OSTEOPOROSIS

UFRJ - IPPMG

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Outline

- How to optimize bone acquisition
- How to assess the bone health
- How to treat osteoporosis

Outline

- How to optimize bone acquisition during infancy, childhood, and adolescence

1. to treat osteoporosis in children and adolescents

Definition

Osteoporosis is a disease characterized by:

- decreased bone mass
- deterioration of bone microarchitetura

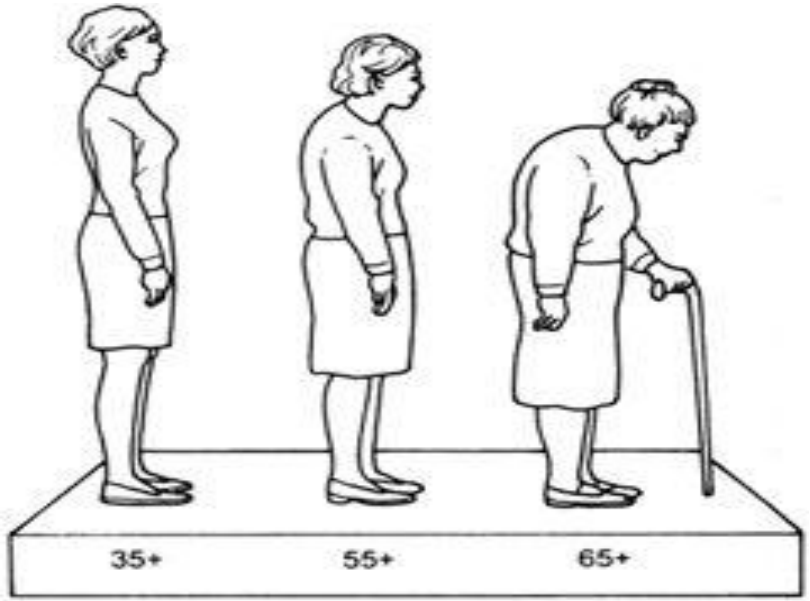
→

- increased fragility,
- susceptibility to fracture

When to think about osteoporosis?

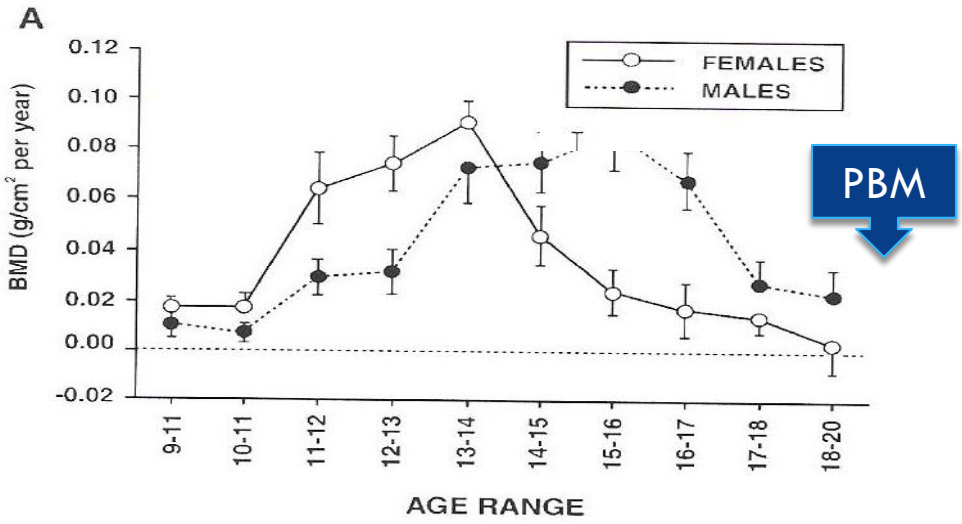
Osteoporose

Just after 50 years old?



OP depends on the **peak of bone mass (PBM)** acquired until the end of the second decade of life.

