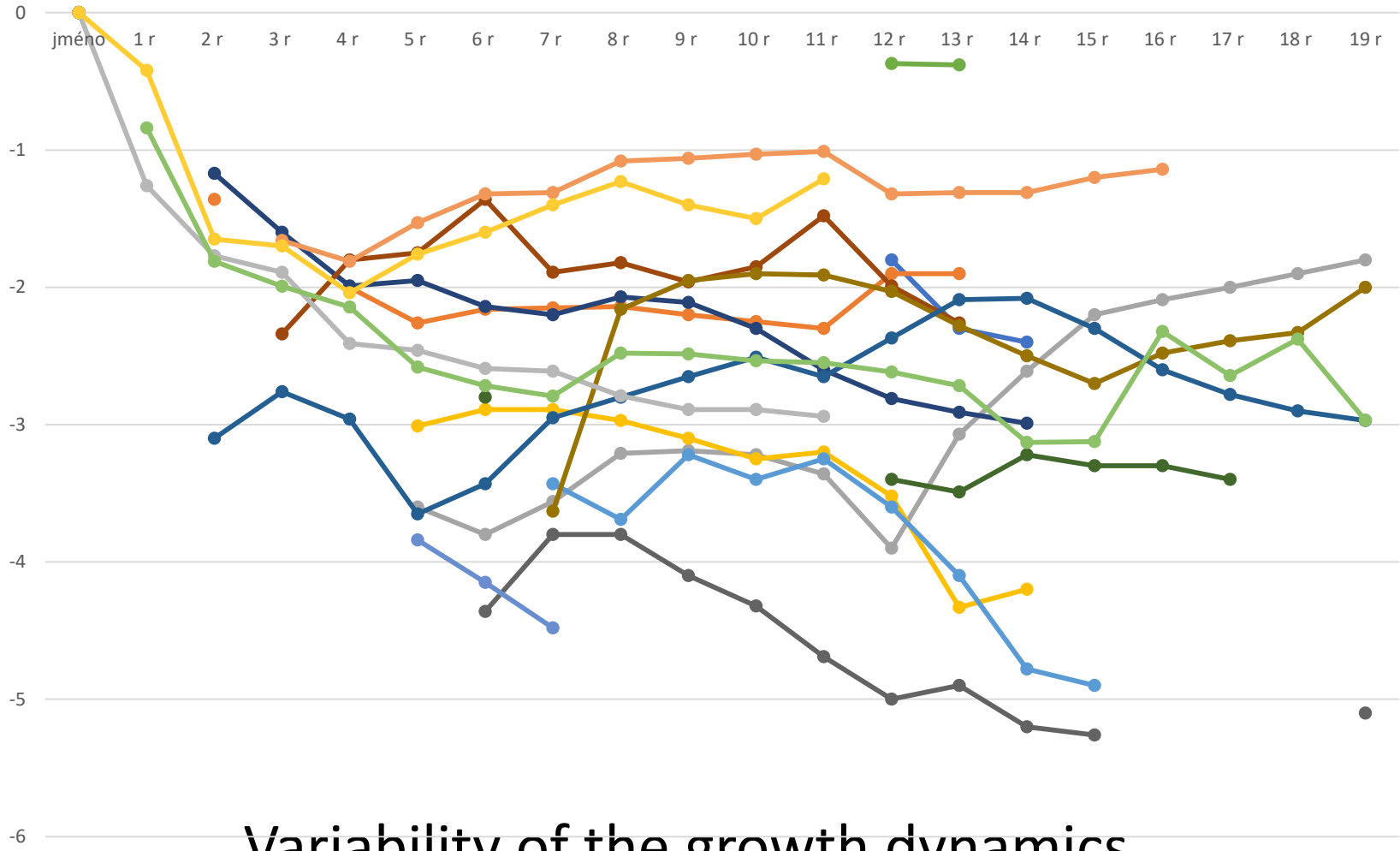
Results

Development of body height of 15 longitudinally followed up patients with hypophosphatemic rickets.



Growth dynamics is in compliance with Linglart´s study. As expected, the substantial growth retardation occurred before 5 years of age. Further worsening of growth dynamics was observed in puberty, however the variability during puberty was considerable.

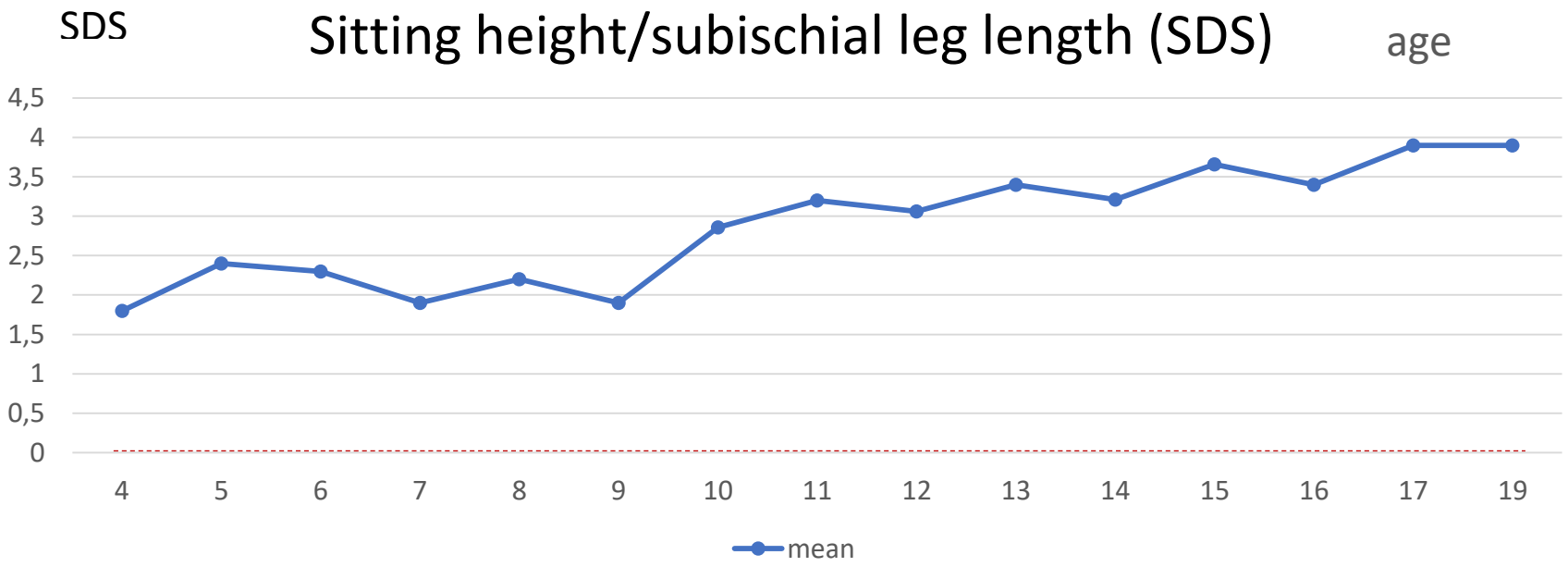
Growth of the Czech patients with hypophosphatemic rickets



