
بسم الله النور

Osteoporosis in Children and Adolescents

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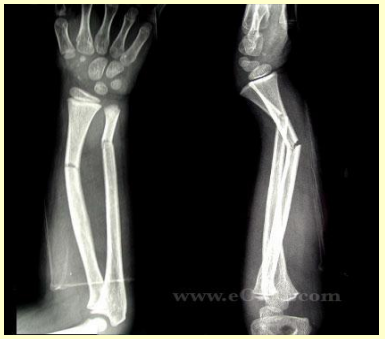
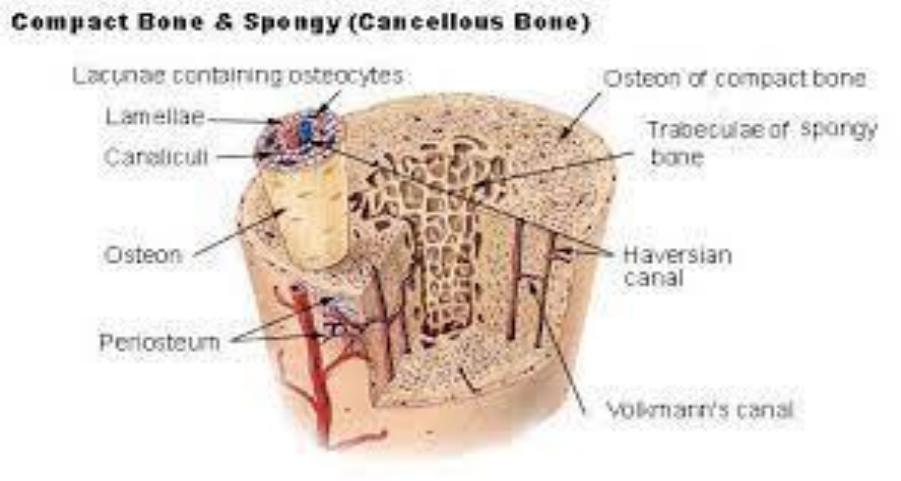
Content

- When osteoporosis should be suspected
- How to prevent it
- Laboratory tests used in screening
- Imaging tests used in screening
- Calcium and vitamin D supplementation
- Bisphosphonates treatment
- New drugs
- Follow-up
- Glucocorticoid-induced osteoporosis



- **Bone is a dynamic tissue comprising mostly of type I collagen fibers packed with hydroxyapatite crystals that ensures resistance to fracture through an optimal balance of flexibility and stiffness**



- **A child's bone undergoes constant bone growth at the epiphyseal growth plates and modeling (bone formation and shaping).**
- **In addition, the process of remodeling replaces old bone with new bone and is a lifelong process.**
- **Remodeling occurs by a unique cooperation of osteoclasts resulting in bone resorption and osteoblasts subsequently replacing this with an unmineralized osteoid, that is later mineralized**

Bone health is an important but often under appreciated issue in childhood

Pediatric bone health

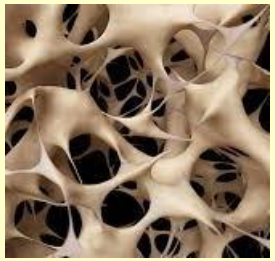
is determined by

- Genetics
- lifestyle
- Diet (proteins)
- Exercise
- Calcium, phosphorus ,vitamin D ,potassium, magnesium, copper, iron, phosphate, zinc ,vitamin A, C and K
- Sunlight
- Avoid tobacco, caffeine and alcohol consumption
- Extreme thinness and adiposity
- Bone harmful treatments and chronic disease.

Definition of osteoporosis

NIH Consensus Conference

A skeletal disorder characterized by compromised bone strength that predisposes to an increased risk of fracture



Definition of osteoporosis

International Society for Clinical Densitometry

ISCD

- Occurrence of one or more vertebral compression fractures in the absence of local disease or high-energy trauma **regardless of the BMD z-score**

Definition of osteoporosis

ISCD

Diagnosis of osteoporosis is indicated by

presence of both a clinically significant fracture history and BMD Z-score ≤ -2.0.

A clinically significant fracture history is

- Two or more long bone fractures by age.” 10 years;
- Three or more long bone fractures at any age up to age 19 years

Definition of low-trauma

- Falling from 3 meter or less
- Falling from a standing height or less

International Society for Clinical Densitometry

ISCD

- **The diagnosis should not be made on the basis of densitometric criteria alone.**
- **It is recognized that recurrent long-bone fractures can occur with normal bone mineral density (BMD).**

prevalence

- 30% of LBW infant : premature osteopenia
- 24% of VLBW infant within 6-12 w: Radiologic Fx
- Peak incidence traumatic fracture between 11 and 12 years in girls and 13 and 14 years in boys
- Most often at the distal radius.

