The orthopaedic problems connected with vitamin D metabolism:

Rickets, Osteomalacia, Hypophosphatemic rickets

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limited liability company

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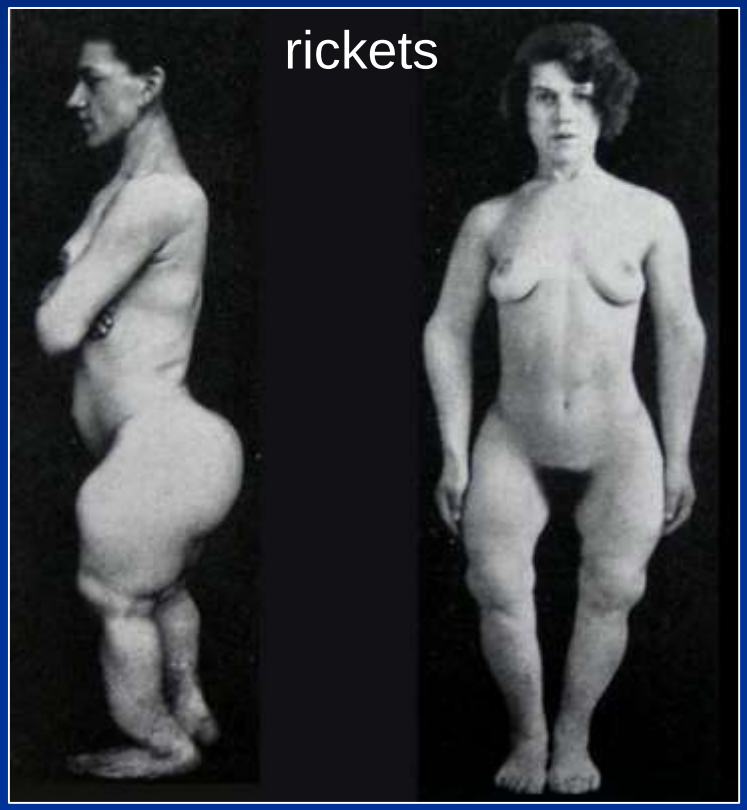
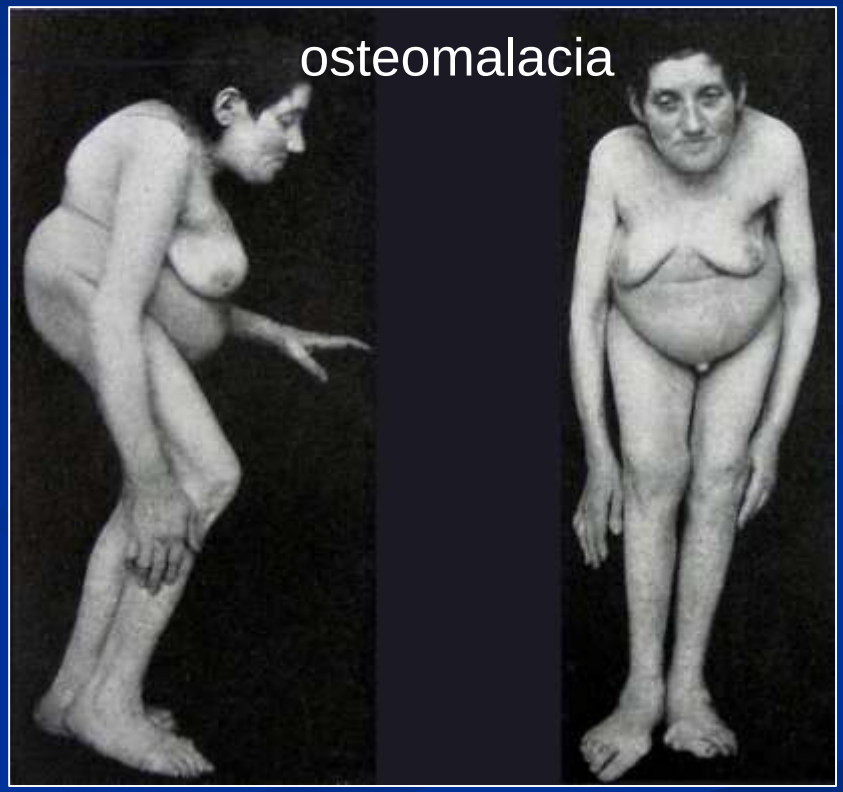
Rickets & Osteomalacia

Rickets represents disturbed mineralisation and desorganisation of growth epiphysis in period of growth when biomechanically severe skeletal deformities evolve.
Osteomalacia is insufficient mineralisation of trabecular and compact bone after finish of growth.





Figures: from Weibel, W.: Lehrbuch der Frauenheilkunde. Siebente Auflage. Berlin und Wien, Urban & Schwarzenberg, 1944, s.366
Photo: skeleton of female rickets, age 45 yrs. Museum of paleopathology, Wien

Rickets & Osteomalacia: **etiopathogenetic classification**

- Abnormal vitamin D metabolism: **Vitamin D deficiency:** inadequate exposure to sunlight, deficient intake of vitamin D
- Dietary calcium deficiency
- Phosphate loss due to renal tubular disorders:

Hypophosphatemic rickets /formely VDRR/ (**X-linked hypophosphatemia**)

Fanconi syndrome, Renal tubular acidosis

- Tumor-related (**Oncogenic rickets**)
- **Hepatic origin**: anticonvulsant therapy, liver disease (failure of 25-hydroxylation)
- **Renal origin**: renal osteodystrophy, vitamin D-dependent rickets
- **Parathyroid disorders**
- **Intestinal origin**: celiac disease, malabsorption

Rickets & Osteomalacia & HR (formely VDRR)

Major clinical findings:

Short stature, bow leg and short lower limbs, waddling gait, protuberant abdomen, rachitic rosaries

Infants: excitability, night sweats, muscle weakness, tetany and cramps, rachitic rosaries, pectus carinatum, Harrison´s groove, craniotabes, caput quadratum/natiforme

Toddlers: *short stature, waddling gait, protuberant abdomen, bow and short lower limbs, kyphoscol*iosis

Adults: **osteomalcia** causes increased excitability, bone pains during gait, by cough, palpation and percussion

Hypophosphatemic rickets (HR) patients do not suffer from muscle weakness, tetany and cramps unlike vitamin D deficiency. Intelectual development is not injured, adult height is in range 130-160 cm.
Heart-shaped pelvis can be obstacle of spontaneous delivery.

Rickets & Osteomalacia & HR

Laboratory findings

Hypophosphatemia (caused by dimished tubular resorption of inorganic phosphate) and hyperphosphaturia

Elevated serum alkaline phosphatase levels (ALP), osteocalcine, bone ALP (BALP), parathormone (PTH) – tertiary hyper-parathyreosis

Elevation of marker of osteoresorption - telopeptide of collagen I /CTX/, formely elevation of urine pyridinoline and deoxy-pyridinoline

Note:

Activation of PTH receptors on osteoblasts stimulates expression of RANKL. RANKL (cytokine) binds on receptor RANK located on preosteoclasts. This binding activates the development of osteoclasts from preosteoclasts.

PTH inhibits production of OPG by osteoblasts. Increase rate of bindings RANKL/OPG encourages osteoclastogenesis – the result is high bone resorption and rickets accompanied by hypo-calcemia and hypo-phosphatemia

RANKL – ligand of receptor activator of nuclear factor kappa B, OPG - osteoprotegerin

Rickets & Osteomalacia & HR

Major radiographic features

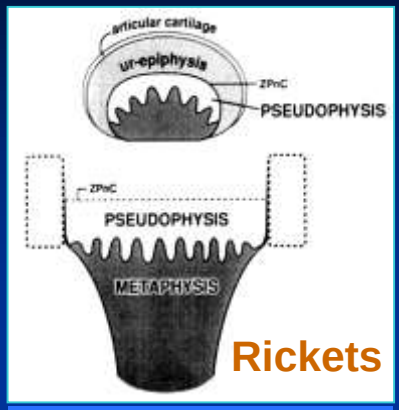
Rickets: mild-moderate-severe rachitic changes:

- bowing of long bones - tubular shape of long bones
- apparently wide epiphyseal plates, flare metaphyses
- sparse pattern of trabecular bone and thinner fiberized cortical bone

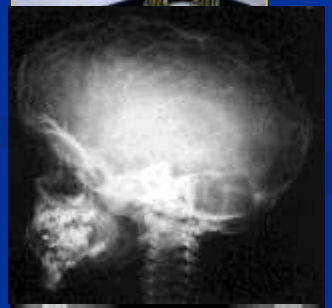
Osteomalacia: bell-shaped thorax, heart-shaped pelvis, kyfoscoliosis with codfish vetebrae, varous or valgous limb deformities, Looser´s zones of remodelling and fractures

HR: mild-moderate rachitic changes:

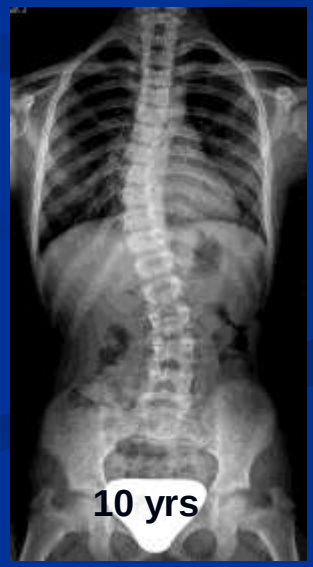
- deformity of long bones and spine,
- early closure of growth plates and craniosynostosis of sagittal suture.
- low bone density in childhood x generalized osteosclerosis in adults
- early osteoarthritis and a spondyloarthritis



Alan Oestreich 2004



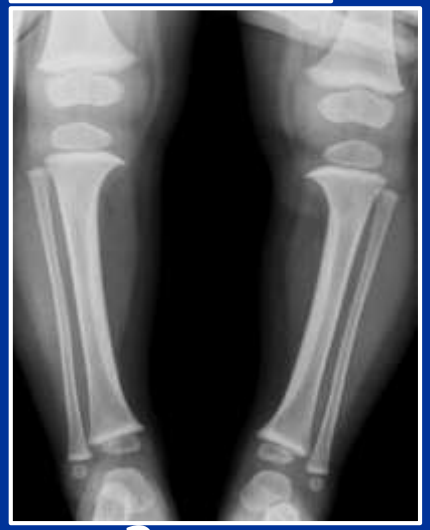
HR



Differential diagnosis of „genua et crura vara“

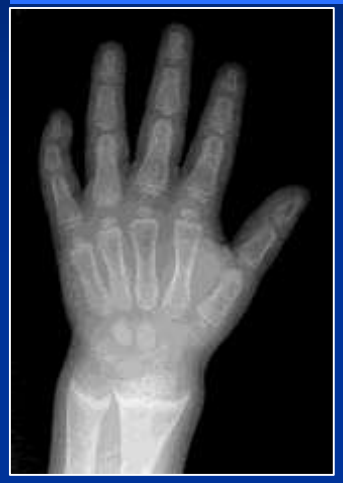
Biochemical findings and X-ray features are crucial

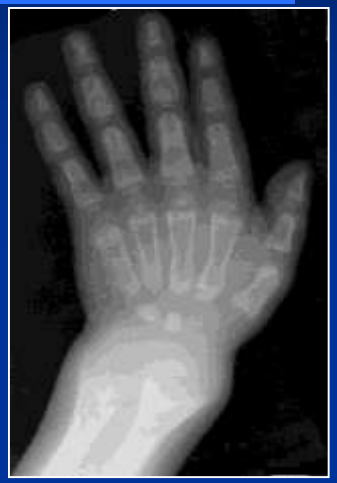
Crura vara „idiopathica“

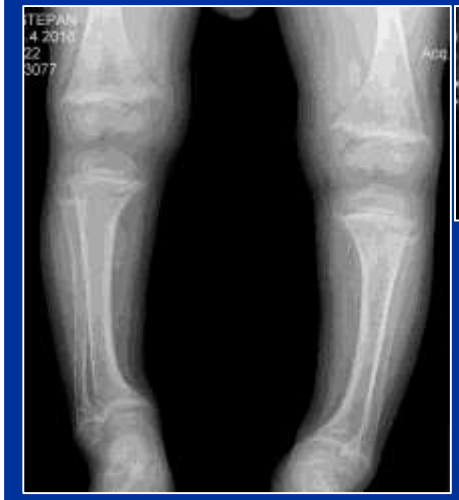


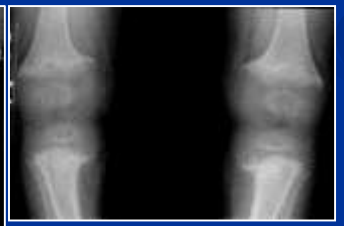
2 yrs.

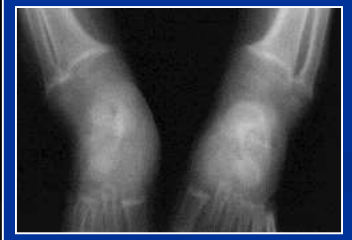
Vit. D deficient rickets







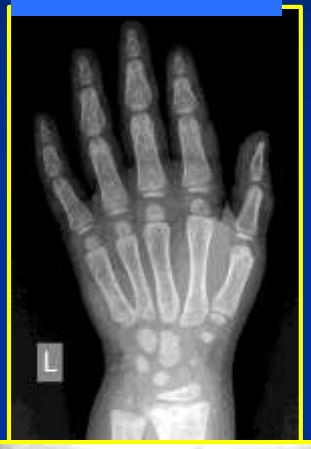


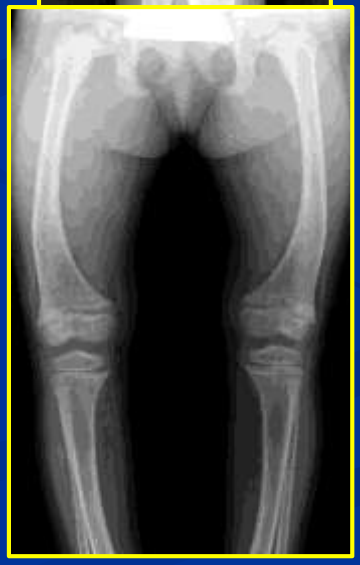


2.5 yrs.