Variability of the growth dynamics

Results

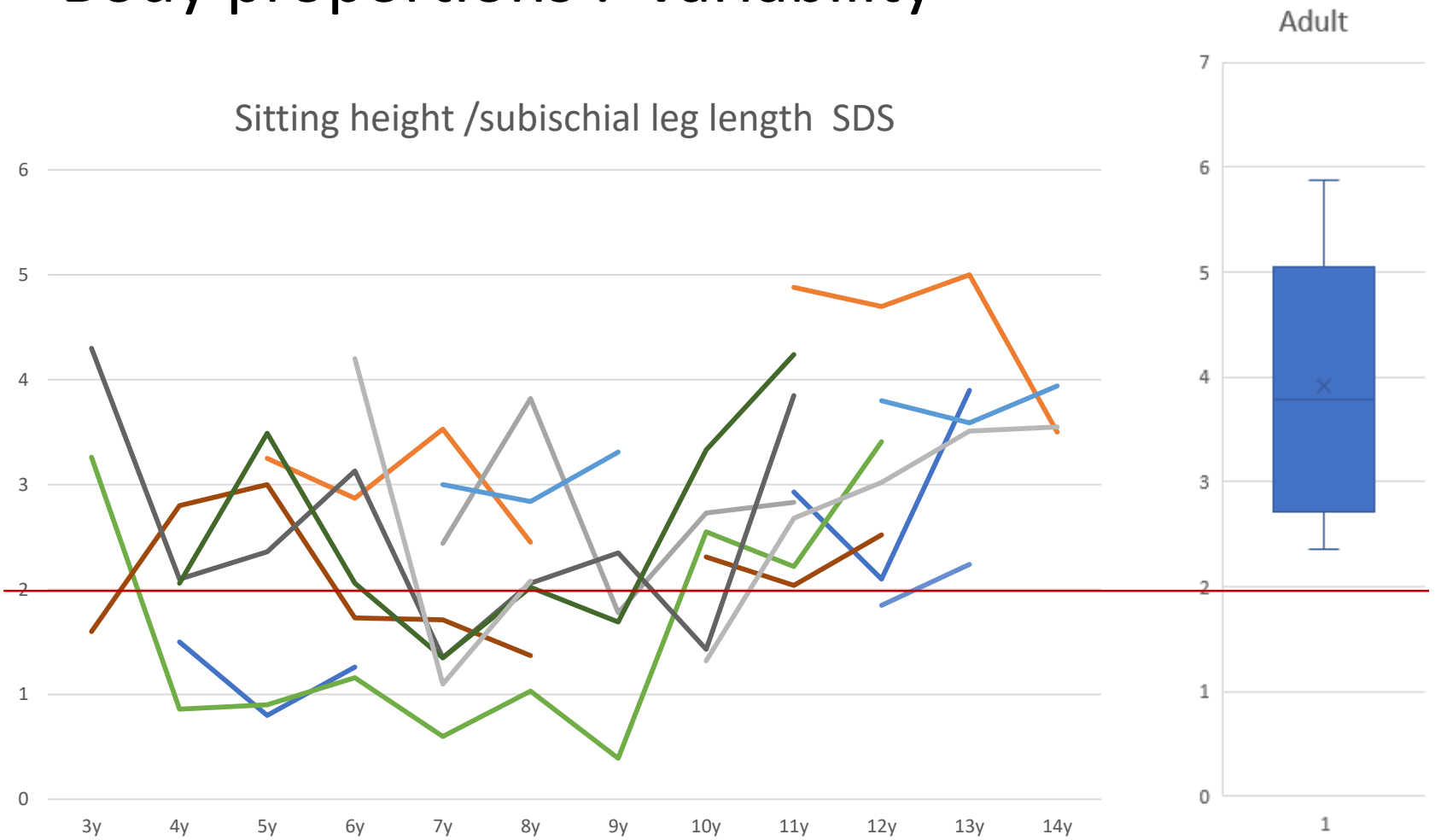
Development of disproportions of patients with hypophosphatemic rickets.



Before puberty the proportionality was significantly disturbed in approximately ¾ children, during puberty disproportional habitus became pronounced in all patients.

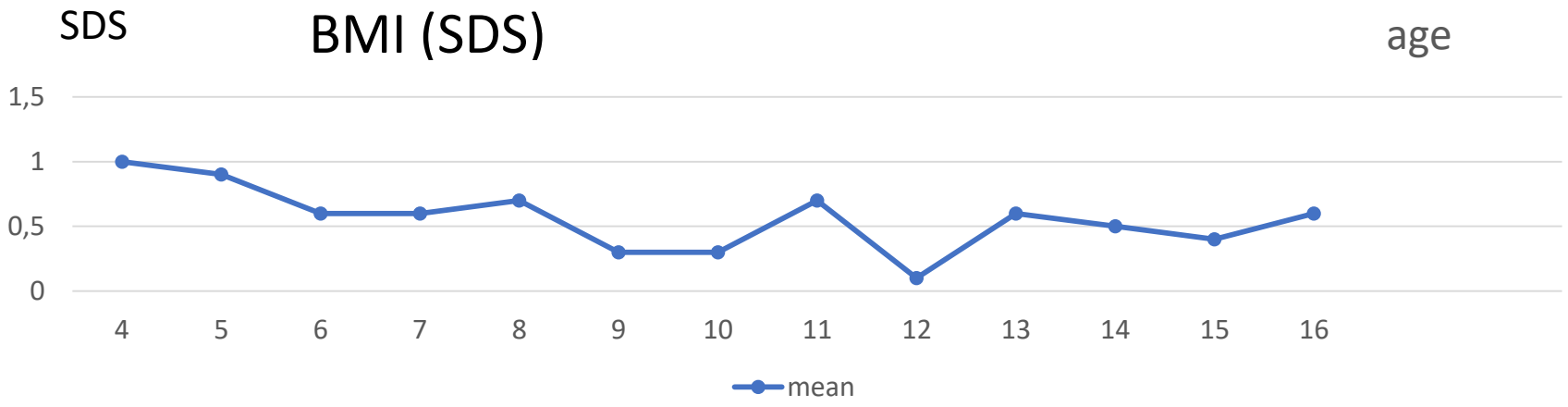
Results

Body proportions : variability

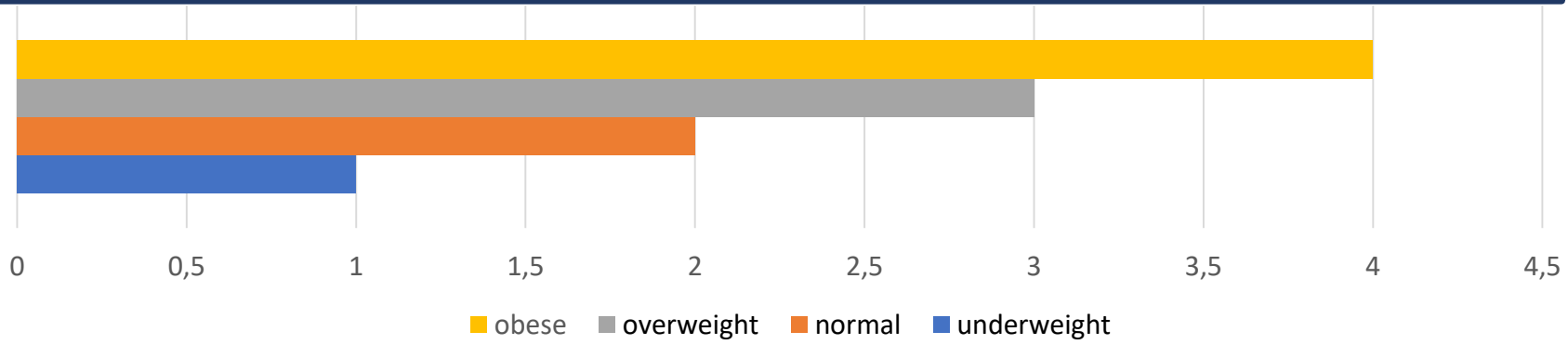


Results

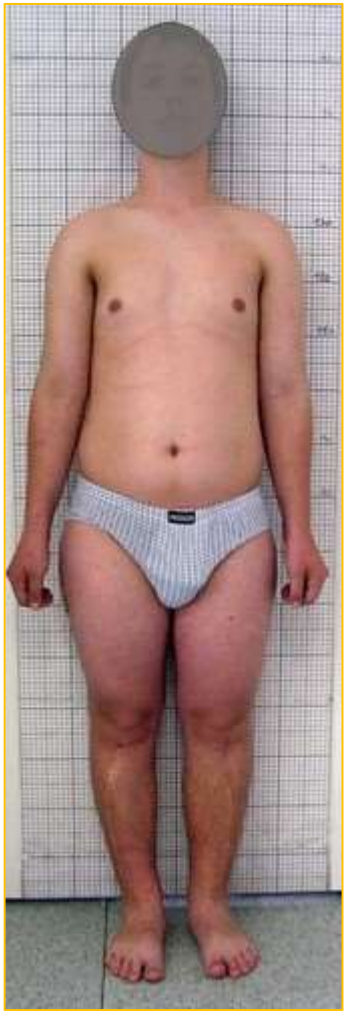
Development of BMI SDS in children with hypophosphatemic rickets.