Peak of bone mass (PBM)



40 x

Girls (98)

- higher accumulation: 11-14y
- rapid fall: after 16 y
  or 2 years after menarche

Boys (100)

- higher accumulation: 13-17y
- no rapid fall until 20 y

G. Theintz. J CLin ENdocrinol Metabol 1992, 75(4): 1060

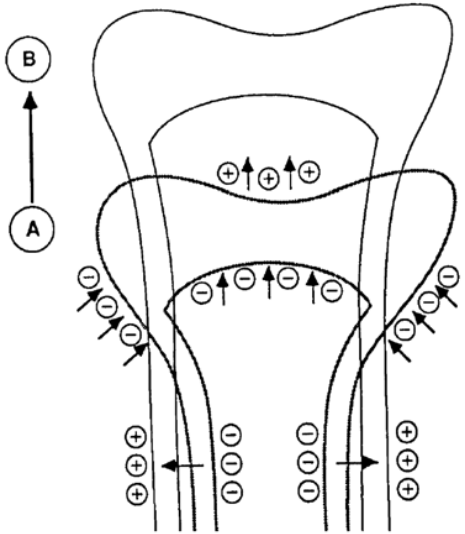
Asynchrony between height and BMC

	Girl – 3 yr	Girl 7 yr	Girl menarche
Height	50%	80%	97%
BMC	27%	40%	80-95%

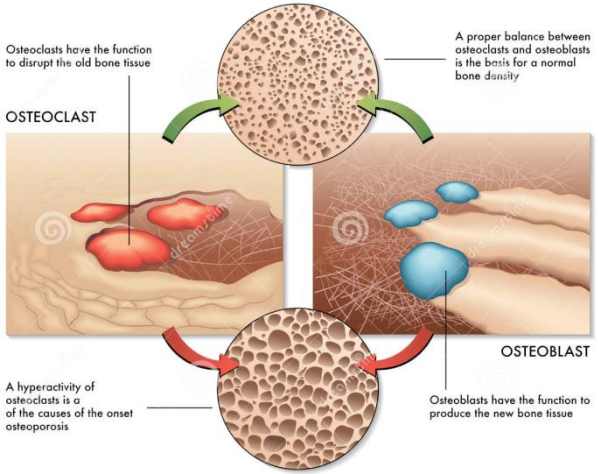
35% - 50% of BMC is acquired during adolescence

Bone modeling and remodeling

In children, bone formation exceeds bone resorption.



Modeling



Remodeling

- Genetic
- Hormones
- Nutrition
- Physical activity
- Inflammation (cytokines)

Favus M. Lipincott Williams & Wilkins; 2003:1–8

Factors affecting bone mass

Nonmodifiable

- Genetics
- Gender
- Ethnicity

Modifiable

- Nutrition
- Exercise
- Lifestyle
- Body weight and composition
- Hormonal status
- Drugs

Prevention

Nonmodifiable determinants of PBM

Genetic factors

- Account for 70% of the variance in bone mass
- No specific responsible gene has been identified.

Gender

- higher bone mass in males

Ethinicity

- higher bone mass in:
  afroamerican > hispanic > white non-hispanic or Asian

Modifiable determinants of PBM
Calcium

- 99% of total body calcium is in the skeleton
- Calcium is absorbed
  - Passive transport (10-15%)
  - Active transport (mediated by vit. D)
- Optimum calcium intake is responsible for **5 to 10%** of variation in the PBM.