Childhood Fractures

- **Lower extremity fractures are common in immobilized children**
- **Spine fractures are more common in young patients with childhood leukemia, osteogenesis imperfecta, or exposure to glucocorticoids.**

Is there a difference between *definition of osteoporosis in* children and adults?

WHO:

BMD that lies T-score <2.5 standard deviations or more below the average value for young healthy women

- Instead, low BMCs or aBMDs **are defined by Z-scores of -2.0** or less adjusted for age, sex and body size
- Normative data that **inadequately account** for bone changes caused by puberty or chronic disease all present challenges

Can low BMD predict fracture?

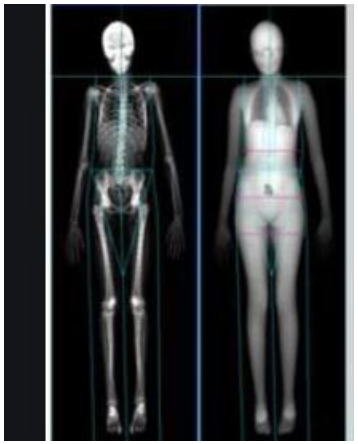
- A BMC/BMD Z-score > -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk." especially in those patients suffering from disorders that favor secondary osteoporosis

- Relationship between BMD and fracture risk are still limited
- **BMD alone does not explain fracture risk**

low BMD in children

Results when

- There is an imbalance between the rates of bone formation and resorption



Pathophysiology

- **Peak bone mass**, the “bone bank” on which an individual will draw for their entire adult life, is likely achieved by **late adolescence**, with the critical window for accumulation occurring much earlier.
- If this peak is not optimal, it will facilitate the development of osteoporosis in adulthood

- Dietary calcium supplementation in the **preadolescent years** may be a key factor in optimizing peak bone mass
- when **dietary calcium supplementation** is stopped
- Data suggest that the increase in bone mass is not maintain

Pathophysiology

Bone will not accrue normally when

- There are deficits of calcium, phosphate, and/or VitaminD
- Or bone is not exposed to normal physical/mechanical stresses and strains

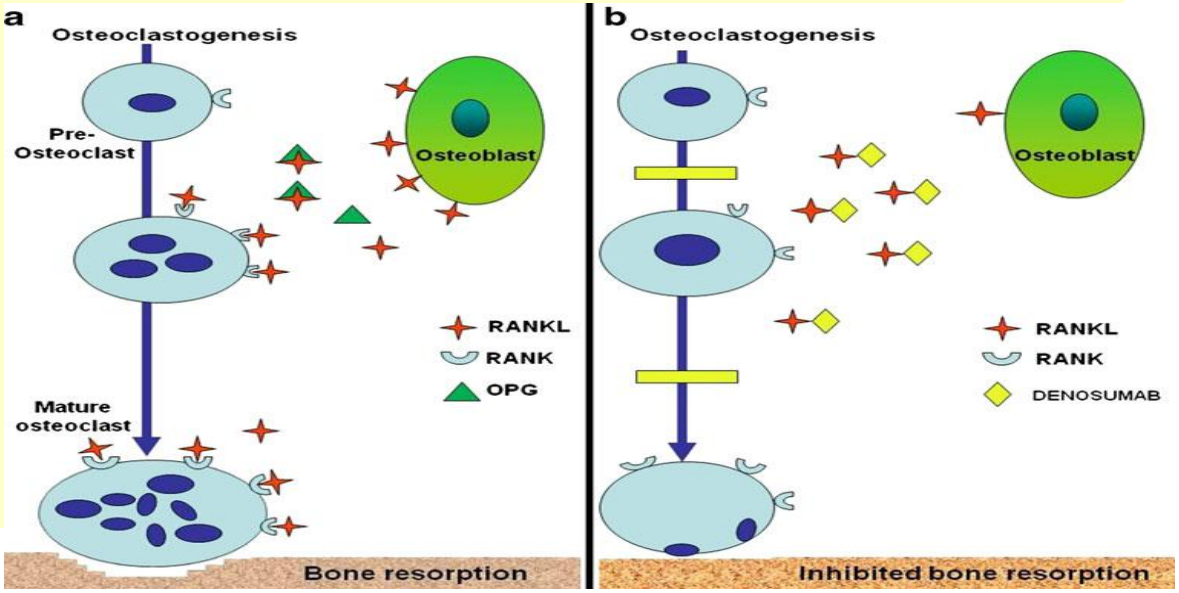
Pathophysiology

Secondary bone loss due to

- immobilization
- weight-bearing physical activity contributed to significantly greater BMC accrual after adjustment for age, height velocity, Tanner stage
- stress response (endogenous glucocorticoids)
- Chronic disease