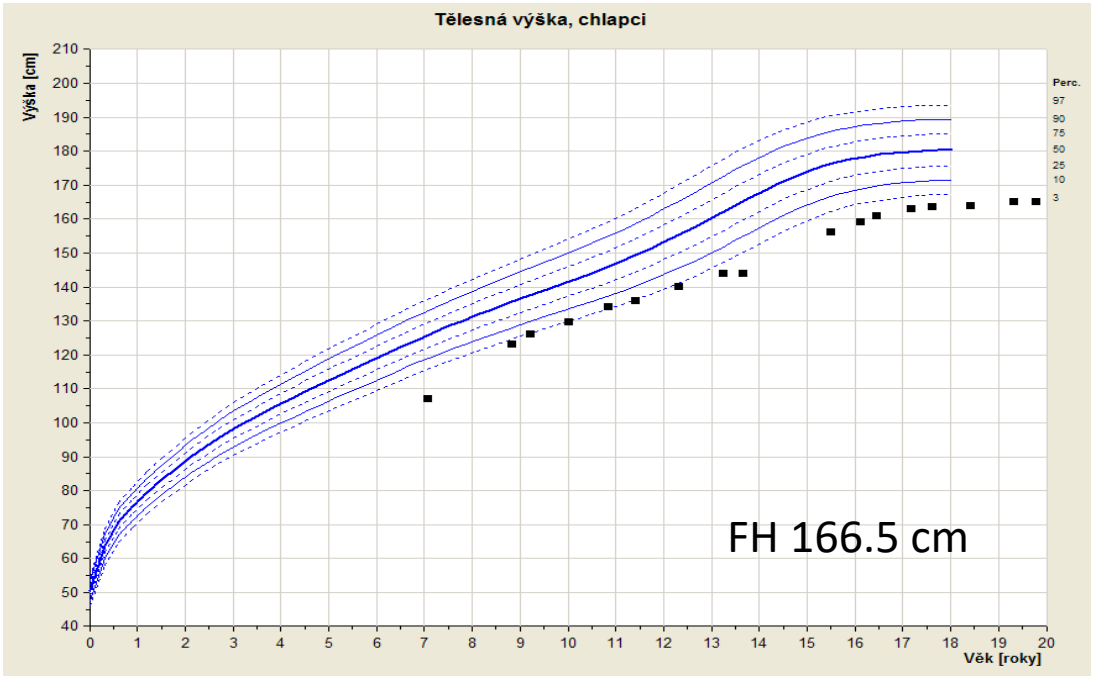


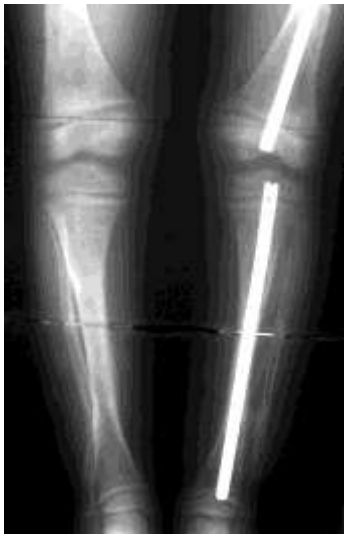
In adults the mean BMI is 29.7 ± 8.2. Most patients (70 %) are obese or overweight.



Results
Case 1

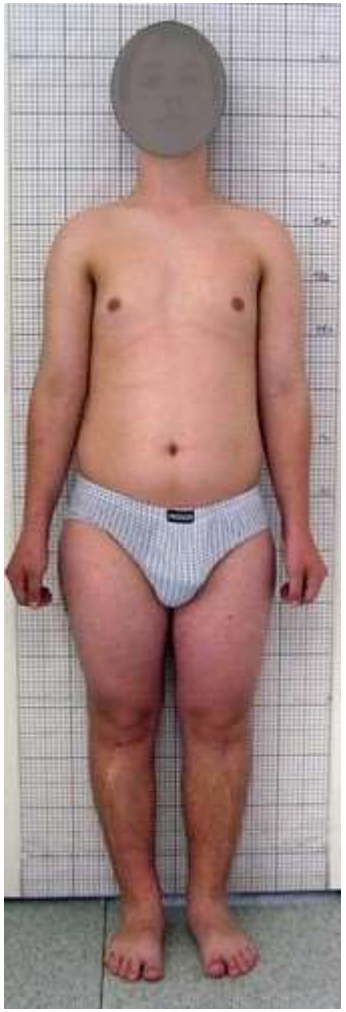


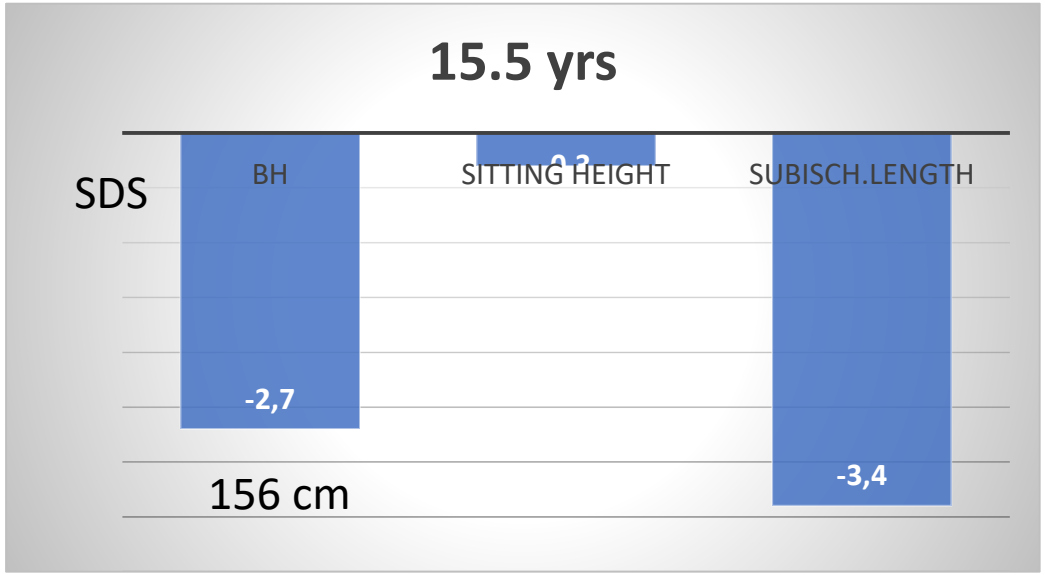




He uderwent segmental and corrective osteotomy with derotation
Intramedullar fixation
Last surgery at the age of 16 yrs

Results
Case 1

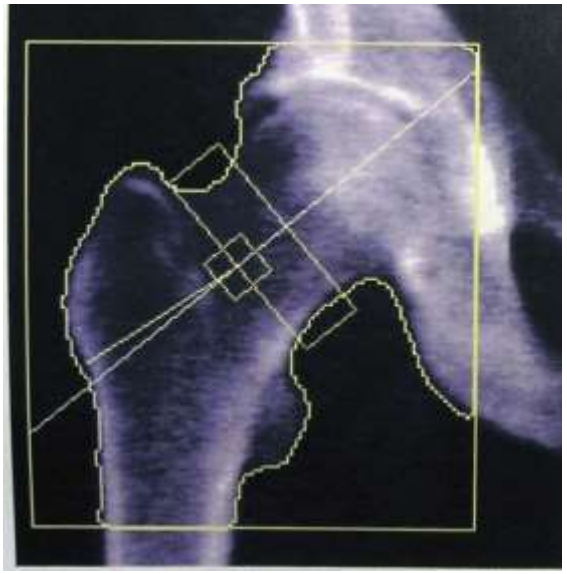




Disproportional stature : ratio sitting height/subischial leg length +4,3 SD.