Age	Calcium (mg/d)
0 - 6 mo	200
6 -12 mo	260
1 - 3 y	700
4 - 8 y	1000
9 - 18 y	1300

Sources of calcium

Milk and dairy products

- Milk - 240 ml = 300 mg
- Natural cheese - 45 ml = 300 mg
- Yogurt – 240 ml = 300 mg

Other

- Green leafy vegetables
- Calcium fortified cereals
  fruit juices
- Nuts

Age	Calcium (mg/d)
0 - 6 mo	200
6 -12 mo	260
1 - 3 y	700
4 - 8 y	1000
9 - 18 y	1300

Calcium supplements only in diseases, use of glucocorticoid or milk intolerance

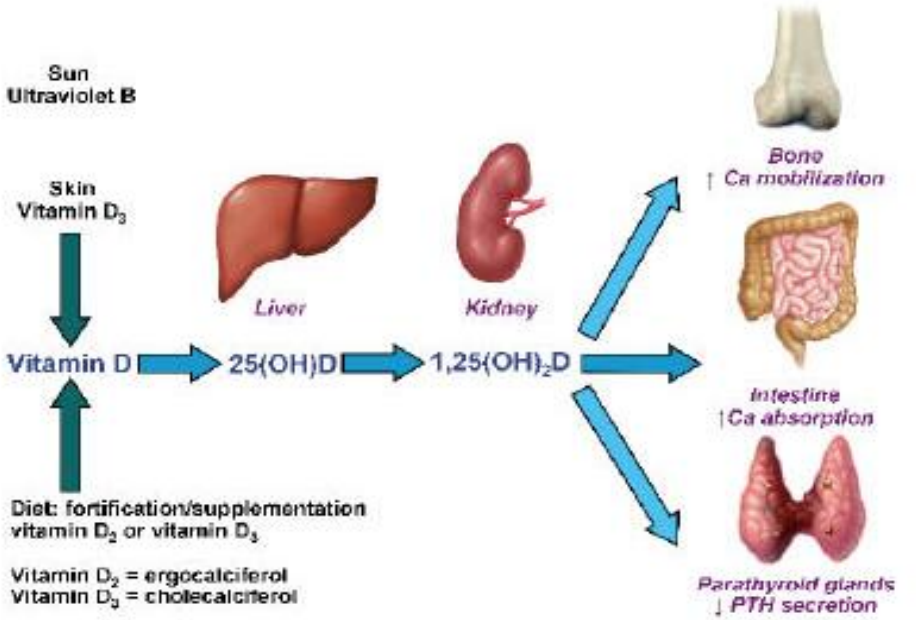
Soda consumption and sodium

- **Soda consumption** is associated with lower intake of milk and calcium

- **High sodium** diet promotes increased urinary calcium excretion
  - calcium share the same transport in the proximal tubule

Modifiable determinants of PBM
Vitamin D

Vitamin D is necessary for active transport of calcium.



Without vitamin D, only 10-15% of dietary calcium is absorved.