2 yrs.

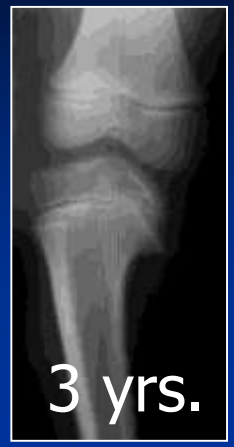
HR





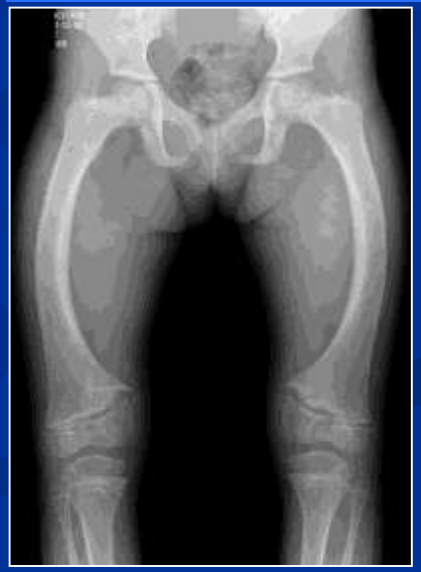
5 yrs. 9 mo.

M. Blount



3 yrs.

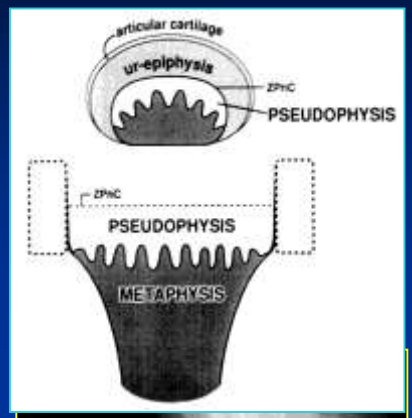
M.D. Schmid

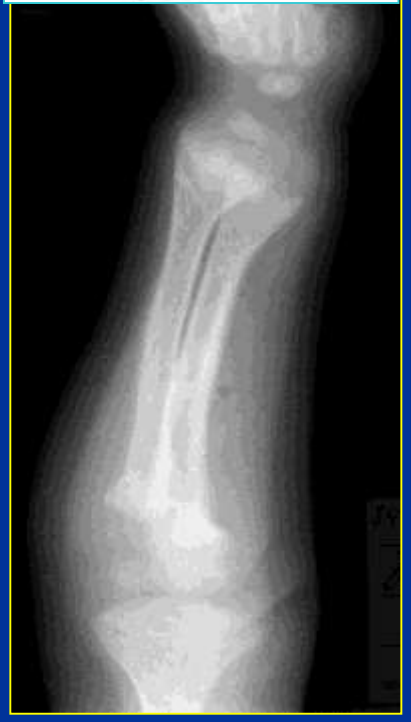


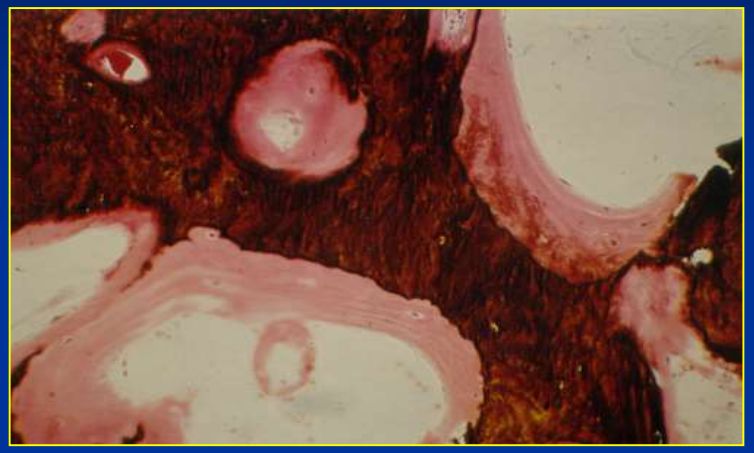
5.5 yrs.

Acute vitamin D deficient rickets (VDR)

X-ray features, histology

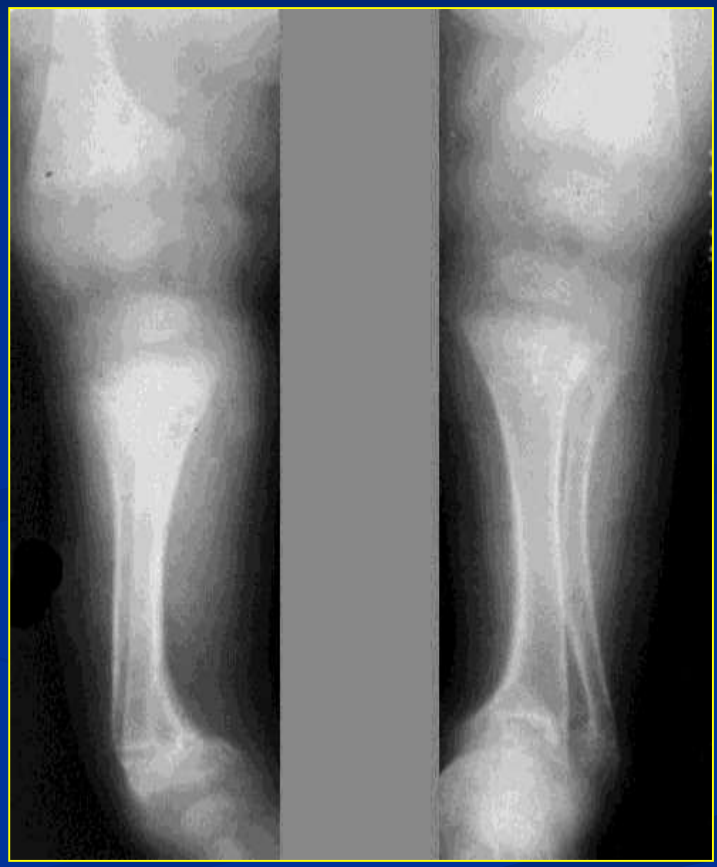






- Deformities at the ends of rachtic bones
- Zone of provisional calcification is not limited - pseudoepiphysis

- Histology: widening of unossified osteoid seams at the trabeculae (dyed Hematox.- Eosin)



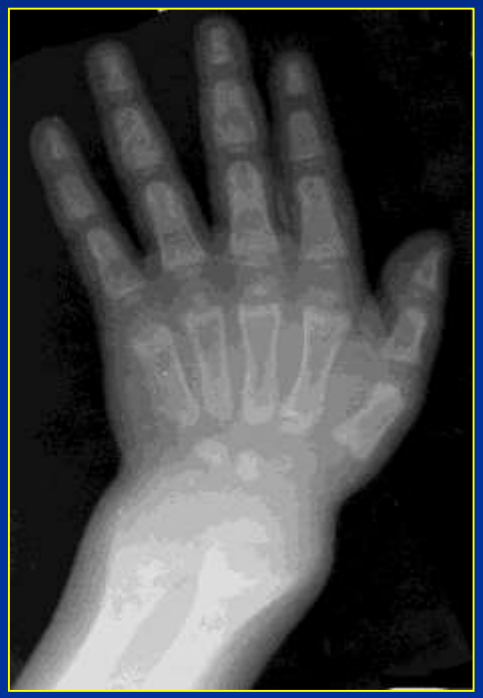
Acute vitamin D deficient rickets (VDR)

Mulatto boy

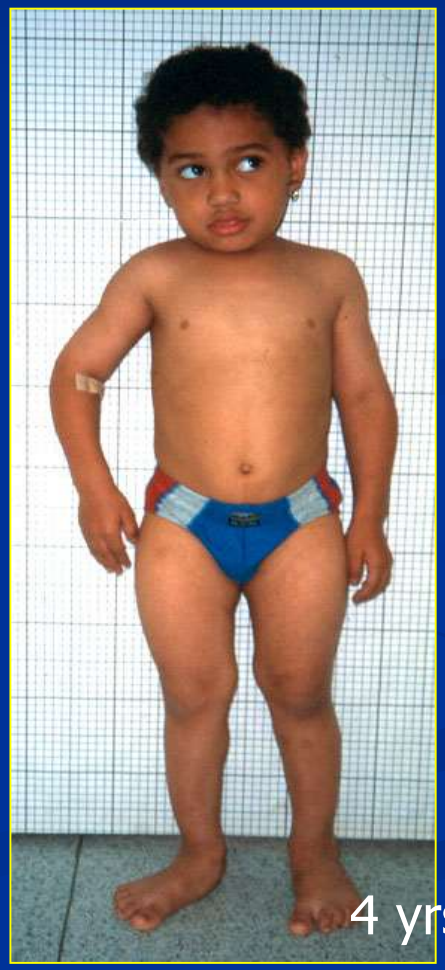
Markers of bone metabolism were significantly higher.

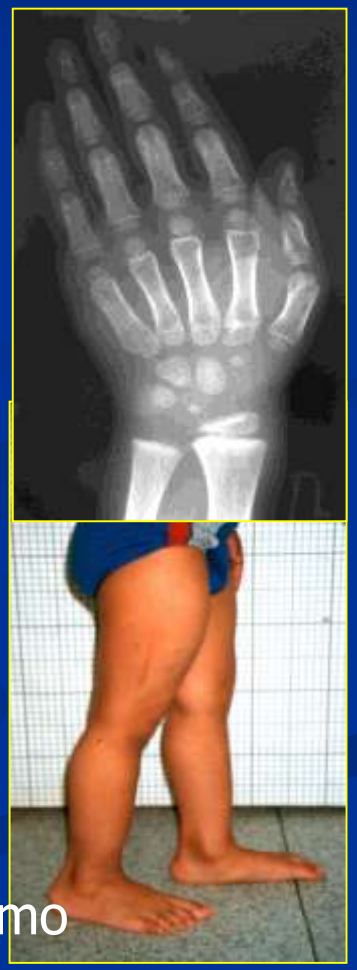
Therapy: cholecalciferol i.m. (Vigantol 100 000 UI) 3x per 1 month, later Vigantol 2 drops every morning, milk and dairy products, Calcium efferv. 500 mg every evening

2yrs 5 mo



Harris´ lines
- distal area of metacarpal bones



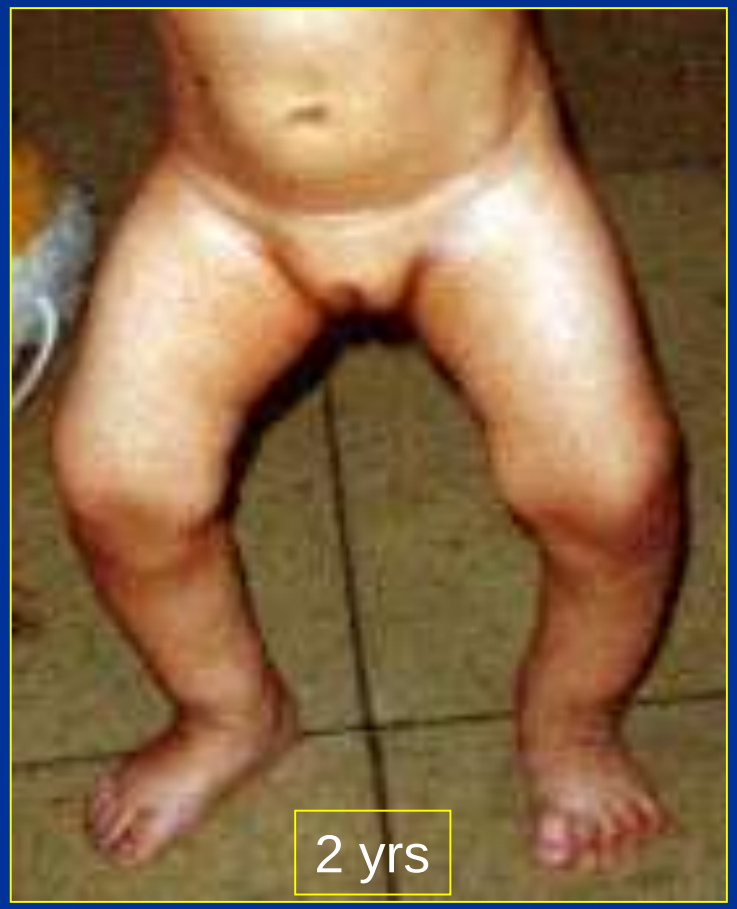


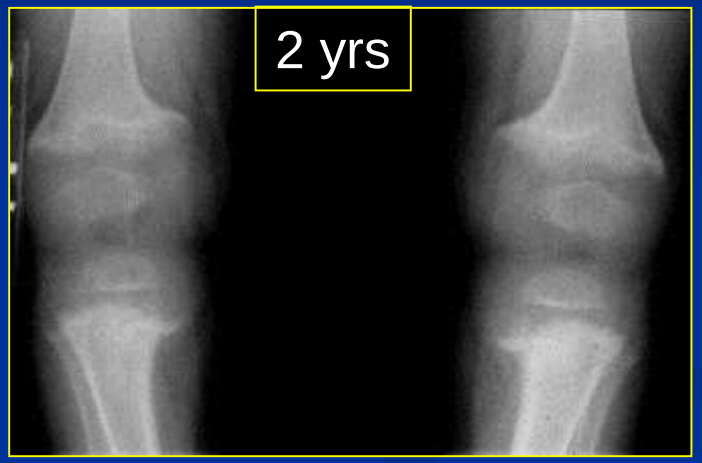
4 yrs 8 mo

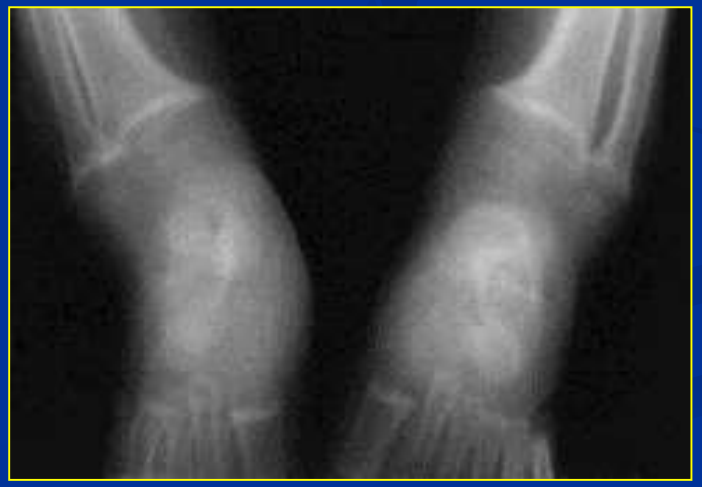
Acute vitamin D deficient rickets (VDR)