Laboratory testing proved repeatedly increased bone turnover. PTH was in normal range.

Bone mineral density uneven



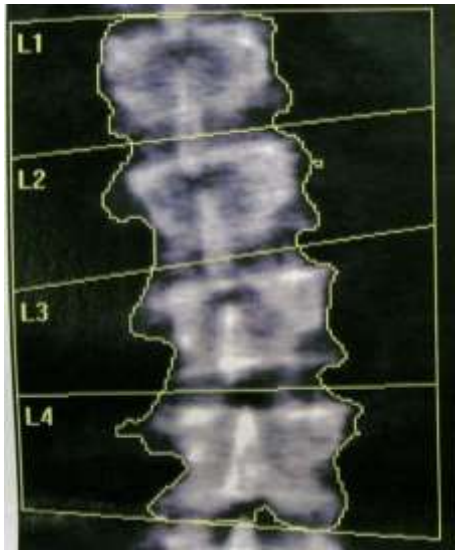
31 yrs **right femur** osteopenia

DXA Results Summary:

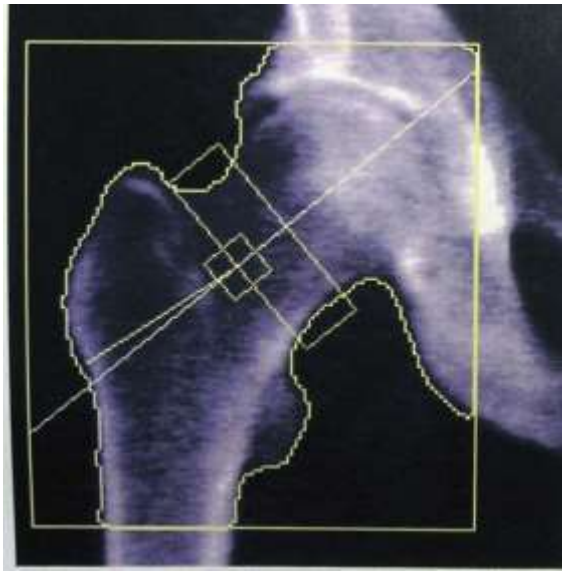
Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
Neck	**5.89**	**4.40**	**0.746**	**-1.4**	**80**	**-1.2**	**82**
Troch	10.82	7.42	0.686	-0.7	88	-0.7	89
Inter	22.17	24.13	1.089	-0.6	91	-0.6	91
Total	38.88	35.95	0.925	-0.7	90	-0.7	90
Ward's	1.31	0.73	0.557	-1.6	71	-1.4	74

DXA Results Summary: **Spine** Sclerotic changes

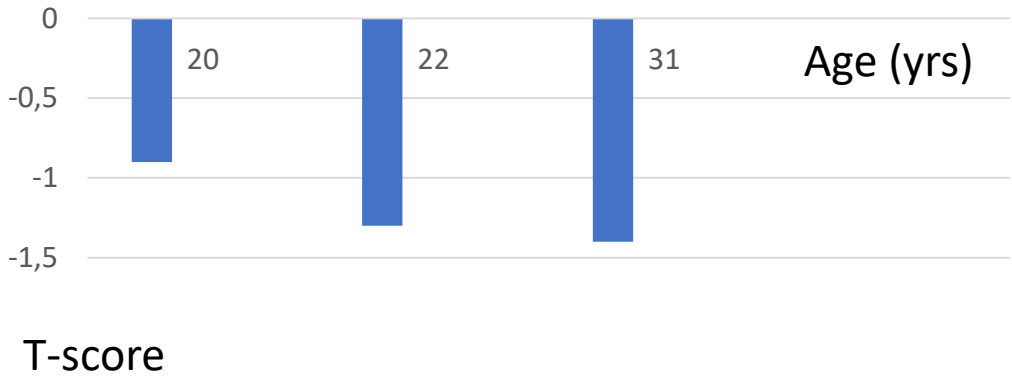
Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
L1	16.20	21.99	1.357	2.6	126	2.6	126
L2	16.78	23.55	1.404	2.8	128	2.8	128
L3	18.03	26.79	1.486	3.5	135	3.5	135
L4	19.99	30.53	1.527	4.0	140	4.0	140
Total	**71.00**	**102.85**	**1.449**	**3.3**	**133**	**3.3**	**133**