Pathophysiology

- Another mechanism linked to bone loss is the **inflammatory response.**
- This involves the production of IL–1 beta and IL-6, TNF alpha.
- These can increase bone resorption via stimulation of osteoblast production of RANKL



Etiology

- **Genetic conditions: 60-80%**
- **Osteogenesis imperfecta**
- **Idiopathic juvenile osteoporosis**
- **Turner syndrome**
- **Marfan's syndrome**
- **Homocystinuria**
- **Ehlers-Danlos syndrome**
- **primary osteoporosis due to mutations in WNT1 and PLS3 genes**
- **Menkes disease**
- **Osteoporosis pseudoglioma syndrome**

Causes of secondary osteoporosis

- **Chronic illness**
- **Endocrine disorders**
- **Medications**
- **Glucocorticoids**
- **Anticonvulsants**
- **Chemotherapy**
- **Leuprolide acetate**
- **Proton pump inhibitors**
- **Depot medroxyprogesterone acetate**

Causes of secondary osteoporosis

Renal diseases	Nephrotic Syndrome Chronic renal failure
Psychiatric illnesses	Anorexia nervosa
Infectious diseases	HIV infection Immunodeficiencies
Endocrine diseases	Delayed puberty Hypogonadism Turner syndrome Klinefelter Syndrome Growth hormone deficiency Acromegaly Hyperthyroidism Diabetes Hyperprolactinemia Cushing syndrome Adrenal insufficiency Hyperparathyroidism Vitamin D metabolism disorders
Inborn errors of metabolism	Glycogen storage disease Galactosemia Gaucher disease
Skin conditions	Epidermolysis bullosa
Iatrogenesis	Systemic glucocorticoids Cyclosporine Methotrexate Heparin Anticonvulsants

Causes of secondary osteoporosis

Neuromuscular disorders	Cerebral palsy Duchenne muscular dystrophy Rett syndrome Myopathies Diseases resulting in long-term immobilization
Hematological diseases	Leukemias Hemophilia Thalassemia
Systemic autoimmune diseases	Juvenile systemic lupus erythematosus Juvenile dermatomyositis Systemic juvenile idiopathic arthritis Systemic sclerosis
Lung diseases	Cystic fibrosis
Gastrointestinal diseases	Celiac disease Inflammatory bowel disease Chronic liver disease Cow's milk protein allergy

Osteogenesis imperfecta

- A rare genetic disorder of type 1 collagen
- present with varying degrees of fracture, blue sclerae, dentinogenesis imperfecta, ligament laxity, and hearing impairment.
- Bone biopsy shows decreased cortical and cancellous bone mass.
- Dominant mutations in ***COL1A1*** **and** ***COL1A2*** account for 95% of OI cases.

idiopathic juvenile osteoporosis

- **IJO is a primary bone disorder of unknown etiology.**
- **It tends to affect young people in late childhood/early adolescence**
- **Characteristic features are bone pain, difficulties in walking,**
- **while it can result in recurrent long-bone metaphyseal and vertebral compression fractures**
- **Spontaneously remits after puberty.**

idiopathic juvenile osteoporosis

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- **Residual long-bone and vertebral deformities can be disabling, even once the bone mass has recovered**
- Patients have reduced BMD and reduced trabecular bone density

Clinical Presentation of osteoporosis

- Asymptomatic
- Bone pain
- In pediatrics, hip, femur, and vertebral fractures are rare
- Fractures that take place **after minimal trauma** may be concerning.
- History of axial skeletal fractures or multiple fractures from low biomechanical force may be indicators of skeletal fragility and **should raise concern for osteoporosis.**

Physical Examination

- General examination can be normal.
- joint hypermobility or hypomobility.
- kyphosis, kyphoscoliosis
- Short stature
- A decrease upper to lower segment ratio.
- Pectus deformities (both)
- . long bone deformities.
- Limping or splinting due to pain.
- Blue sclerae, dentinogenesis imperfecta,.