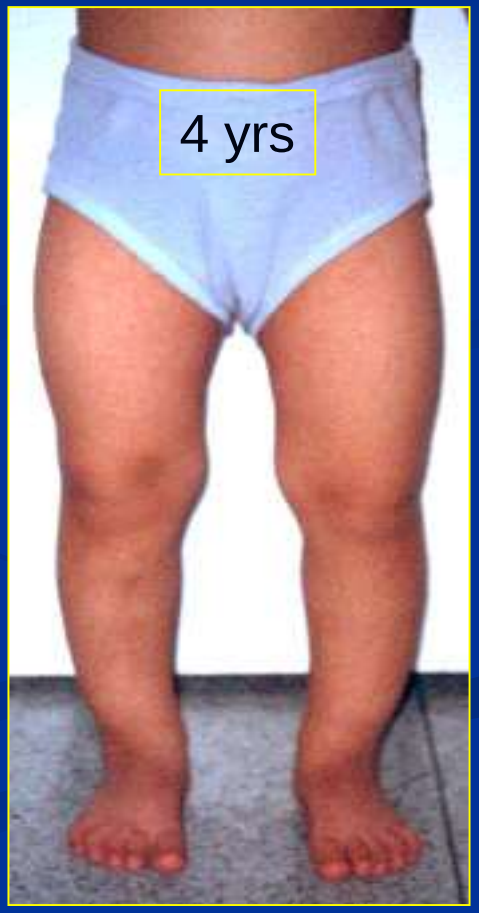
Gipsy girl

markers of bone metabolism were significantly higher (ALP, OC, BAP x UPD a UDPD)









Hypophosphatemic rickets

- Consequense of congenital defects in the reabsorption of filtrated phosphate and vitamin D metabolism
- Fibroblast growth factor (FGF 23) inhibits renal transport of phosphate from proximal tubulus of kidney back to circulation and causes hypophosphatemia and hyperphosphaturia (reason for rickets/osteomalacia).

26. Group of abnormal mineralization (Bonafe 2015)

Hypophosphatemic rickets, X-linked dominant

Gene defect PHEX was localized at Xp22.2-p22.1, in the PHEX around 160 mutations were identified. Prevalence 1 : 20 000

Hypophosphatemic rickets, autosomal dominant (12p13.3, FGF 23)
Hypophosphatemic rickets, autosomal recessive, type 1 (4q21, DMP1)
Hypophosphatemic rickets, autosomal recessive, type 2 (6q23, ENPP1)
Hypophosphatemic rickets with hypercalciuria, X-linked recessive (Xp11.22, CICN5)
Hypophosphatemic rickets with hypercalciuria, autosomal recessive (9q34, SLC34A3)

HYPOPHOSPHATEMIC RICKETS (VDRR)
Conventional treatment

*Medicamentous treatment

combination of oral P and 1,25(OH)2 vitamin D

Side effects:

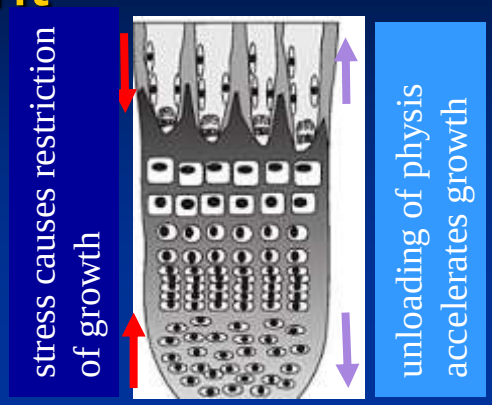
- too much P – secondary/tertiary hyperparathyroidism
- excess of 1,25(OH)2 vitamin D – hypercalcemia, hypercalciuria, nephrocalcinosis

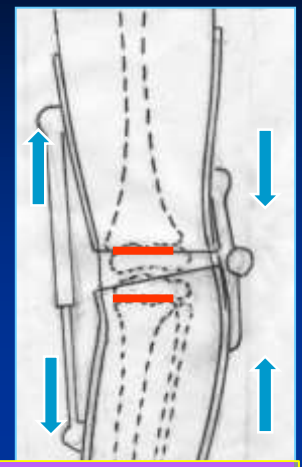
*Orthotic correction (3 point principle)

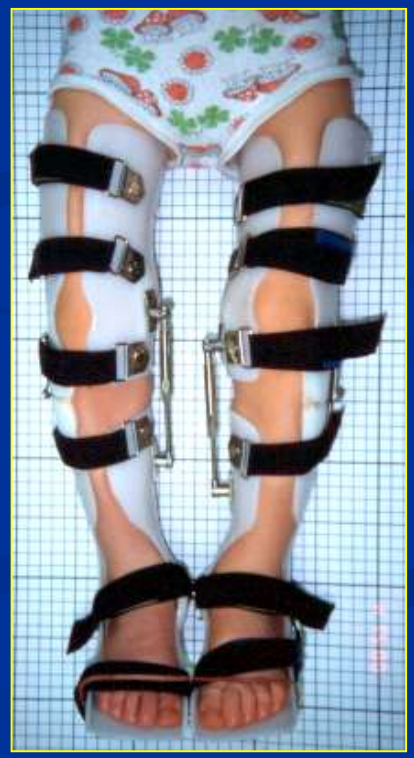
Orthosis with bending pre-stressing - varosity x valgosity correction

Derotation orthosis (correction of inward shank torsion)

Brace







derotation orthosis by Becker

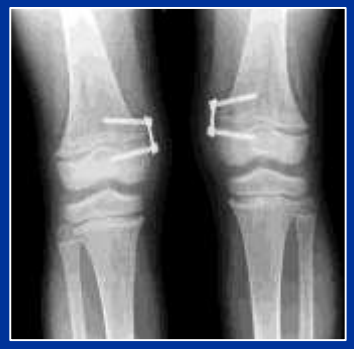
HYPOPHOSPHATEMIC RICKETS (VDRR)
Conventional treatment

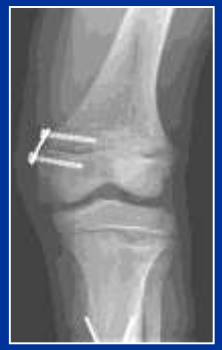
*Surgery:

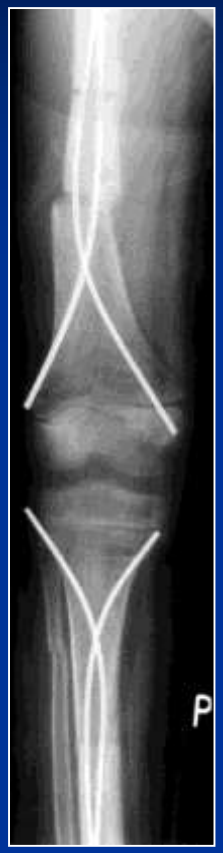
Corrective or multiple osteotomy (OT)

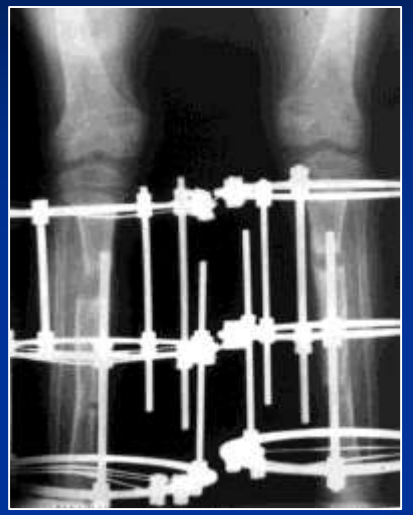
Children: intramedullary, plate and/or external fixation

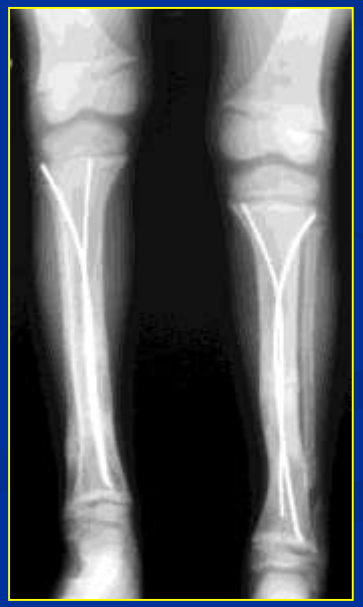
hemi-epiphysiodesis: temporary (8-plates) or permanent (drilling method by Macnicol)

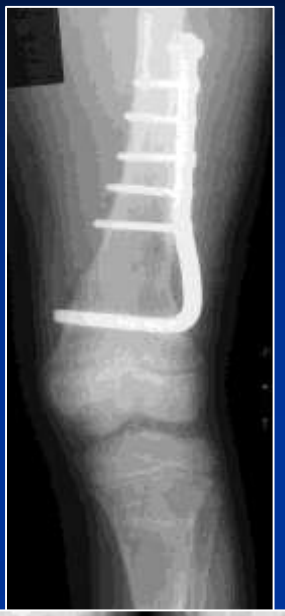


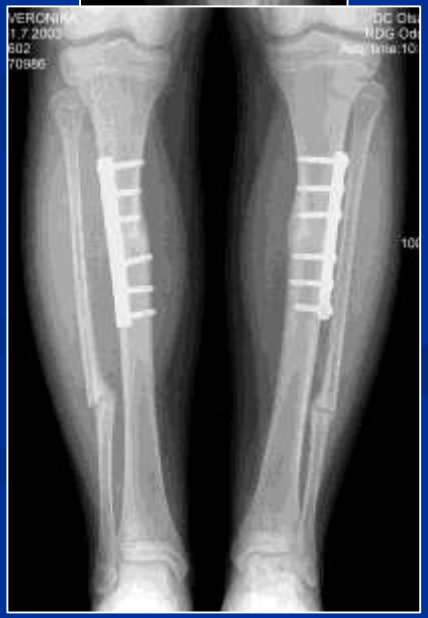










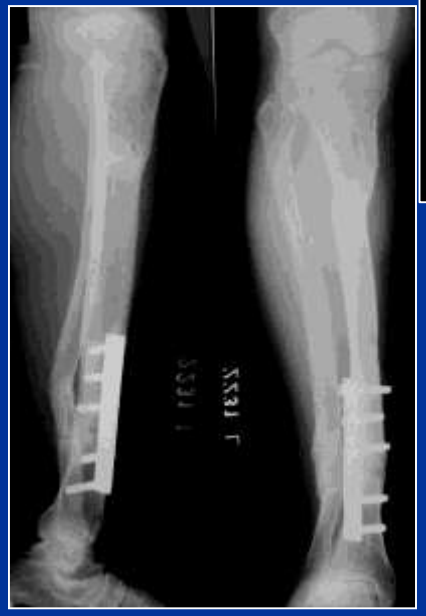


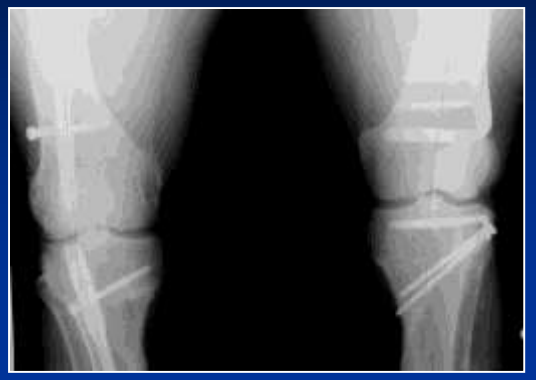
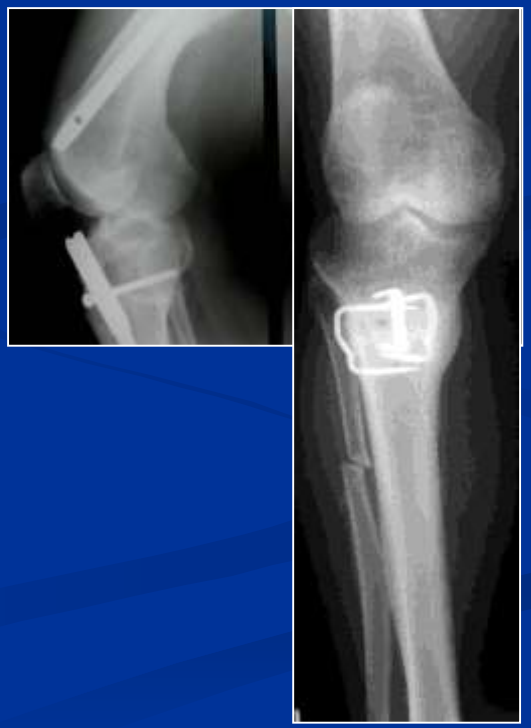
HYPOPHOSPHATEMIC RICKETS (VDRR)

*Surgary:

Adults: intramedullary fixed nailing, plate and/or external fixation

Note: Delayed healing of osteotomies and fractures


HYPOPHOSPHATEMIC RICKETS (HR)
Patients and Methods

- In a cohort of **29 patients** (20 females, 9 males) the **HR d**iagnosis was specified according to radio-clinical and biochemical examination in Faculty Hospital Motol and Centre for Defects of Locomotor Apparatus in Prague in years 1987 - 2018
- Probands were born in years 1940 – 2007.
- Retrospective evaluation of basic anthropometric parameters of this group was presented by **dr. Zemková**.
- Medicamentous treatment - combination of oral P and 1,25(OH)2 vitamin D - was introduced when HR diagnosis was specified from 1987.
- 14 children were treated by surgery of lower extremities.