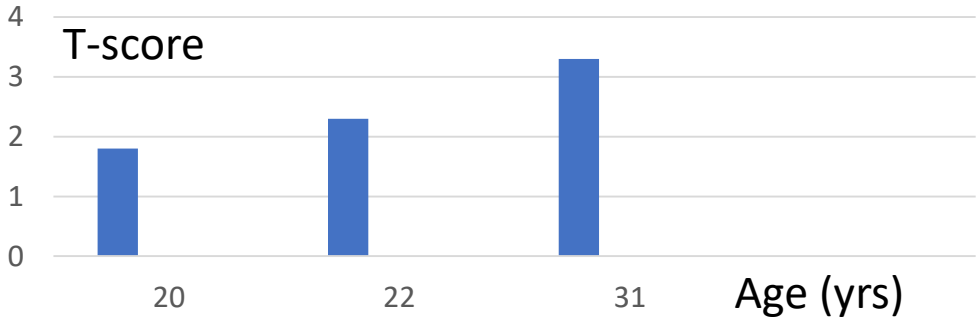
Bone mineral density in adulthood

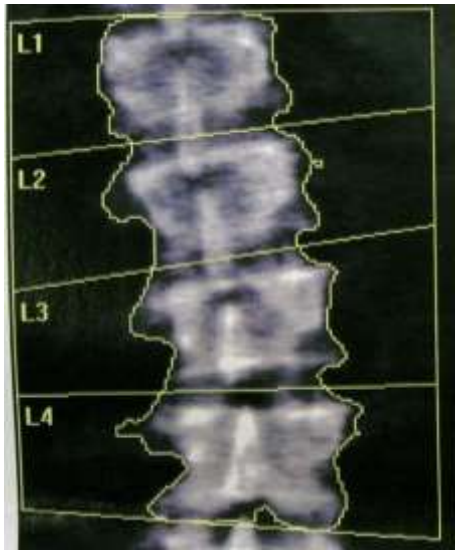


31 yrs **right femur** osteopenia

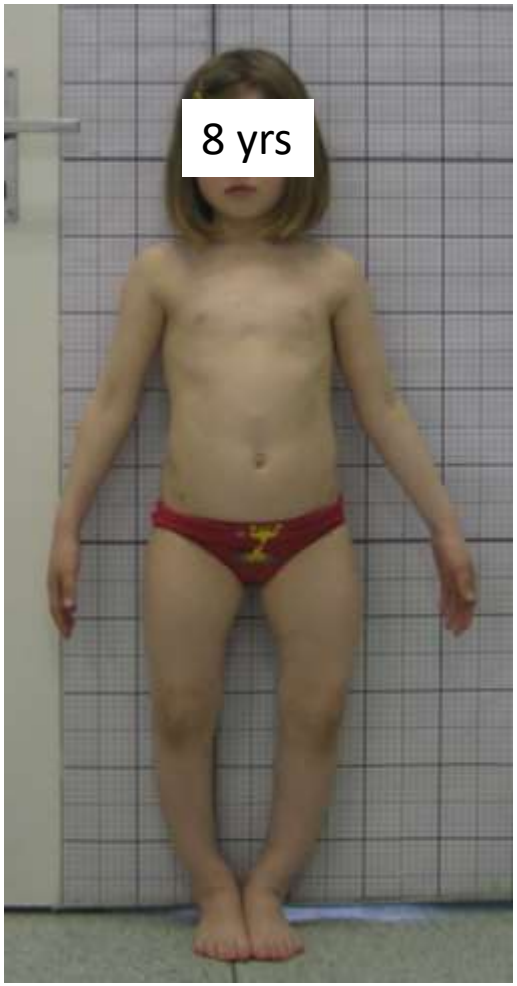


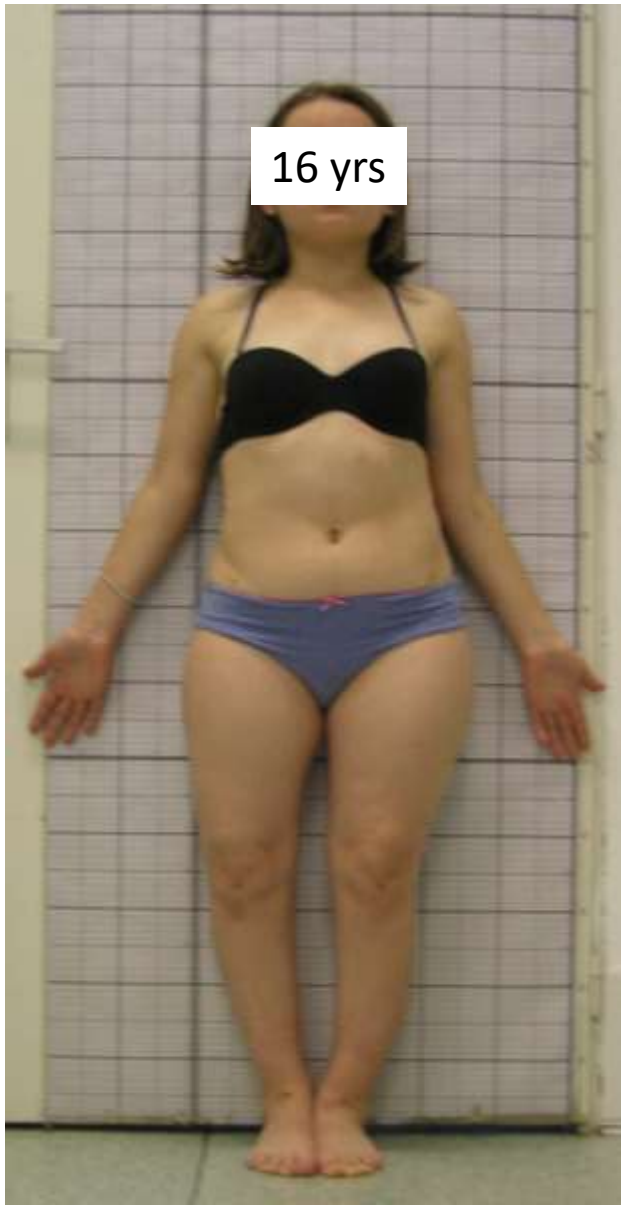
Spine Sclerotic changes



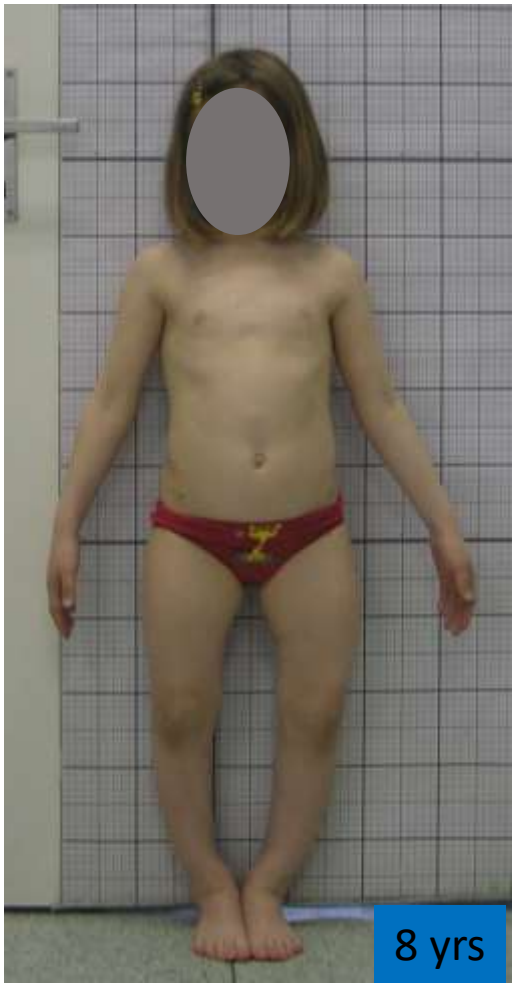


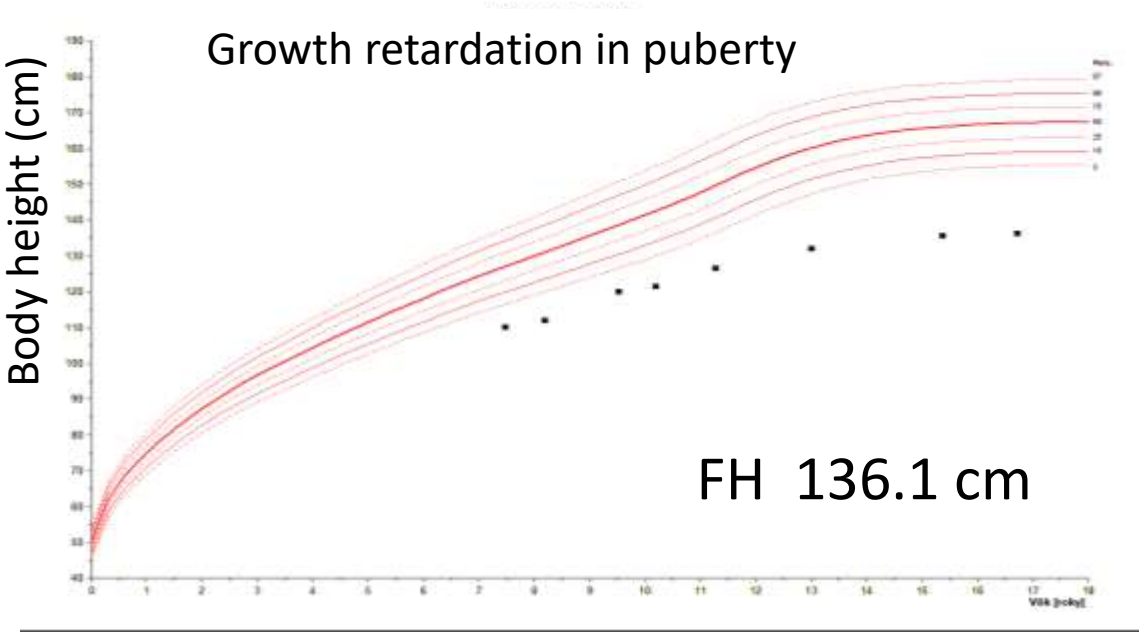
Results
Case 2

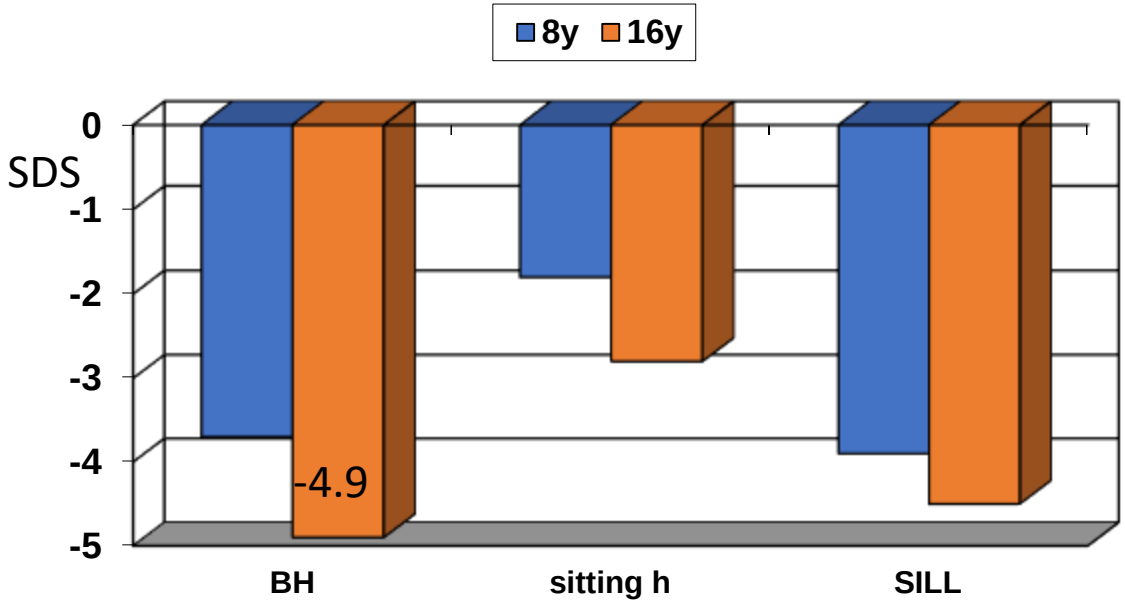