25 (OH) vitamina D

- Deficiente: <20 ng/mL
- Insuficiente: >20 ng <30 ng/mL
- Suficiente > 30 ng/mL

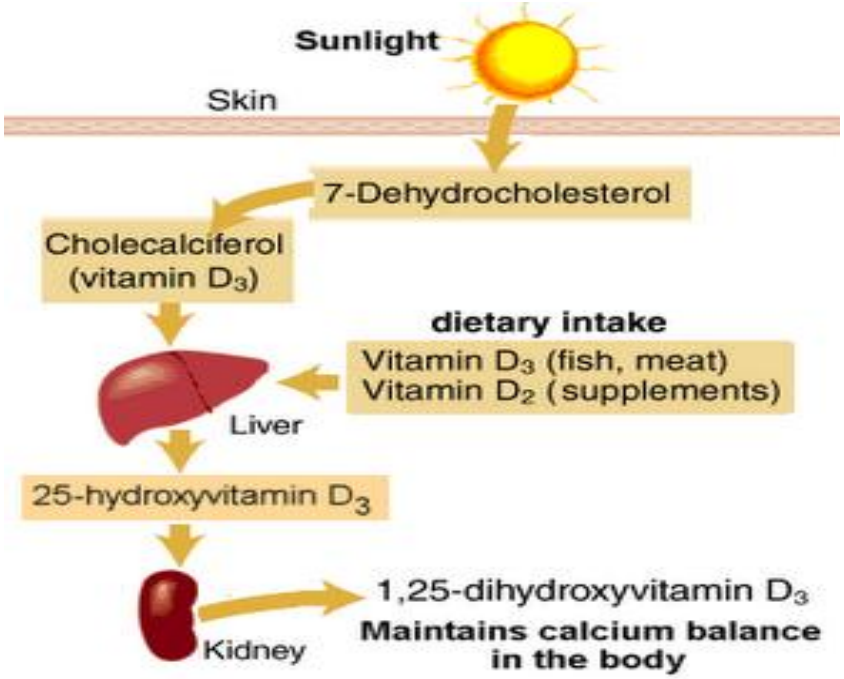
Preventing vitamin D deficiency

Vitamin D deficiency → reduces bone mass

Age	Vitamin D (IU/d)
0 - 6 mo	400
6 - 12 mo	400
1 - 3 y	600
4 - 8 y	600
9- 18 y	600

Obese children and patients on glucocorticoids, anticonvulsants, chemotherapy and antiretroviral may require 2 to 4 times the recommended dose.

Vitamin D metabolism



- No sunlight exposure
- Liver disease
- Renal disease

Sources of vitamin D

- **Sunlight**

- **Diet**
  - cod liver oil
  - fatty fish (salmon, sardines, tuna)
  - fortified foods
    - infant formula, cow milk, yogurts, cheeses, juices, and breakfast cereals

- **Supplementation**
  - < 1 year = 400 IU/d
  - 1 year and older = 600 IU/d

Modifiable determinants of PBM

Exercise

Walking, jogging, jumping and dancing are better for bone health than swimming or bicycle riding.

- Immobilization causes rapid decline in bone mass.
- Mechanical forces (exercises) applied to the skeleton increase bone formation and improve bone mineral accrual.
- The greatest effect is observed in early puberty.
- 3 to 4 times in a week, minimum 30 minutes

Modifiable determinants of PBM
Body weight and composition

- Bone Mineral Density (BMD) is directly correlated with the Body Mass Index.

Maintenance of a healthy body weight is recommended to optimize bone health.

Modifiable determinants of PBM
Lifestyle

Adults

Smoking

Caffeine

Alcohol

Children

These behaviors should be avoided in children and adolescents

Lifestyle choices may confer additional risk for BMD deficits.

Modifiable determinants of PBM

Hormonal status

- Estrogen deficiency is associated with increased bone resorption and increased fracture risk.

- Glucocorticoid excess increases bone resorption and impairs bone formation.

Modifiable determinants of PMB Drugs

- Glucocorticoids
- Anticonvulsants
- Heparin

Take home messages

- Prevention of osteoporosis begins in the infancy.
- Peak of bone mass is reached at the end of the second decade.
- Pediatricians should be aware that is important to improve the modifiable determinants such as: calcium, vitamin D, exercises, body weight and composition and hormonal status

Outline

- How to assess the bone health in children and adolescents

Osteoporosis

Primary osteoporosis

- Rare
- Usually a genetic disease
- Intrinsic bone abnormality

Secondary osteoporosis

- Chronic disease
- Treatment with some drugs

Primary osteoporosis

- Osteogenesis imperfecta
- Idiopathic juvenile osteoporosis
- X-linked hypophosphatemic rickets
- Hypophosphatasia
- Homocystinuria
- Wilson's disease
- Ehler-Danlos syndrome
- Marfan syndrome and others

J Pediatrics 2014, 40:55

Secondary osteoporosis

- **Rheumatic diseases:** JIA, SLE, JDM, inflammatory bowel diseases
- **Nutritional deficiencies and malabsorption**
  - Celiac disease, cystic fibrosis
- **Impaired mobility**
  - Cerebral palsy, spina bifida, Duchenne dystrophy, etc.
- **Infiltrative disorders**
  - Leukemia, inborn errors of metabolism
- **Endocrinopathies**
  - **Excess:** glucocorticoid, PTH, thyroxine
  - **Deficit:** hypogonadism, growth hormone
- **Medications:**
  - glucocorticoid, antiepileptics, chemotherapeutic radiotherapy, heparina, dicumarínicos, proton pump inhibitors, serotonin reuptake inhibitors, depot medroxyprogesterone acetate/contraceptives