HYPOPHOSPHATEMIC RICKETS (VDRR)

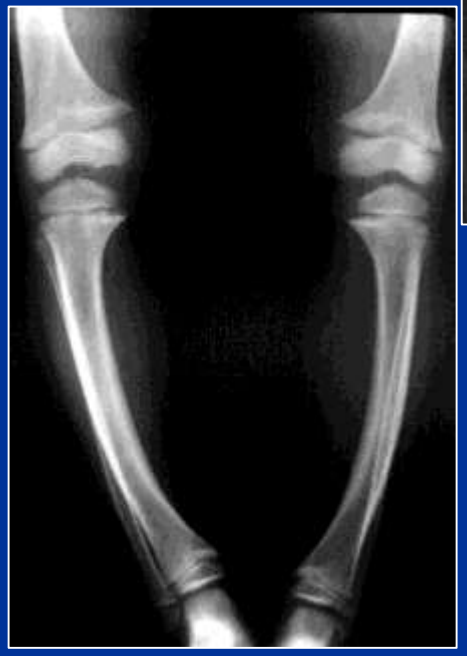
Examples of surgery results: **Case 1 - boy**

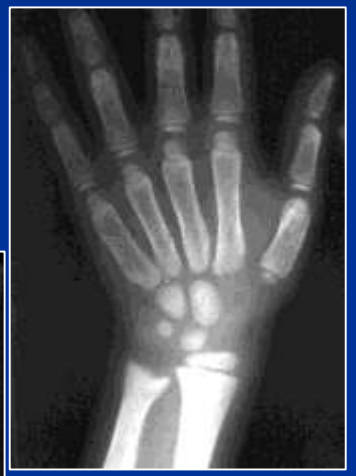
Susp. HR in 4 yrs. acording to X-rays (crura vara, flare metaphyses, irregular wide epiphyseal plates). Older sister and both parents do not suffer from HR.

HR was confirmed **in 6.5 years** by radiographic findings, histological investigation and biochemistry. Supplementation by Calcitriol (Rocaltrol Roche) and inorganic phosphate (Phosphore Sandoz) was introduced in **12.5 yrs**.

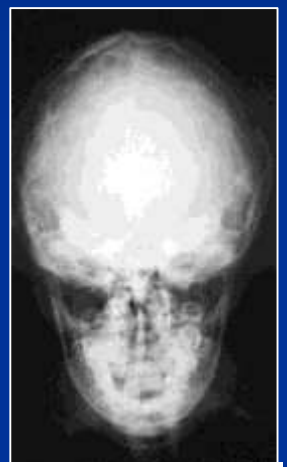
sutl

6 yrs.
105 cm (-2.8 SD)
18 kg (-1.5 SD)

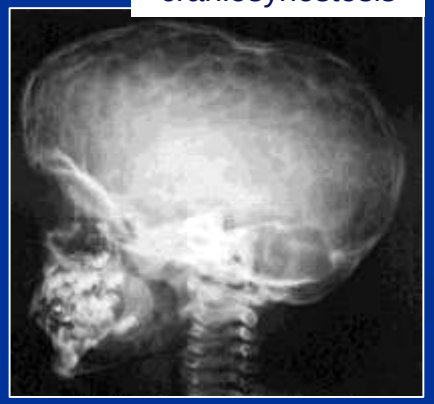




6 yrs

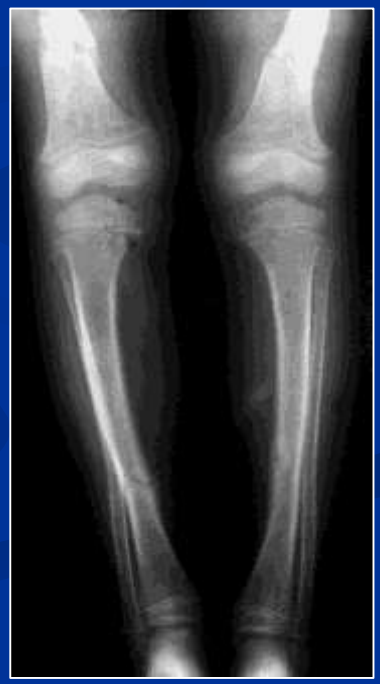


craniosynostosis



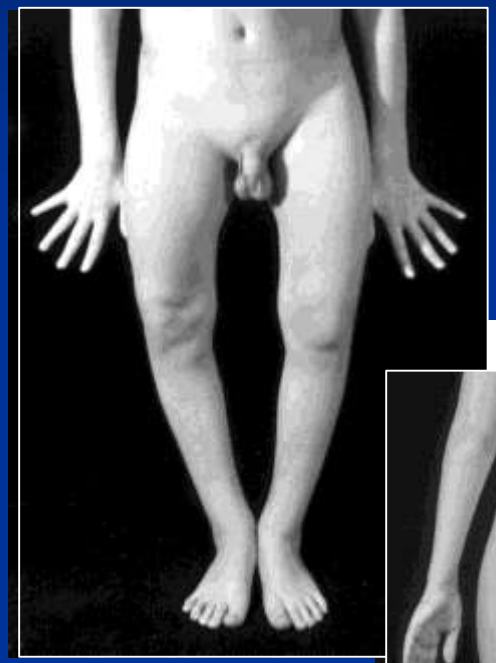
6 yrs. serrated OT of both femurs and both tibias (with fibula) sec. Huc, double spica cast (2 mo.)

6.5 yrs

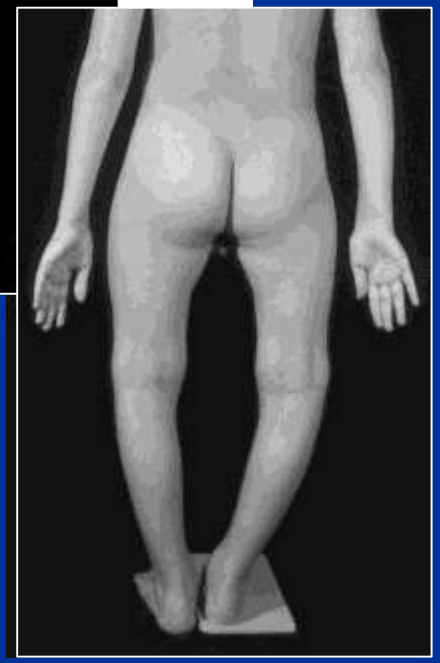


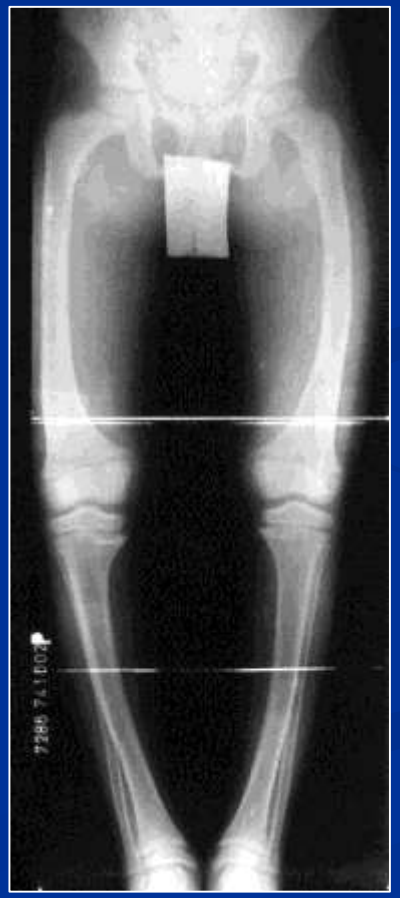
HYPOPHOSPHATEMIC RICKETS (VDRR)
Examples of surgery results: **Case 1 - boy**

During next years we observed progress of leg deformities with growth

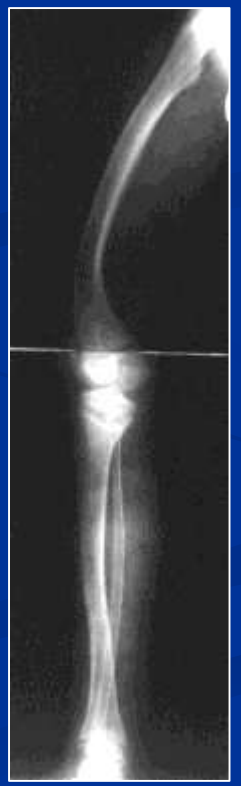


10 yrs





12 yrs

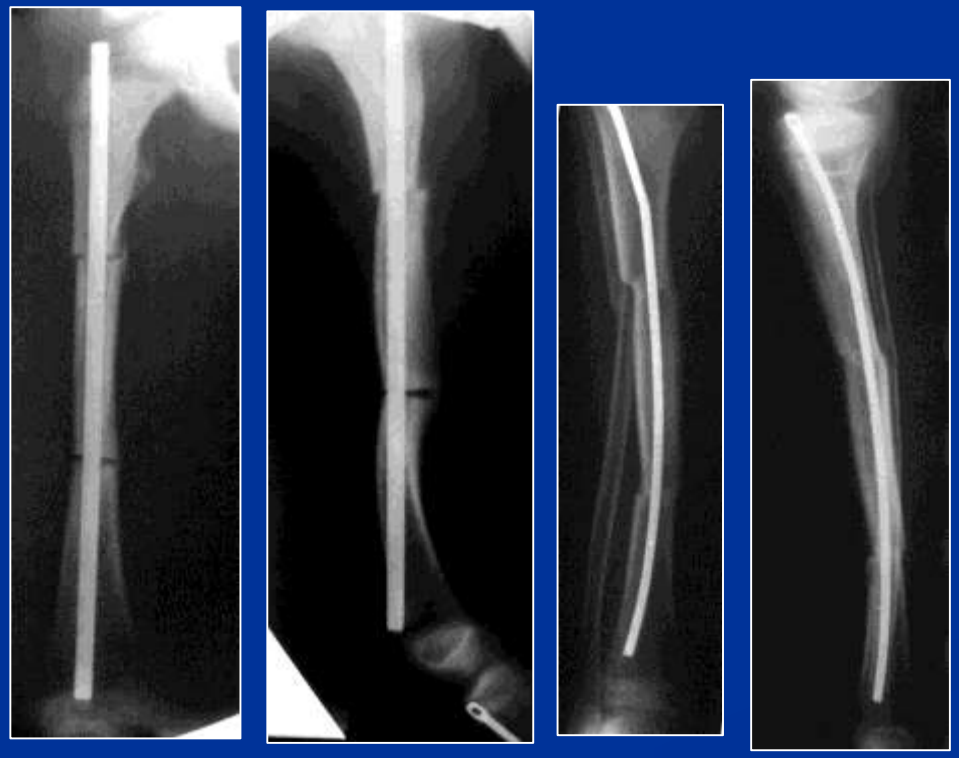


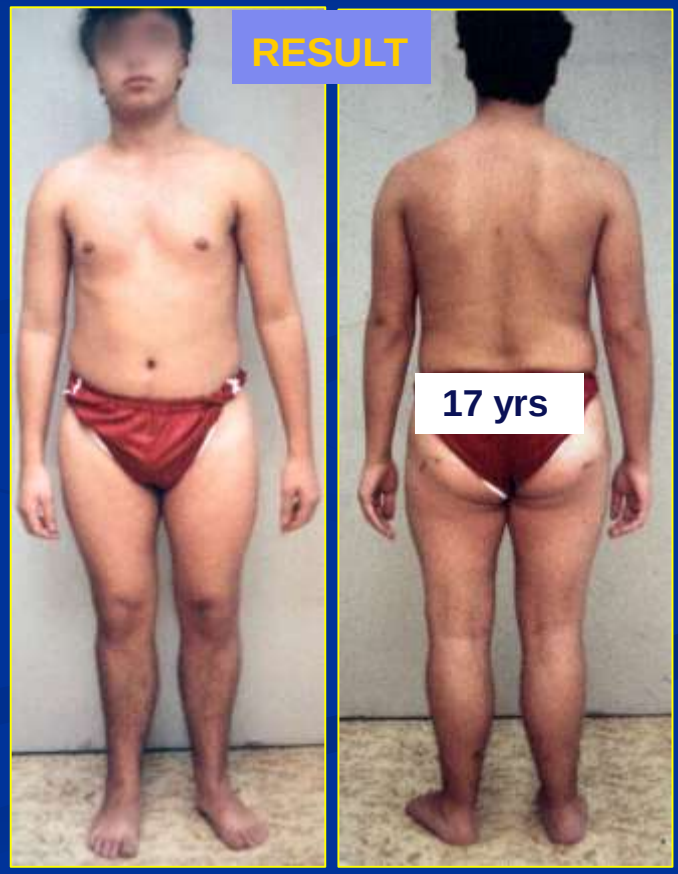
12.5 yrs.
131 cm (-3.4 SD)
26 kg (-3.3 SD)