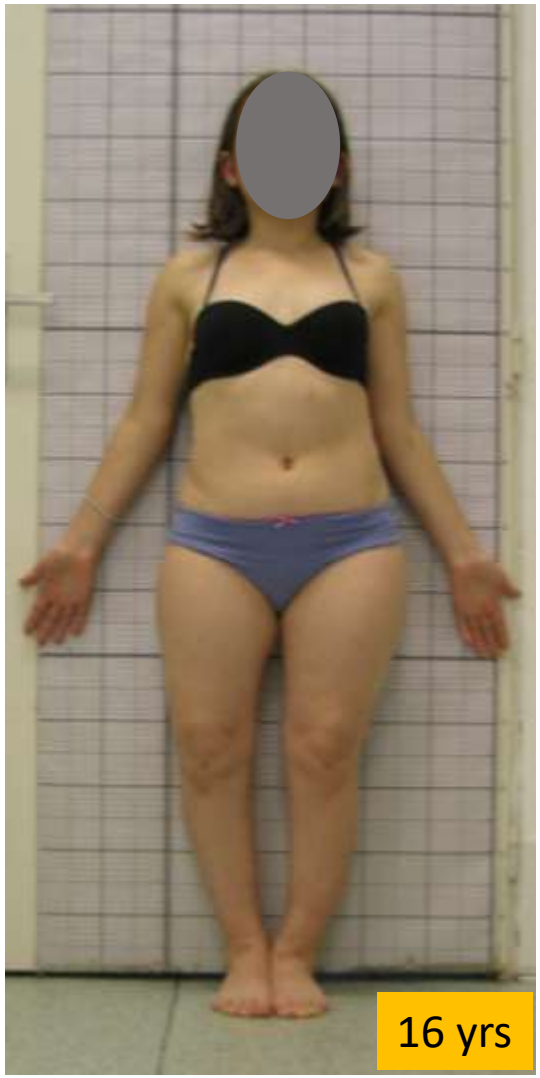
Results
Case 2

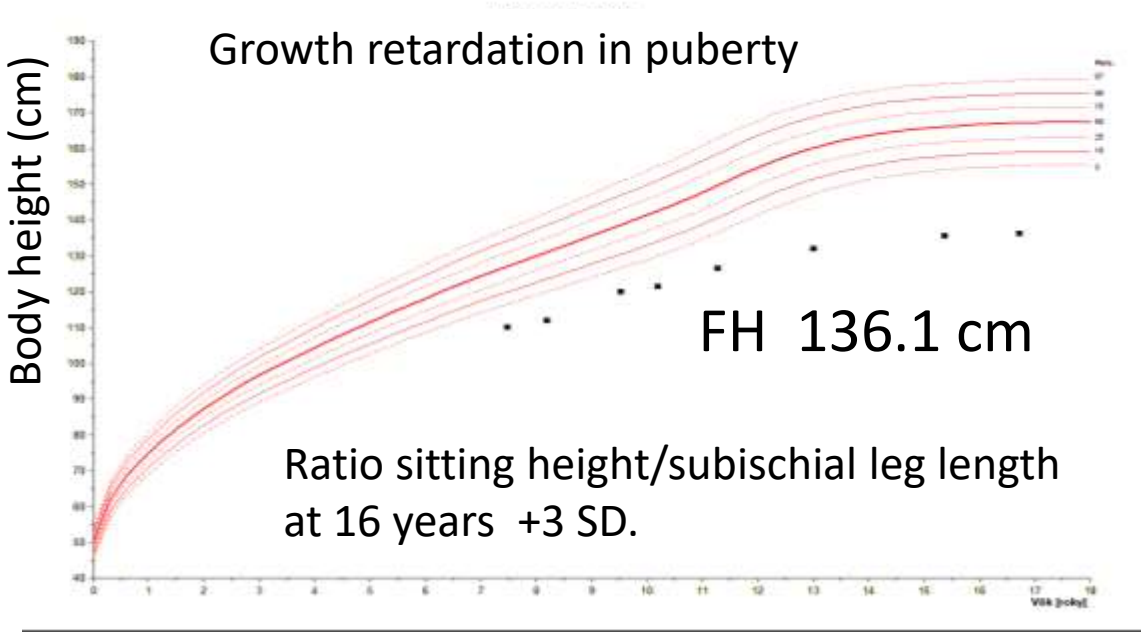


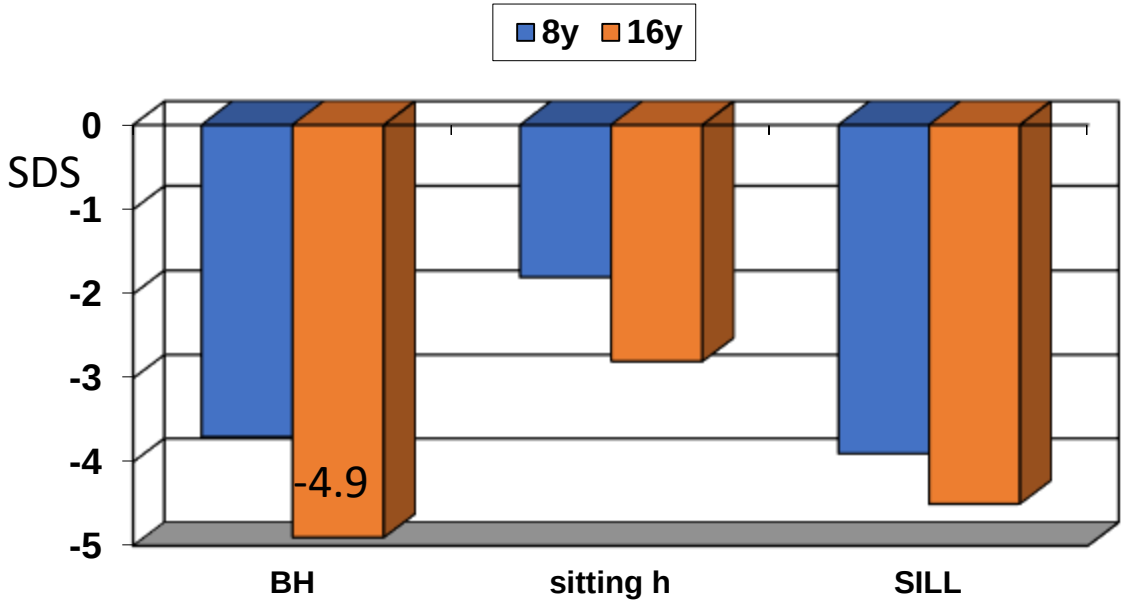




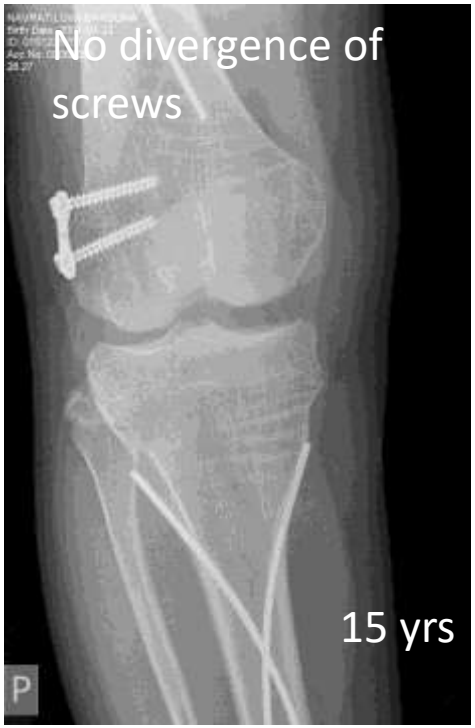
Results
Case 2



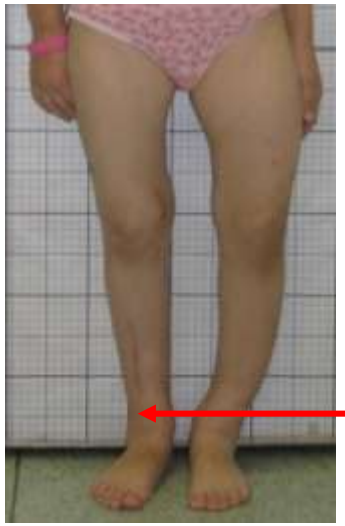




Results
Case 2



Bone age 11.5-12 yrs
at surgery
Remaining growth at 12 yrs
Normal 2 cm
corrected 70% 1.4 cm
Real 0 cm