Secondary osteoporosis

Glucocorticoid-induced osteoporosis (GIO)

- Most common form of secondary osteoporosis
- 6% of the children with autoimmune disease, taking GC can present compression vertebral fractures in the first year of use.
- Combination of increased bone resorption, decreased bone formation
- Fracture risk increases markedly in the 1st 3 months after GC initiation (doses > 5 - 7,5 mg/d)

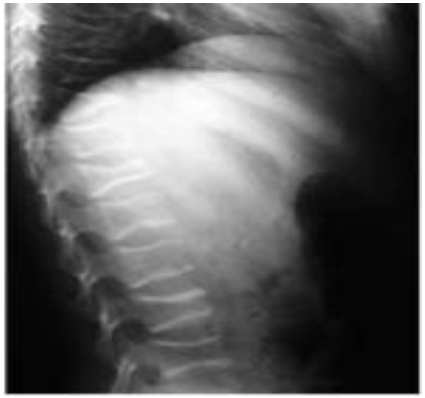
Osteoporosis
History and Physical exam

History	Physical exam
◆ Silent ◆ Fracture of long bones ◆ Low back pain (vertebral fractures) ◆ Painful feet	◆ PE can be normal ◆ Height, weight, Tanner ◆ Pain (mild to moderate) ◆ Sclera color ◆ Fractures and deformities ◆ Deviation of spine and limbs

Investigate: underlying disease and use of drugs

Juvenile Idiopathic Osteoporosis

- Low back pain
- Pain in feet, hips, ankles
- Kyphosis
- Chest short
- Limp
- Fractures



Osteoporosis

X- Rays

- Cheap, available but lacks sensibility
- It is necessary loss 30-40% of bone mass to diagnose osteoporosis
- Important to evaluate integrity of the bone and deformities caused by microfractures

Osteoporosis

X- Rays

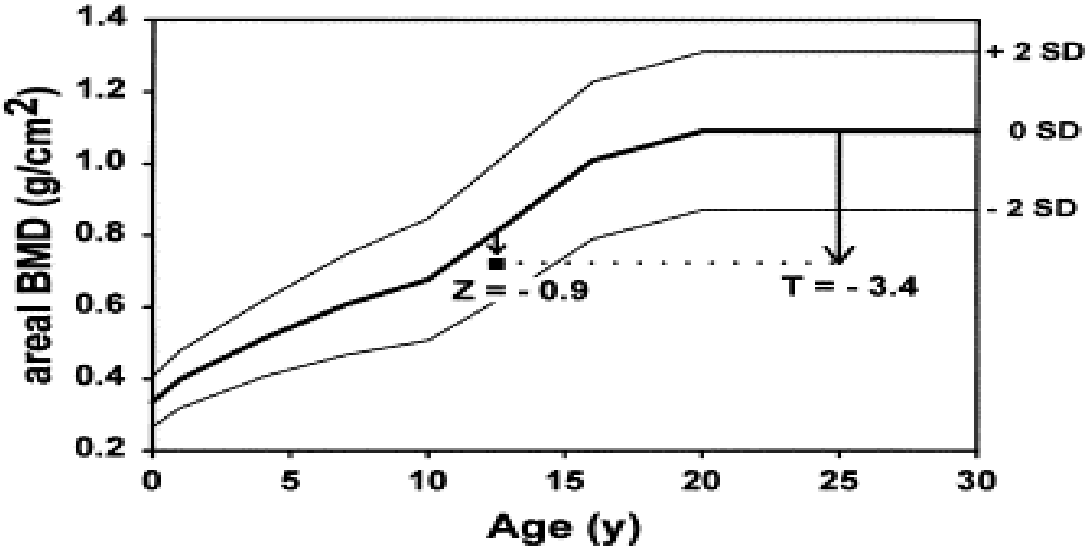
Fractures

Thin bones

Vertebrae deformity

DUAL ENERGY X-RAY (DXA)