HYPOPHOSPHATEMIC RICKETS (VDRR)
Examples of surgery results: Case 1 - boy

13.5 yrs. - double level corrective OT of both R femur (intramedullar fixation by Küntscher) and R tibia with fibula (IM fixation by Ender) was made, and simple spica cast (1 mo.)
13.8 yrs. - the same procedure on the left side
14.5 yrs. - 147 cm, 43 kg, extraction of Küntscher and Ender nails from both legs and corrective OT of proximal tibia (valgosation and external rotation) was performed

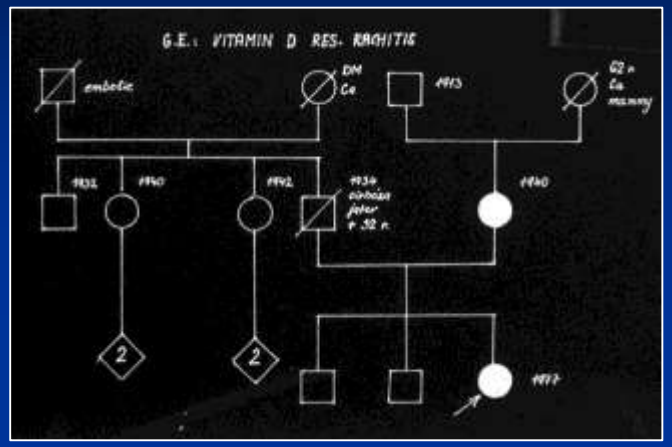
13.6 yrs. - 140 cm, 39 kg: R leg X-rays after surgery

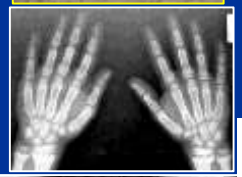




HYPOPHOSPHATEMIC RICKETS (VDRR)

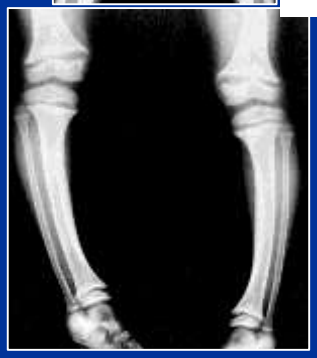
Examples of surgery results: **Case 2 - girl**

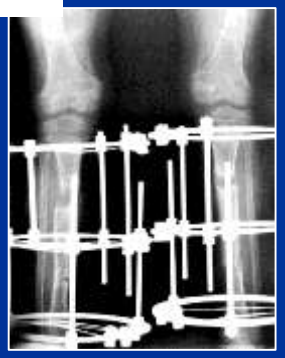




6.5 yrs
99 cm (-4.4 SD)

7 yrs





XLH was diagnosed in mother of the proband.

Supplementation by Calcitriol and inorganic phosphate was introduced.

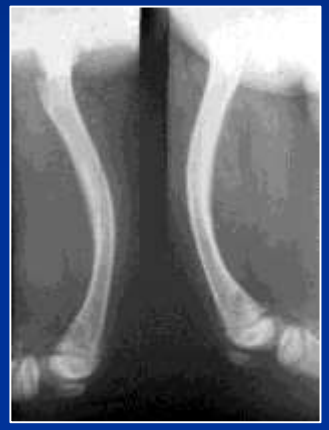
In 7 yrs

9 yrs.

HYPOPHOSPHATEMIC RICKETS (VDRR)

Examples of surgery results: **Case 2 - girl**

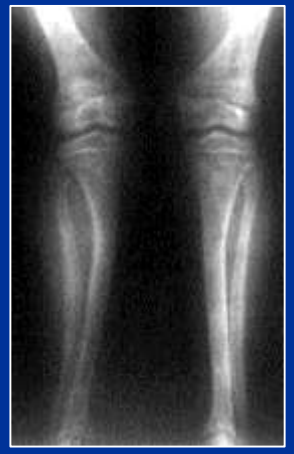
Valgus deformities of both tibia and anterolateral bowing of femoral diaphysis progressed during growth.
15 yrs we carried out multiple segmental OT of the R femur and R tibia in one stage. **16 yrs** the same procedure was done on the left side. **17 yrs** corrective OT of distal tibia.
Healing of all osteotomies was almost 3 times longer – remodelling lasted more than 2 years.

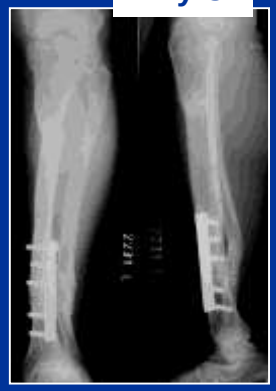


Histology proved widening of unossified osteoid seams at the trabeculae (volume of osteoid more than 5 %).

19 yrs
134 cm
53 kg

12 yrs





Photos of young woman showed significant improvement of biomechanical axis of legs.

25 yrs
135 cm
56 kg

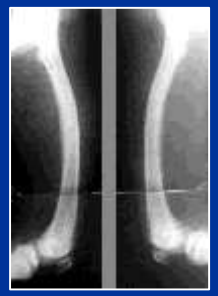
HYPHOSPHATEMIC RICKETS (VDRR)

Examples of surgery results: **Case 3 -girl**

XLH was diagnosed in 4 years of age. The same diagnosis in her father who has more severe involvement of skeleton.

11.5 yrs (1987)- supplementation by Calcitriol and Calcium efferv. was introduced.

146 cm (-1.8 SD)
37.5 kg (-1.1 SD)

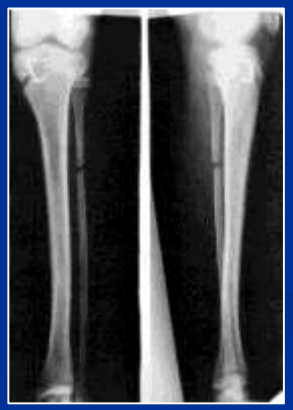


In 12 yrs double level corrective OT of both R femur (intramedullar fixation by Küntscher) and R tibia with fibula (IM fixation by Ender) were performed.

In 13 yrs double level corrective OT of L femur (intramedullar fixation by Küntscher) and OT of L fibula and OT alta arcuata of L tibia.

R shank after surgery

L shank after surgery



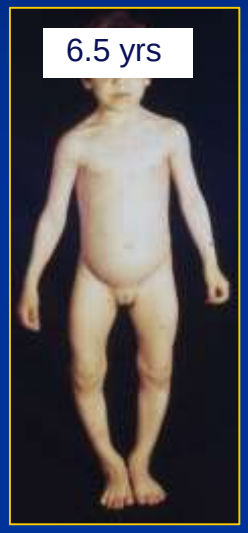
13 yrs 9 mo.

15 yrs

HYPOPHOSPHATEMIC RICKETS (VDRR)

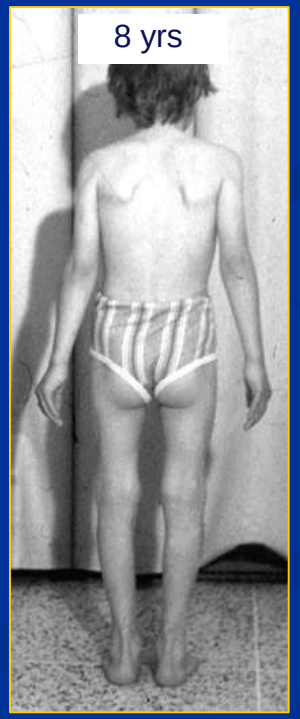
Examples of surgery results: **Case 4 - girl**

HR was confirmed in a girl **in 6.5 years** of age by histological investigation and biochemical examination. Supplementation by Calcitriol and inorganic phosphate was introduced. Two siblings and both parents do not suffer from XLH.



In 7 yrs. double level corrective OT of both tibia, fixation by Ilizarov *external fixator was made.*

In 16 yrs. *inward rotation OT (20°) of L tibia with OT of fibula was carried out.*



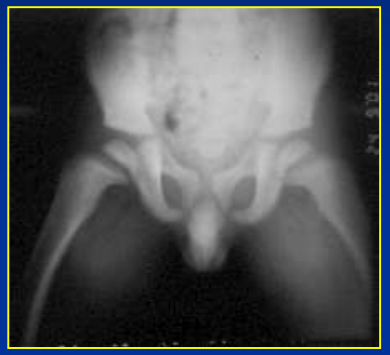
12,5 yrs.
131 cm (-3.9 SD)
26 kg(-3.3 SD)

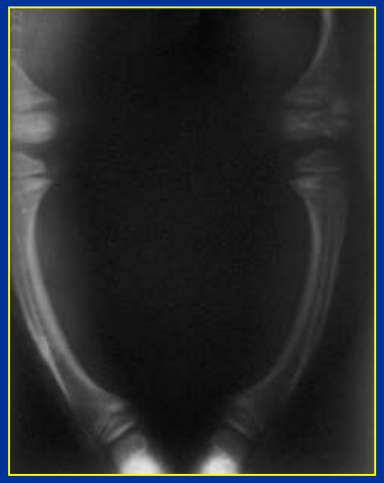
In 22 yrs.
mild varosity of knee joints (IC distance 3 cm)

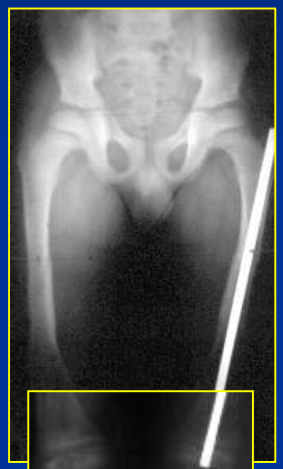
156 cm (-1.8 SD)
44 kg BMI 18.1

HYPOPHOSPHATEMIC RICKETS (VDRR)
Examples of surgery results: **Case 5 - boy**

XLH dignosed in 6 yrs. acording to X-rays and biochemical exmination. Supplementation by Calcitriol (Rocaltrol Roche) and inorganic phosphate (Phosphore Sandoz) was introduced.







18 yrs.

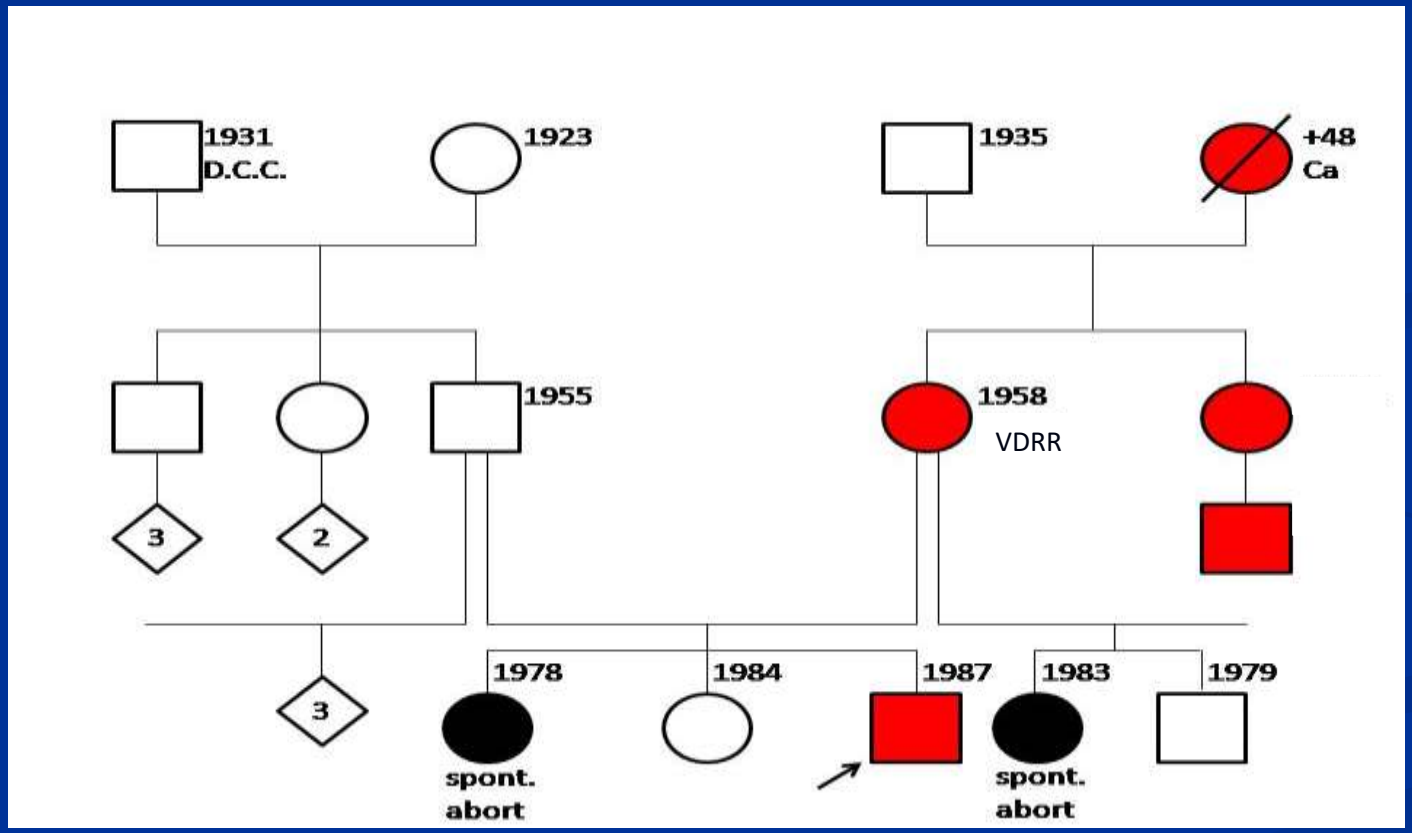
Surgery in 7 yrs: in two stages 2 level OT of femurs & shanks, Küntscher nail fixation.
In 11 yrs.: OT supracondylica fem. l. dx. – valgisation 15° and external rotation 30°.