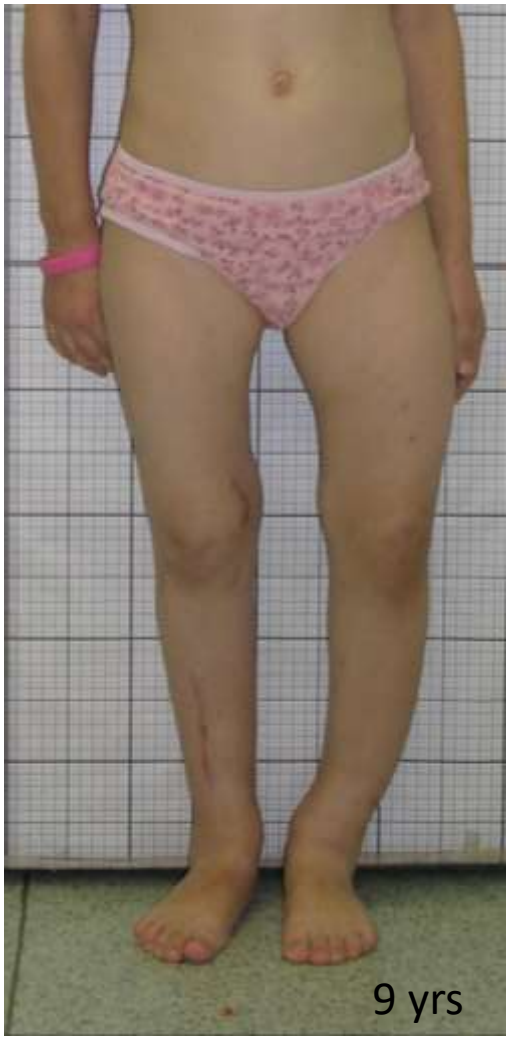


SURGERY:
corrective osteotomy of femur and tibia with derotation and intramedullar fixation
8 years right extremity
9 years left leg

With growth progess of leg deformities:
12 years – temporary hemiepiphysiodesis of distal femur (8-plate)
Drilling epiphysiodesis of distal fibulae and partial epiphysiodesis of distal tibiae bil.

no correction of the axis of lower extremities – **the remaining growth was lower than expected (despite of normal bone age)**

Results
Case 2



Laboratory tests at the age of 10 years

Ca 2.3 mmol/l (2.2 – 2.7)
P 0.73 mmol/l (1.1 – 1.9)
ALP 5.79 ukat/l (6.2)
Bone ALP 2.74 ukat/l (0.19 – 0.37)
Osteokalcin 103 ng/ml (41.7 -111.3)
Beta CTX 2.8 ug/L (0.16 – 0.46)
Increased bone turnover
Repeatedly increased PTH

Bone mineral density in the normal range

Conclusions

- Body height was significantly different from healthy population (-3.2 SD) and girls were even shorter than patients with hypophosphatemic rickets by *Linglart 2014*
- As expected, the substantial **growth retardation** occurred before 5 years of age. Further worsening of growth dynamics was observed in puberty, however the **variability during puberty** was considerable.
- Most patients underwent surgical treatment.

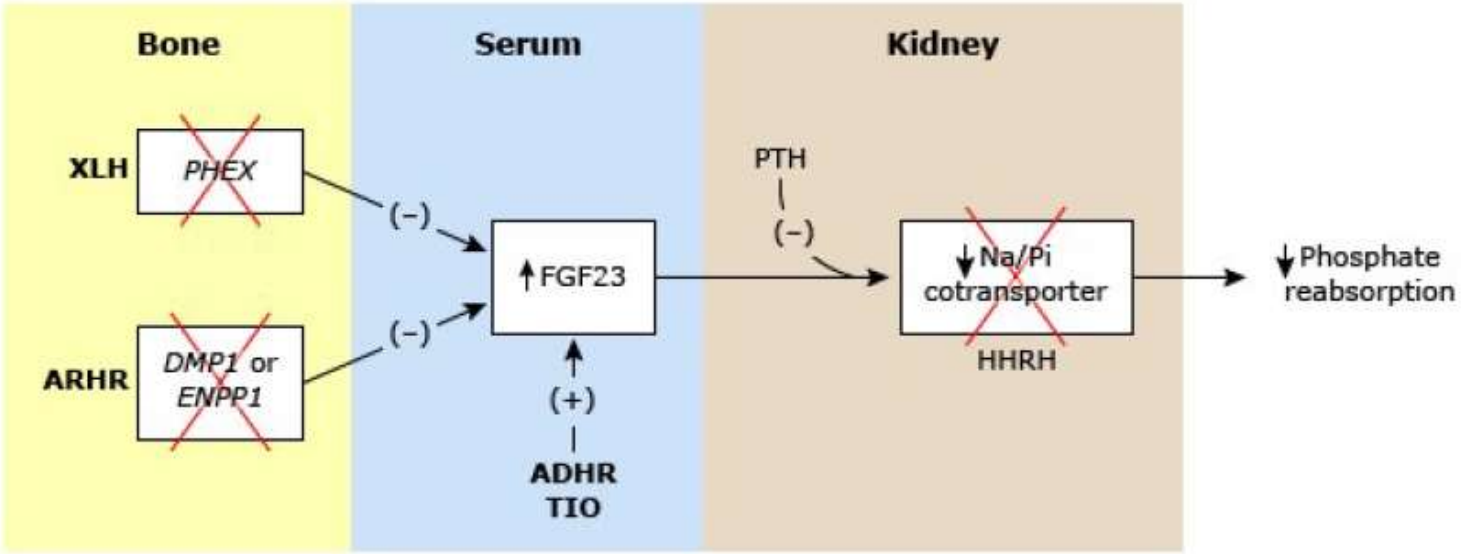
Conclusions

- Body proportions were significantly disturbed. In most patients worsening occurred during puberty.
- Most adult patients were obese or overweight.