Z-score (not t-score as in adults)



- **Prefered sites**
  - Total body minus the head
  - Lumbar spine
- **Results** → g/cm2 (BMC/area)
- **Z-score**
  - compares with same age
- **T-score**
  - compares to young adult

DXA - advantages

- Easy
- Low dose of radiation
- Rapid scanning (1 to 5 min)
- Results – bone density
- DXA – evaluate the response to therapy

Bone resistance depends on bone mass, geometry and microarchitecture.

DXA in adults: diagnosis

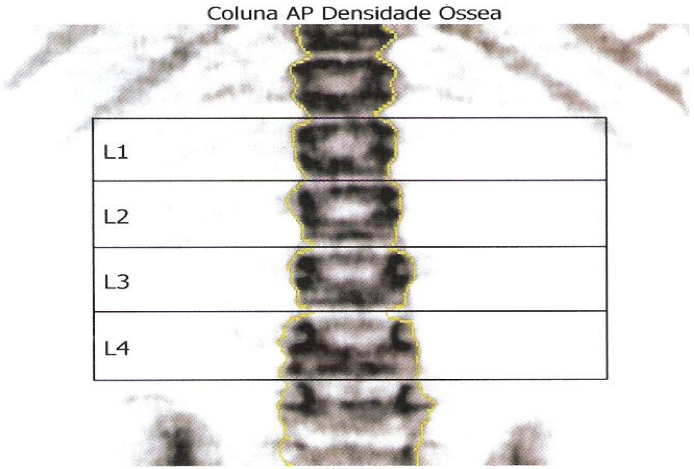
Osteoporosis

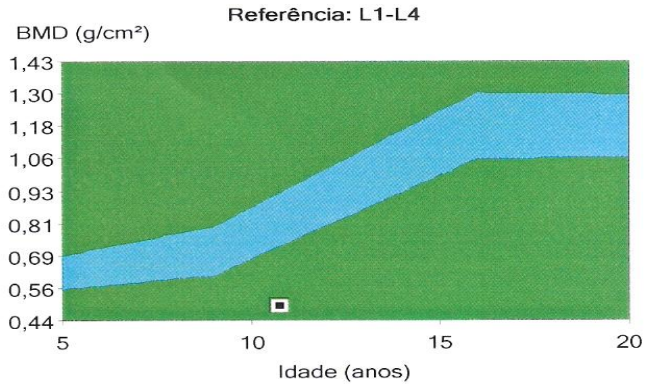
- BMD is 2,5 or more SD below the young adult mean
- T-score equal or less than -2.5

Osteopenia

- BMD is 1 SD below the young adult mean
- T score equal or less than -1,0

What is the diagnosis?





Região	BMD [1] (g/cm²)	Corr. Etária [3] (%)	Corr. Etária [3] Z-Score
L1	0,492	64	-2,6
L2	0,479	57	-3,4
L3	0,507	60	-3,2
L4	0,510	60	-3,1
L1-L2	0,485	61	-2,9
L1-L3	0,493	61	-3,0
L1-L4	0,498	60	-3,1
L2-L3	0,494	58	-3,3
L2-L4	0,500	59	-3,2
L3-L4	0,509	60	-3,1

BMD (Z-score < - 2)
low density for chronologic age

DXA in children: diagnosis of low BMD

Due to influence of the bone size in the values of DMO,
it is not possible to establish the fracture risk based only on DXA.