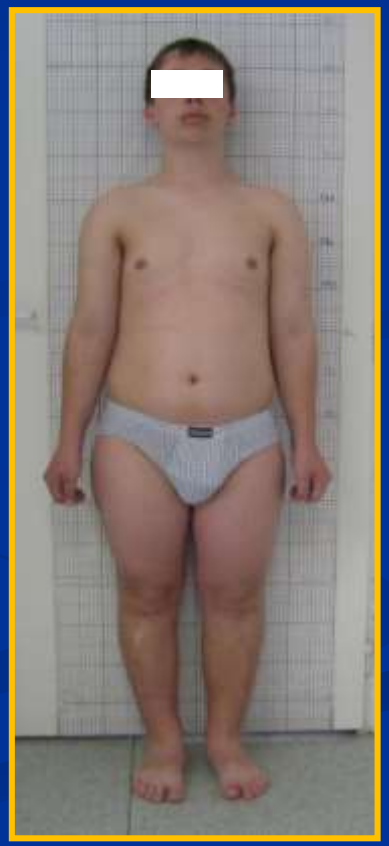
X-LINKED HYPOPHOSPHATEMIC RICKETS (XLH)

Examples of surgery results: **Case 5 - boy**

XD linked inheritance

transmission to the 3rd generation, mother, her sister and her son suffer from XLH, too.



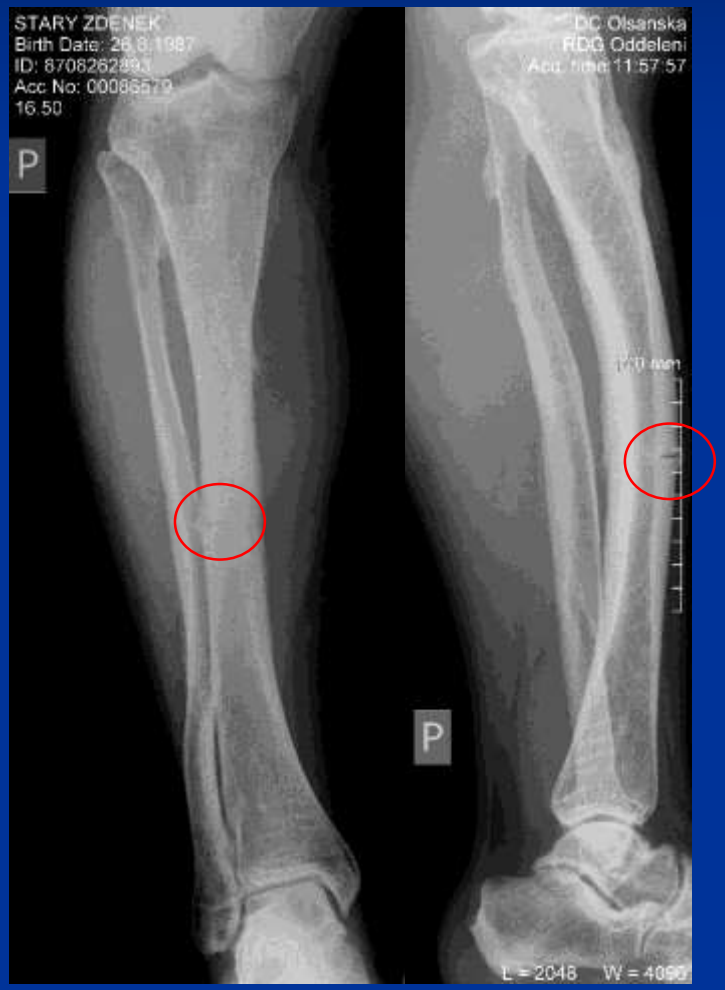


21 yrs.164 cm

HYPOPHOSPHATEMIC RICKETS (XLH)

Examples of surgery results: **Case 5 - boy**

30.5 yrs. – stress fracture of ventral corticalis of R tibia



30.5 let: 166 cm, 80.8 kg.

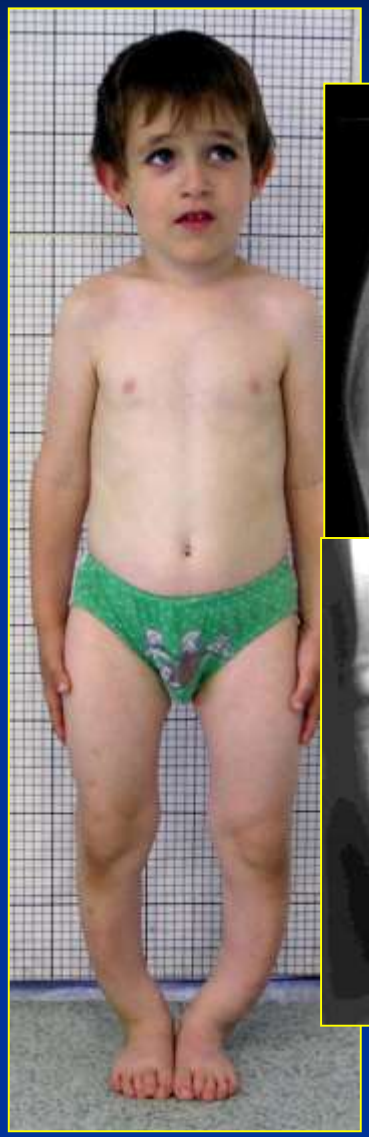
Densitometric exam. DEXA (Hologic Discovery A (S/N 85046):
lumbar spine: **hyperostosis** (BMD total - T/Z-score 3.5/3.5)
Neck of both hips and L forearm: **osteopenia**
Whole body density - normal area
Fat tissue: 31.9 %, 82nd percentile (US population).
BMI: 29.6 - **overweight**

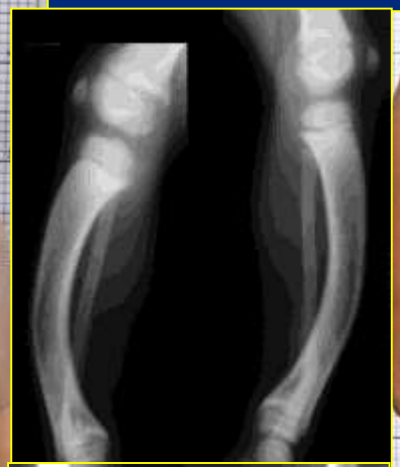
Biochemicaly: low P anorg., higher total ALP, higher CTX a PINP, low vitamine D
normal bone ALP, PTH a 1,25 (OH)2 vit. D
normal Calcium total and ionized
normal Calcium and phosphate waste in urin

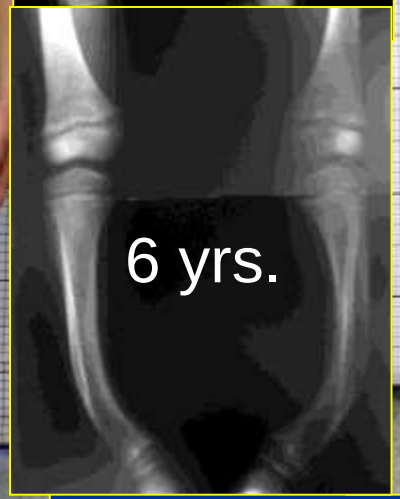
Medication: Rocaltrol 0,50 ug 1 caps in morning, Rocaltrol 0,25 ug 1 caps in evening.

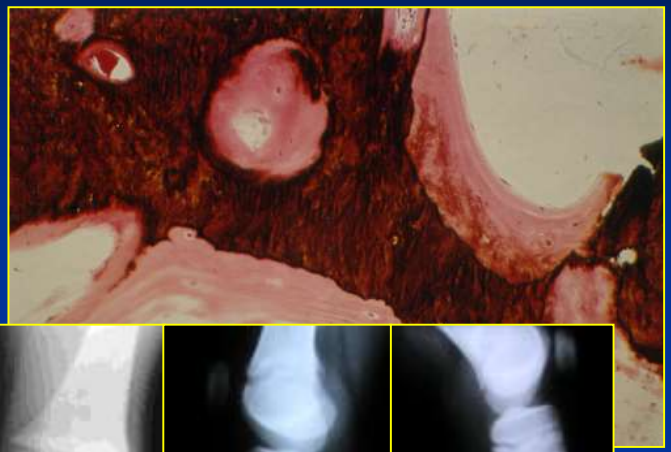
HYPOPHOSPHATEMIC RICKETS (XLH)

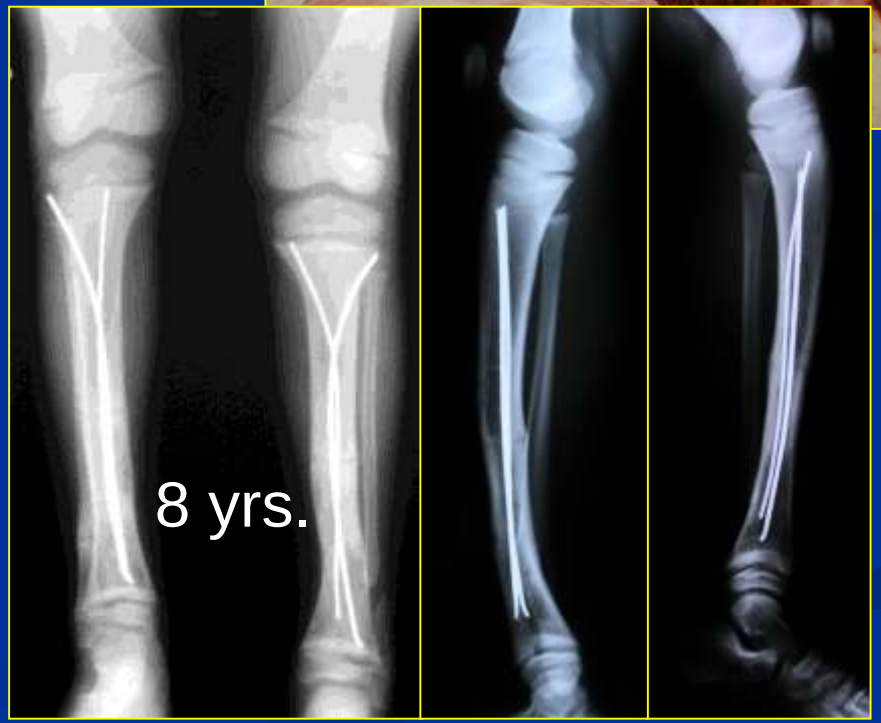
Examples of surgery results: **Case 6 - boy**











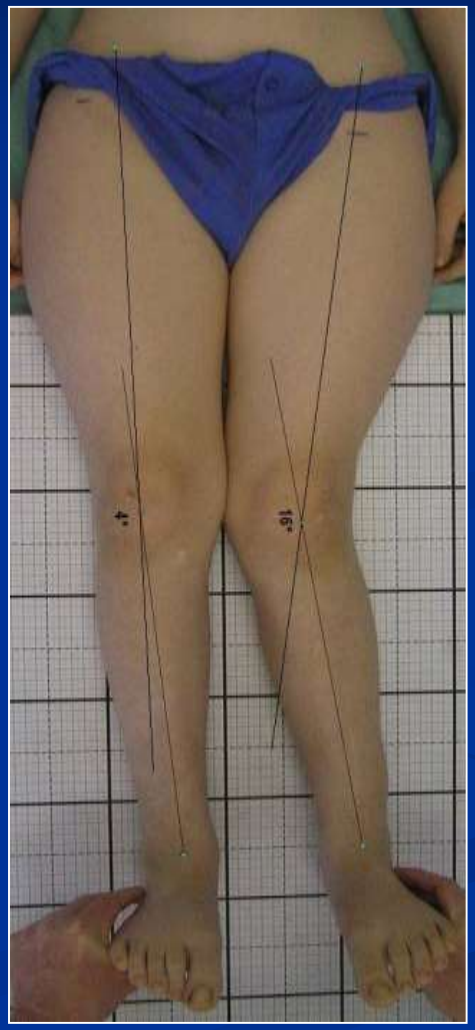
Surgery: 2 level OT of shanks + elastic nails (ESIN)

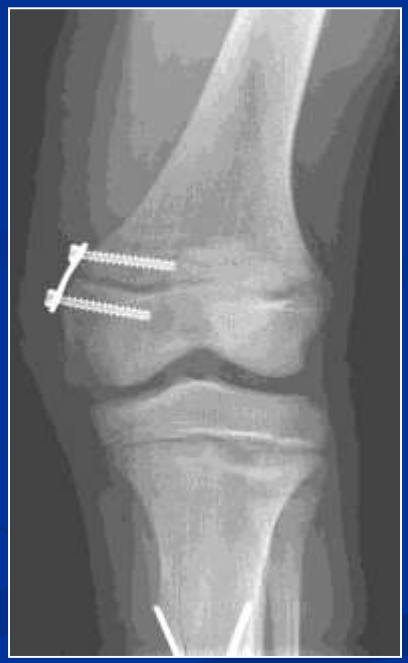
HYPOPHOSPHATEMIC RICKETS (XLH)
Examples of surgery results: **Case 6 - boy**

Mother is affected, too.