- Patients treated conventionally by phosphate and calcitriol significantly differ from healthy population. **Existing therapy does not prevent growth retardation, disproportional habitus and bone deformities.**

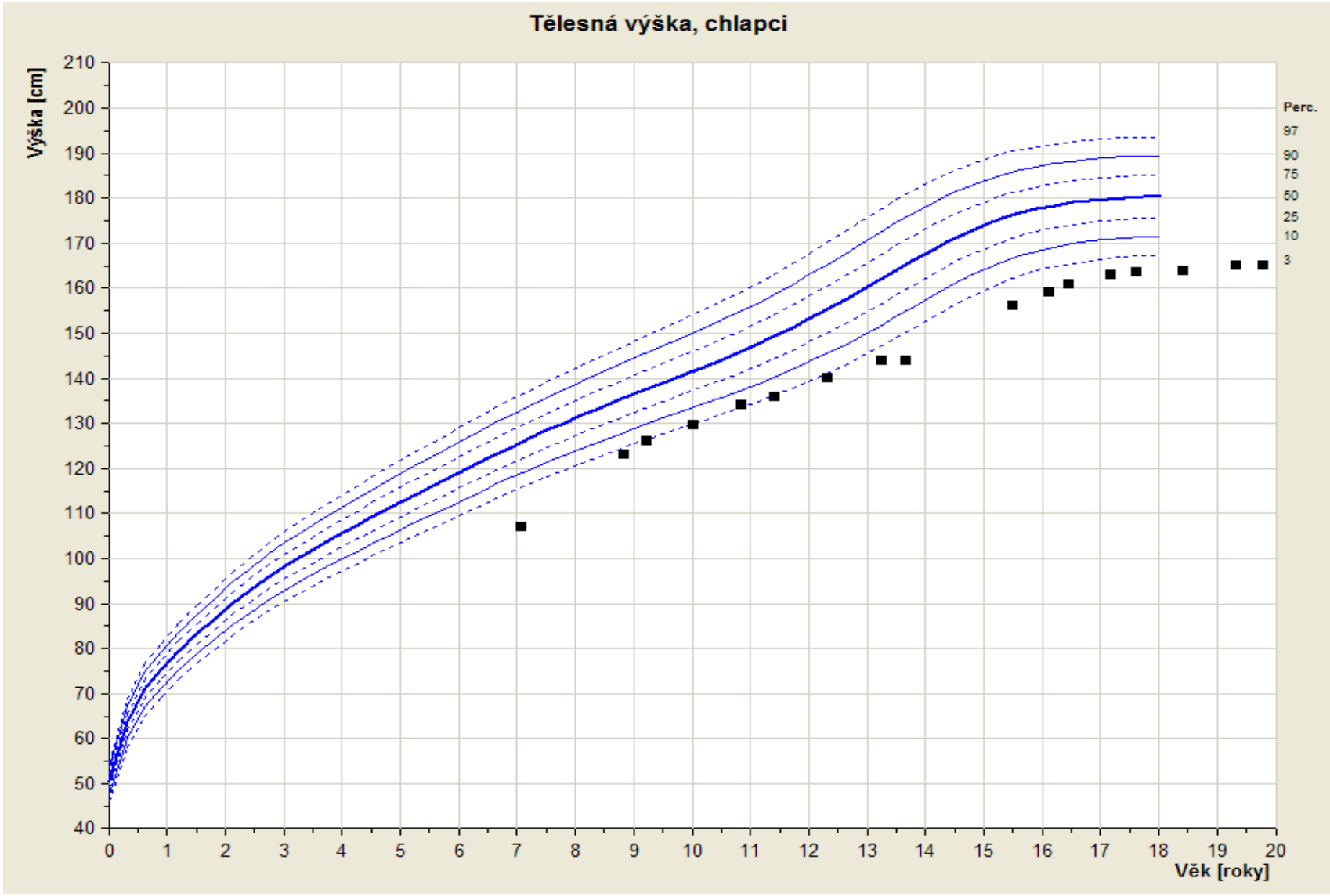

Thanks for your attention

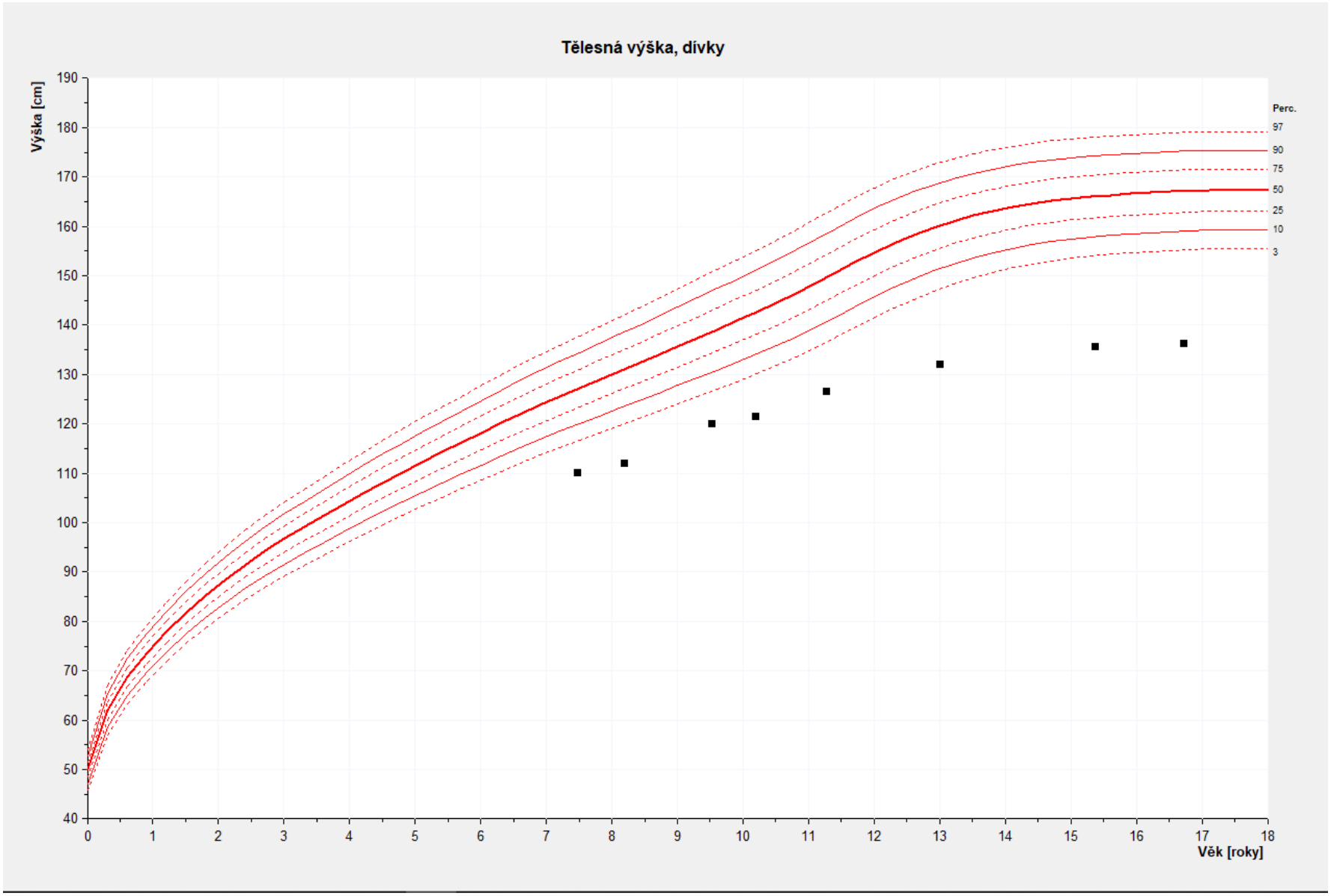
Pathways of renal phosphate wasting in hereditary hypophosphatemic rickets and tumor-induced osteomalacia



Levels of FGF23 are increased by inactivating mutations in *PHEX* (as in XLH) or *DMP1* (as in ARHR), by activating mutations in FGF23 (as in ADHR), or by tumor production of FGF23 (as in TIO). Each of these disorders leads to excessive activity of FGF23, which suppresses the Na/Pi cotransporter and causes renal phosphate-wasting. In HHRH the renal phosphate-wasting is caused by a mutation in the Na/Pi cotransporter itself.

XLH: X-linked hypophosphatemic rickets.
PHEX: phosphate regulating endopeptidase on the X chromosome gene.
ARHR: autosomal recessive hypophosphatemic rickets.
DMP1: dentin matrix protein 1 gene.
ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1 gene.
FGF23: fibroblast growth factor 23.
ADHR: autosomal dominant hypophosphatemic rickets.
TIO: tumor-induced osteomalacia.
PTH: parathyroid hormone.
Na/Pi: sodium-phosphate.
HHRH: hereditary hypophosphatemic rickets with hypercalciuria.


Tělesná výška, chlapci
Výška [cm]
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Věk [roky]
Perc.
97
90
75
50
25
10
3


Tělesná výška, dívky
Výška [cm]
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Věk [roky]
Perc.
97
90
75
50
25
10
3