Low BMD or BMC
For age and sex

z score $\leq$ -2

+

Clinically significant fracture history

- a long-bone fracture of the lower extremity
- 2 or more long-bone fracture of upper extremity
- a vertebral compression fracture

"Osteopenia" is not used in pediatric DXA reports

2007/2013 Second Pediatric Position Development Conference

When to order a DXA in children?

- Clinically significant fractures
  - defined as falling from standing height or less (not fingers and toes).
- Osteoporosis seen in X-rays
- All chronic diseases that affect bones
  - genetic, rheumatic, neurological, inflamatories
  - adolescent athlete + amenorrhea more than > 6 months
- Use of some medications that affect bones
  - glucocorticoid, antiretroviral, anticonvulsants

Imaging exams

- **Quantitative computed tomography (QCT)**
  - QTC measures the true volumetric BMD (g/cm3)
  - Access bone microarchitecture (trabecular and cortical bone)
  - Radiation exposure is high.
  - Expensive
  - Used primarily in researches.

- **Quantitative ultrasonography (QUS)**
  - QUS measures the speed of an ultrasound wave through bone.
  - Advantages: safe, non invasive, low cost, fast, noradiation, portability
  - Disadvantages: poor precision and difficult interpretation (lack of pediatric reference data)

Pediatr Radiol 2014, 44(12):1573

Laboratory exams

Children with low BMD

- Hemogram
- Calcium (serum, urine)
- Phosphorus (serum, urine)
- Alkaline phosphatase
- Vitamin D
- Parathormone, T4 L, TSH

Bone remodeling

- Bone formation
  - N1NP
- Bone resorption
  - CTx

Take home messages

- DXA is the best method to measure BMD.
- DXA in children is insufficient to diagnose osteoporosis.
- Osteoporosis in children: low BMD + clinically significant fracture.
- The utility of biomarkers in children is restricted.

Outline

- How to treat osteoporosis in children and adolescents

First line treatment

1. Improve the treatment of the underlying disorder
2. Decrease glucocorticoids
3. General measures

Treatment of the underlying disorder

Control the activity of the underlying disorder.

- Celiac disease ……gluten - free diet
- Endocrinopathies ……prescribe hormones
- Rheumatic diseases ……control of inflammation

Improve treatment

- Decrease glucocorticoids

Treatment: General measures

- Appropriate nutrition, calcium intake
- Vitamin D correction
- Body weight and composition
- Encourage weight-bearing physical activity
- Hormonal status

Vitamin D: correction

Vitamin D3, calcitriol and alfacalcitriol

Patient	IU/day
Healthy children	400 to 600 IU/d
Vitamin deficient children	Attack: 50.000 IU/wk for 6 to 8 weeks or 2.000 IU/d for 6 – 8 weeks Maintenance: 400 to 600 U/day
Vitamin D deficient children plus: malabsorption, obesity, medications	4.000 – 6.000/d for 6 – 8 weeks

Repeat serum 25 OH-D at the end of treatment.

Biphosphonates

- Drugs not approved for children (inhibit bone resorption)
- Action: decrease bone resorption
- First use in osteogenesis imperfecta (1998)
- Multiple studies: heterogeneous, different definitions of osteoporosis and few controlled trials.

Biphosphonates: Which one ?

No study comparing efficacy.
Choice based on the safety profile in a particular patient.

- **Intravenous**
  - Pamidronate
  - Zoledronate
- **Oral**
  - Alendronate
  - Risedronate

Biphosphonates - doses

Biphosphonate	Route	Doses
Pamidronate	IV	0,5 – 1 mg/Kg/d-3 days each 3-4 months 1 mg/Kg/dose each 1-3 months
Alendronate	Oral	1-2 mg/kg/d < 40 kg: 5 mg/d >40 kg: 10 mg/day < 20 kg: 5 mg/d or 35 mg/wk > 20 kg: 10 mg/d or 70 mg/wk
Zoledronate	IV	0,025 mg/kg each 3 months 0,05 mg/kg each 4 months 0,05 mg/kg each 6 months
Risedronate	Oral	0,05 mg/Kg/d