During growth spurt progression of asymmetric genua valga: T-F angle R/L was 4°/16°

Eight plate hemi-epiphysiodesis of distal left femur was introduced in 13 yrs.: **bone age**: TW3 RUS 12.4 but **sexual maturation** 13.5-14 yrs. (in rickets biological age underestimated)





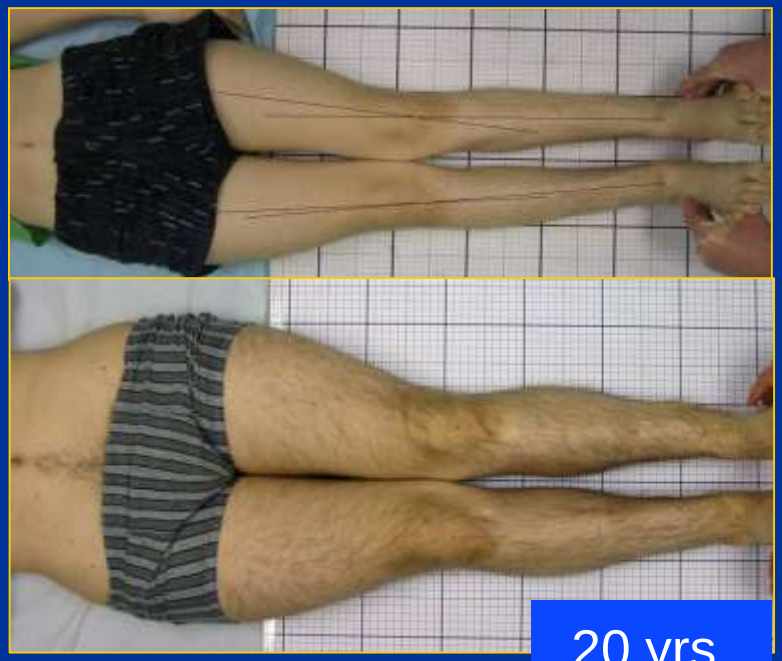
13 yrs.

HYPOPHOSPHATEMIC RICKETS (XLH)

Examples of surgery results: **Case 6**

13 yrs.

before surgery left T-F angle 16°



20 yrs.

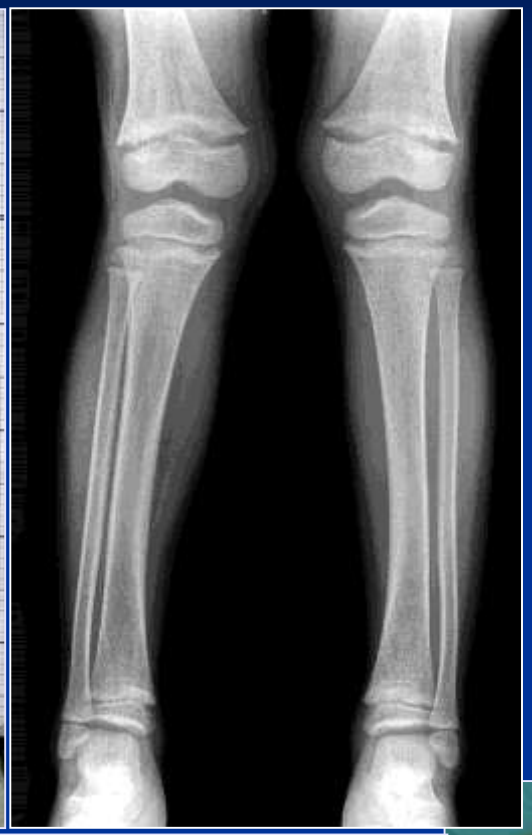
after surgery left T-F angle 7°

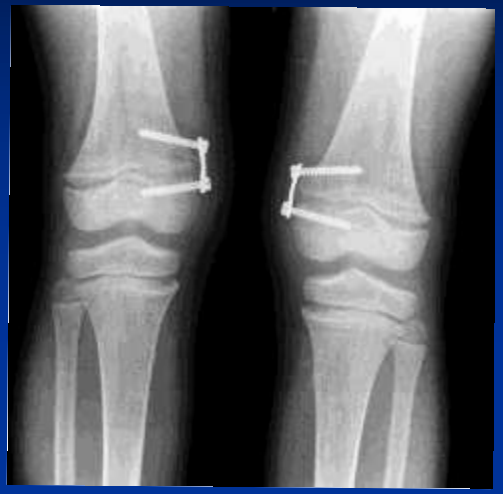
20 yrs.

T-F angle R/L 4°/7°

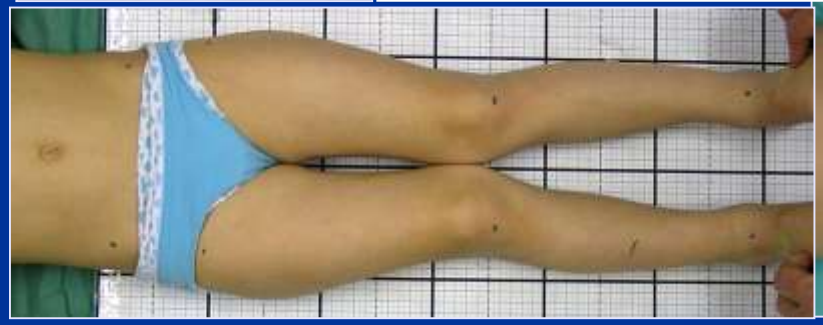
HYPOPHOSPHATEMIC RICKETS (XLH)

Examples of surgery results: **Case 7 - girl**



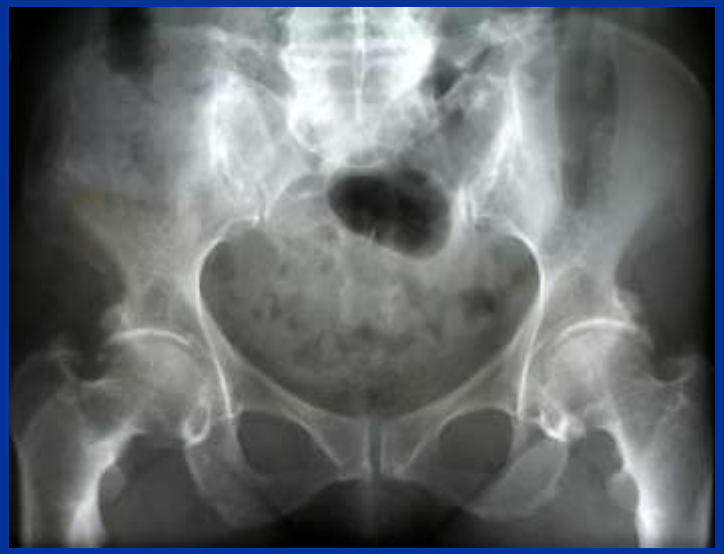


Girl 7 yrs.: Hemi-epiphysiodesis bil.
After 12 months extraction of 8 plates.

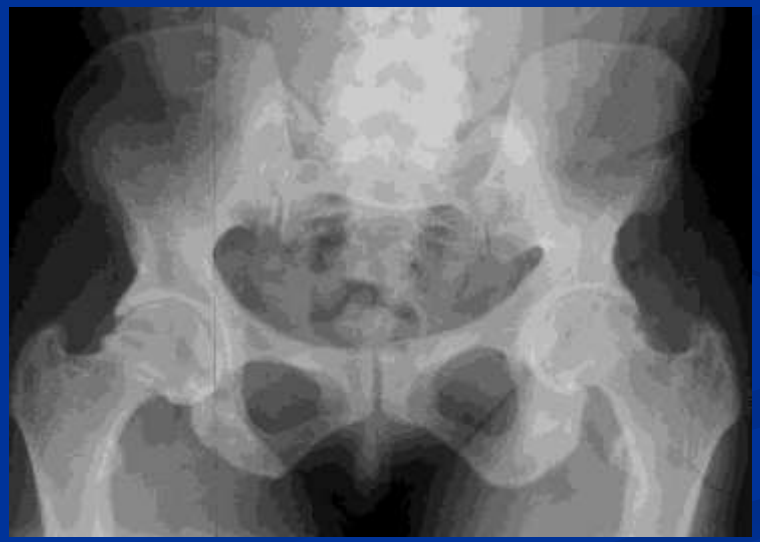


HYPOPHOSPHATEMIC RICKETS (XLH)
Adults

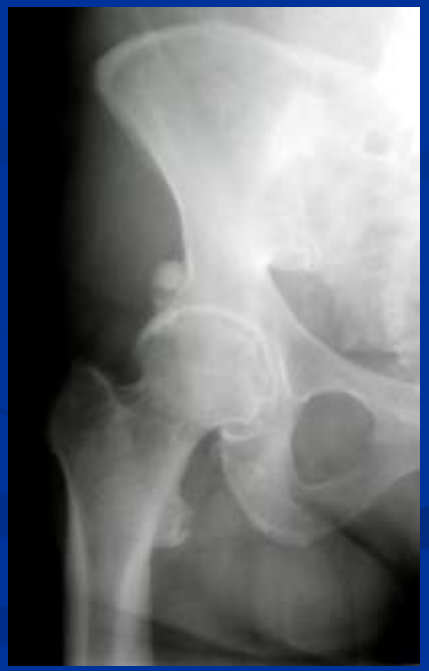
In adults we diagnosed **early osteoarthritis** of the hip and knee joints & **spondylarthritis.** It could be explained from biomechanical point of view as a consequence of **generalized osteosclerosis**. Very tough sclerotic subchondral bone disturbs joint cartilage during common daily activities. **Delayed healing of osteotomies is caused v.s. by disturbed bone metabolism.**



30 yrs – hip impingement, pincer type



50 yrs



60 yrs

HYPOPHOSPHATEMIC RICKETS (VDDR)
Conclusions

- Cohort of 29 Czech XLH patients contains more serious patients, most of them were indicated to surgical treatment.
- Conventional treatment both **substitution** of Calcitriol with inorganic phosphate, and **surgical treatment** did not changed significantly anthropometric parameters of presented patients (growth dynamics, adult height, proporcionality of stature).
- Biochemical markers without reference to substitution and age were disturbed in childhood and adults, too.
- Skeletal deformities progressed during whole growth period even after surgery.
- **We conclude that conventional treatment is not sufficient prevention of growth retardation, disproportionality and progression of skeletal deformities during growth period**.

HYPOPHOSPHATEMIC RICKETS
Perspective treatment

- Long term supplementation by Calcitriol and inorganic phosphate is often attended by **side effects** like secondary/tertiary hyperparathyroidism, hypercalcemia, hypercalciuria and nephrocalcinosis.
- Calcium and phosphate metabolism are disturbed. Mutations in genes influencing **FGF23** inhibit renal transport of phosphate (phosphate reabsorption) and cause renal phosphate wasting.
- There are encouraging studies of successful treatment with **human IgG1 monoclonal antibody** (Burosumab - KRN23) *against FGF23 in children with XLH* (Linglart et al. 2014, Carpenter et al. 2018, Imel EA et al. 2019).

AMBULANT CENTRE
for defects of locomotor apparatus
limited liability company

Thanks for your kind attention

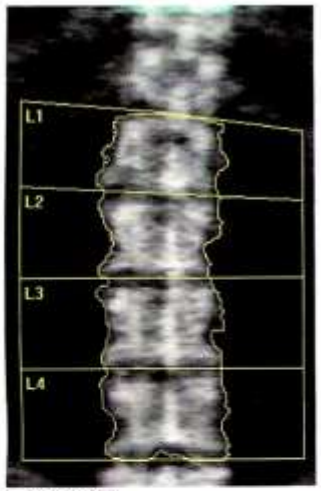
SOCIETY FOR CONNECTIVE TISSUES
J.E.Purkyně
PRAGUE • CZECH REPUBLIC

X-LINKED HYPOPHOSPHATEMIC RICKETS (XLH)

Densitometric examination DEXA proved a low density in childhood but **generalized osteosclerosis in adulthood: a man 39 years**

Name: Hradilek, Ludvik
Patient ID: 7205135718
DOB: 13 May 1972
Sex: Female
Ethnicity: White
Height: 156.0 cm
Weight: 90.0 kg
Age: 39

Referring Physician:



k = 1.156, d0 = 37.7
116 x 150
DAP: 2.3 cGy*cm²

Scan Information:

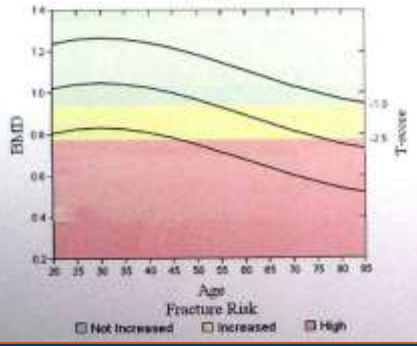
Scan Date: 22 June 2011 ID: A0622110T
Scan Type: f Lumbar Spine
Analysis: 22 June 2011 13:15 Version 13.2:5
Spine
Operator:
Model: Discovery Wi (S/N 85164)
Comment:

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	Z-score
L1	15.44	22.56	1.461	4.3	4.4
L2	15.65	23.70	1.514	4.4	4.6
L3	17.44	27.73	1.589	4.6	4.8
L4	18.70	29.56	1.581	4.7	4.9
Total	67.24	103.55	1.540	4.5	4.7