Biphosphonates: management

- **Vitamin D and calcium intake**
  - be sure about adequate levels of vitamin D and adequate calcium intake

- **Control the treatment with DXA**
  - 1st DXA before starting treatment
  - 6/6 months in the 2 first years
  - Annual after the 3rd year

Biphosphonates: adverse effects

IV biphosphonates

Adverse effects

- Flu-like syndrome (1st-3rd d)
  - Fever, myalgia
- Hypocalcemia, hypophosphoremia and hypomagnesemia

Caution

- Levels of vitamin D?
- Calcium intake?
- Start with lower dose?

Oral biphosphonates

Adverse effect

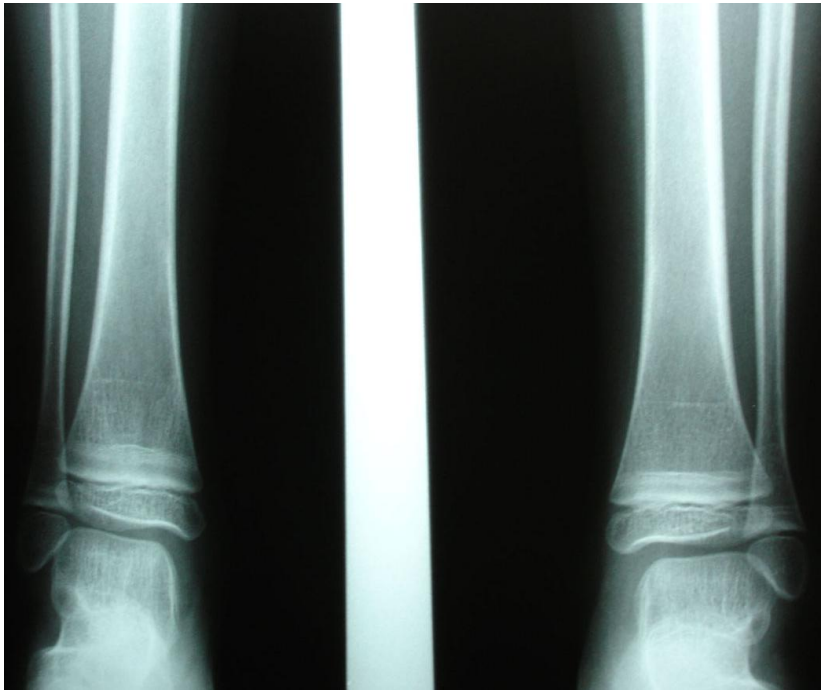
- Esophagitis
- Musculoskeletal pain

Caution

- Levels of vitamin D? calcium?
- Drink with a glass of water
- Stand, walk or sit and remain fasting for 30-45 minutes

Biphosphonates: during the treatment

- Pattern of absorption of biphosphonate in bone is characteristic for children
-
- BF are concentrate in active growth zones such as metaphysis of long bones.
- X-rays: sclerotic bands reflects the previous use of BF



- Boy, 8 y
- 7 cycles of treatment
- The 7 evenly spaced bands show that growth continued during therapy.

before

after

Boy, 6 y

18 months of treatment

Increased height of vertebrae

BMD increased:

0,205 g/cm2

0,371 g/cm2

Decreased the fracture risk?

Biphosphonates: long-term

- Pregnancy (or potential): Not recommended
- Necrosis of jaw has not reported yet.

  Recommendation: odontological review before starting BF
- Osteopetrosis and atypical fracture in patients receiving continuously doses much more higher than recommended
- Withdraw the drug 3 to 4 months before bone surgery

Take home messages

1. First line of treatment is: treatment of underlying disease, low dose (or no dose) of glucocorticoids and general measures to achieve a good PBM.
2. Biphosphonates are drugs not approved for children with osteoporosis but sometimes can be used with relative safety.
3. DXA should be used to guide treatment.

Thank you !