Total BMD CV 1.0%, ACF = 1.027, BCF = 0.985, TH = 9.364
WHO Classification: Normal
Fracture Risk: Not Increased

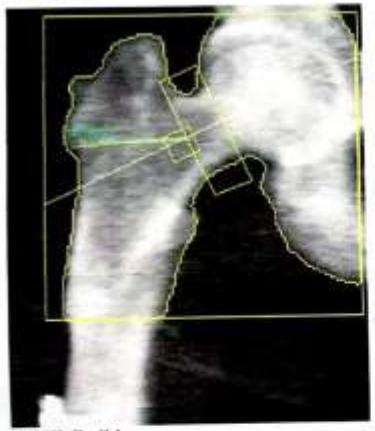
Total



Comment:

Name: Hradilek, Ludvik
Patient ID: 7205135718
DOB: 13 May 1972
Sex: Female
Ethnicity: White
Height: 156.0 cm
Weight: 90.0 kg
Age: 39

Referring Physician:



k = 1.153, d0 = 41.4
112 x 110
NECK: 47 x 15
DAP: 1.7 cGy*cm²

Scan Information:

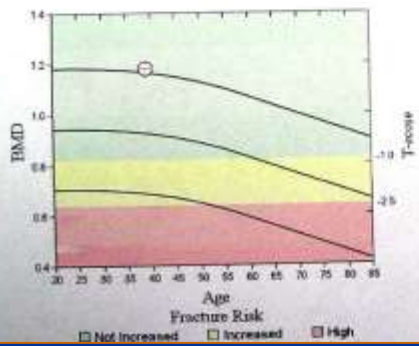
Scan Date: 22 June 2011 ID: A0622110X
Scan Type: f Right Hip
Analysis: 22 June 2011 13:12 Version 13.2:5
Hip
Operator:
Model: Discovery Wi (S/N 85164)
Comment:

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	Z-score
Neck	4.81	5.22	1.087	2.1	2.4
Troch	11.50	9.01	0.784	0.8	0.9
Inter	26.08	35.74	1.371	1.7	1.8
Total	42.39	49.98	1.179	1.9	2.1
Ward's	1.08	0.92	0.855	1.0	1.6

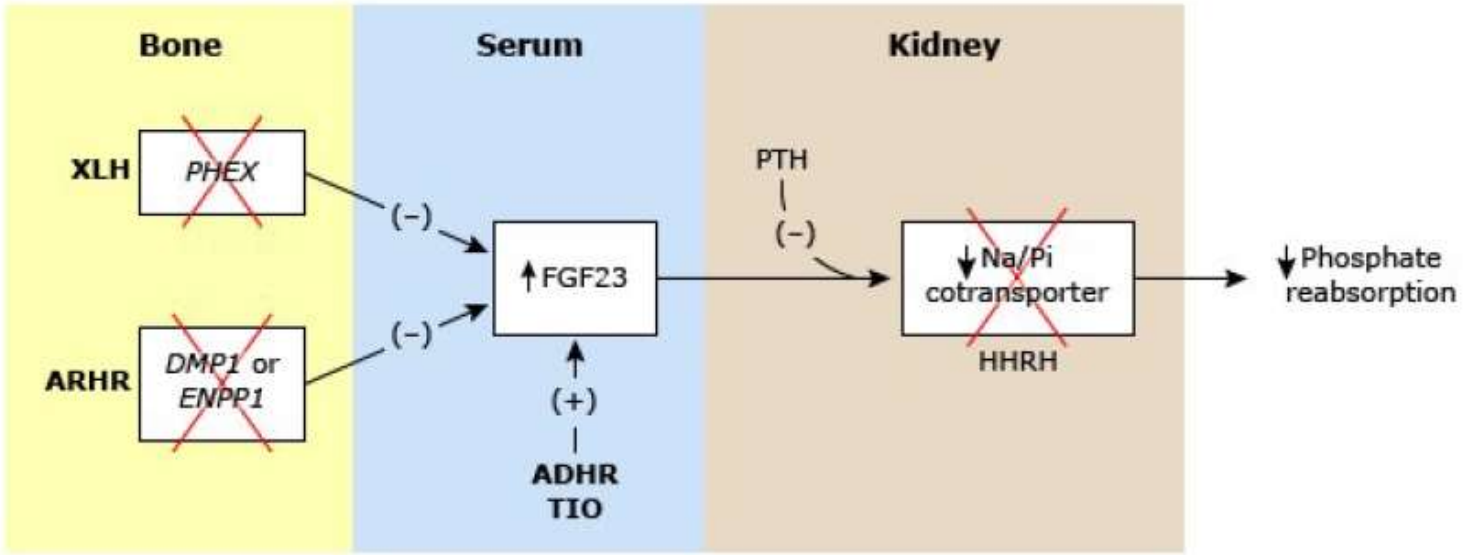
Total BMD CV 1.0%, ACF = 1.027, BCF = 0.985, TH = 7.576
WHO Classification: Normal
Fracture Risk: Not Increased

Total



Comment:

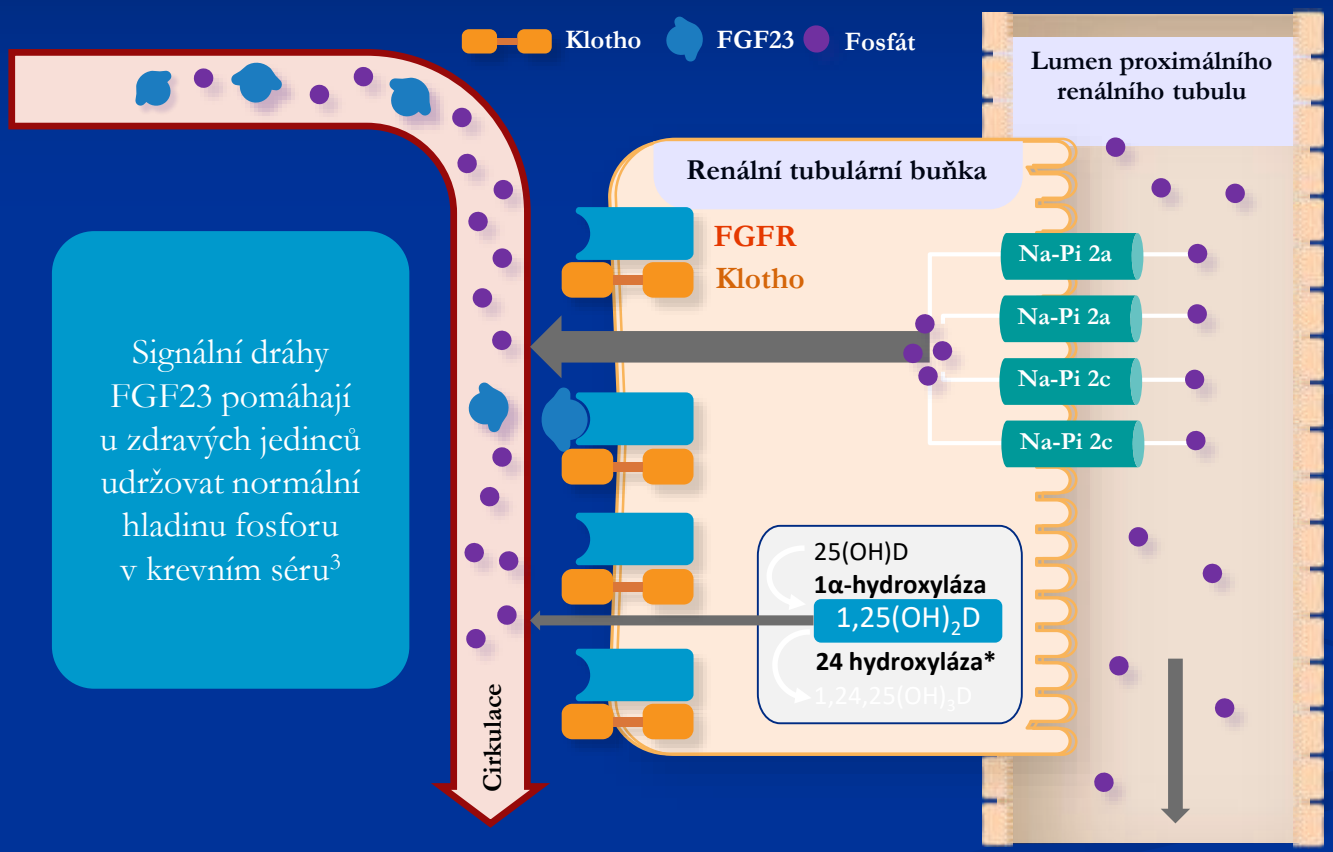
Pathways of renal phosphate wasting in hereditary hypophosphatemic rickets and tumor-induced osteomalacia



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.

Význam cirkulace FGF23 u zdravých jednotlivců[1–6]



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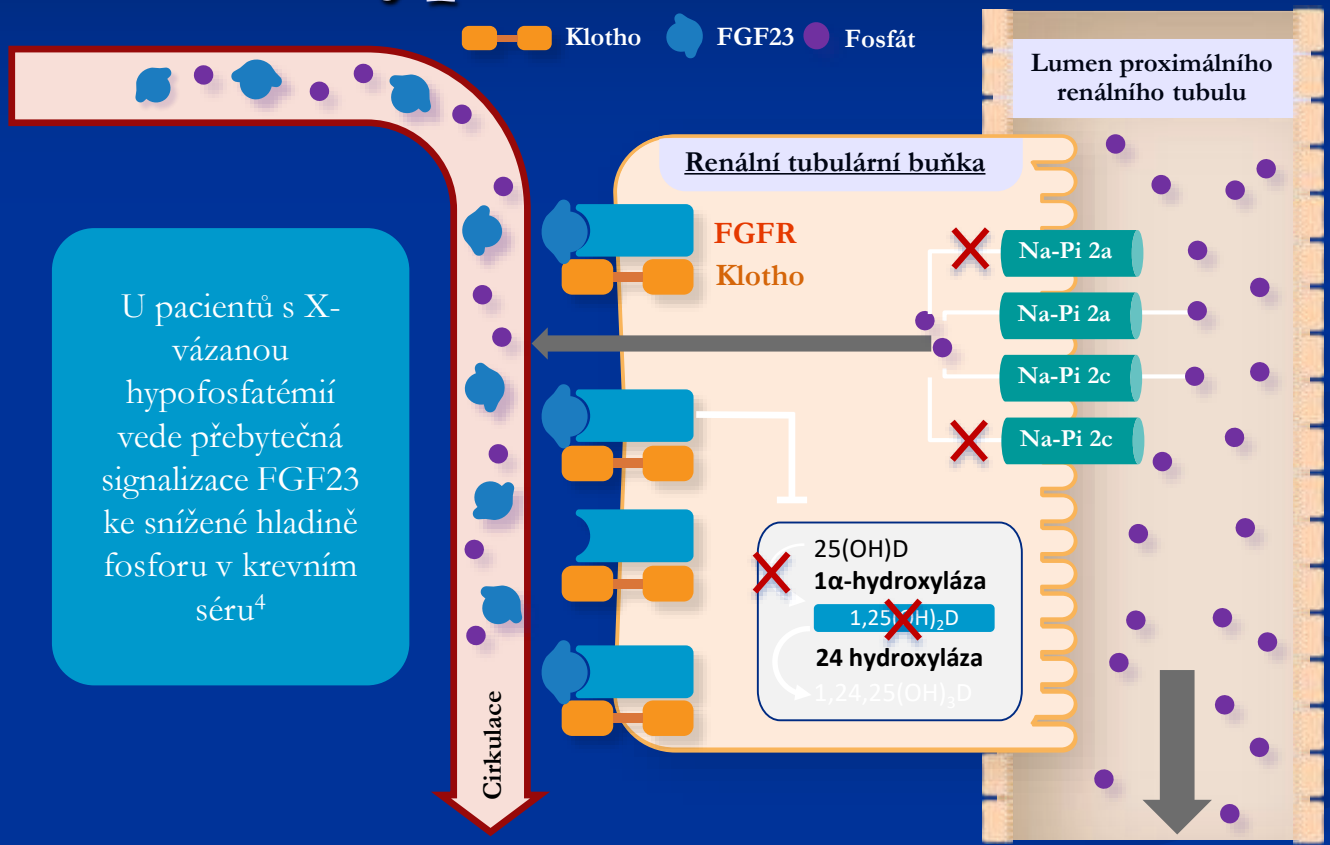
1. Kurosu et al. *J Biol Chem*. 2006;281:6120;
2. Andrukhova et al. *Bone*. 2012;51:621.
3. Penido and Alon. *Pediatr Nephrol*. 2012;27:2039;
4. Carpenter et al. *J Bone Miner Res*. 2011;26:1381;
5. Christakos et al. *Physiol Rev*. 2016;96:365;
6. Bikle. *Chemistry and Biology*. 2014:21:319.

Význam zvýšené cirkulace FGF23 u pacientů s X-vázanou hypofosfatémií[1–3]



U pacientů s X-vázanou hypofosfatémií vede přebytečná signalizace FGF23 ke snížené hladině fosforu v krevním séru[4]

1. Huang *et al*. *Bone Res*. 2013;2:120;
2. Quarles. *J Clin Invest*. 2008;118:3820;
3. Bikle. *Chemistry and Biology*. 2014:21:319;
4. Carpenter *et al*. *J Bone Miner Res*. 2011;26:1381

Burosumab – mechanismus účinku

Burosumab (KRN23) je plně humánní IgG1 monoklonální protilátka proti FGF23, která inhibuje nadměrnou aktivitu FGF23