Laboratory Studies

- .Bone turnover markers are a series of protein or protein derivative biomarkers released during bone remodeling by osteoblasts or osteoclasts
- Bone turnover markers are reflect bone **metabolic activity** at a given time

- In children ,interpretation is much **more complex**
- Although they can help in **monitoring antiresorptive therapy ,compliance and measuring its effectiveness**

Laboratory Studies

- Osteocalcin to assess bone formation rates.
- Serum and urine cross-links of type I collagen (deoxypyridinoline)
- N-telopeptide of type I collagen (NTx)
- Carboxy-terminal telopeptide of type I collagen (CTx),
- Type 1 procollagen (P1NP)

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Basic Diagnostic Studies

Laboratory test	Variables to analyze
Blood count	
Blood chemistry	Calcium, ionized calcium, phosphorus, magnesium, total proteins, creatinine, urea, glucose, 25-hydroxyvitamin D_3, PTH, TSH, free T4
24-hour urine chemistry	Calcium, phosphorus, creatinine, tubular phosphorus reabsorption, sodium
Urine screening	Ca/Creatinine[a]
Bone turnover	Total alkaline phosphatase

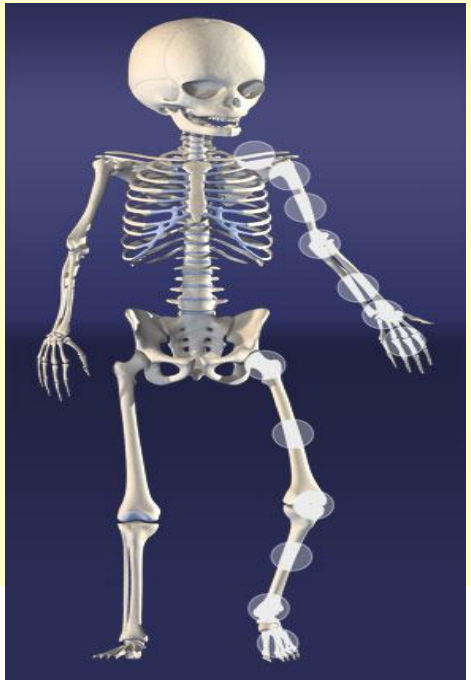
Basic Diagnostic Studies

Analytical determinations to make based on suspicion

Studies
Immunoglobulins
Anti-transglutaminase IgA antibodies
Cortisol
Prolactin
FSH, LH, testosterone
Homocysteine
Genetic studies (genes related to osteogenesis imperfecta and disorders characterized by bone fragility)

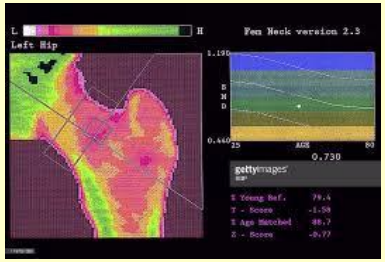
imaging study

- Dual-energy x-ray absorptiometry (DXA) assessments
- Quantitative computed tomography (QCT) scans
- peripheral quantitative computed tomography (PQCT)
- Calcaneal and phalangeal ultrasonography



Why is DXA preferable

- **Dual energy X-ray absorptiometry (DXA) remains the technique of choice to measure bone mass as it is**
- **Highly reproducible**
- **Commonly available**
- **Relatively inexpensive**
- **low radiation exposure.**
- **Robust pediatric reference data**



Quantitative CT Scanning

- It is performed using a computed tomography (CT) scanner and results in a 3D image.
- **Hip and lumbar spine** are the most common choices for evaluation with QCT

Peripheral quantitative computed tomography

- involves a **foot or a lower limb** and much less radiation, can also provide an indirect assessment of bone density.
- It is specifically useful for children with **spinal deformities, contractures or metallic implants**
- **Is not influenced by body or skeletal size**
- The radius and tibia provide valuable information that cannot be obtained by DXA, including
- Bone and muscle geometry
- “true” (volumetric) cortical and trabecular BMD

Bone Histology

- The use of bone histology obtained by iliac crest bone biopsy is no longer routine.

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Choice sites

Children

- **Lumbar spine (LS) and total body less head are the preferred sites**
- **Vertebra(trabecular bone): glucocorticoid excess and hypogonadism**

Choice sites

- **Vertebrae DXA measurement** is recommended for children **under the age of five** **due to its higher reproducibility** and shorter time necessary for conducting this test
- For children **under the age of three**, total body BMD is not recommended on a routine basis due to its lack of reproducibility in such young children; **rather BMC should be used**

Choice sites

- **The hip** is not a preferred measurement site in growing children because of variability in skeletal development
- **Hip region** (total hip or femoral neck): are not as reliable in younger **patients (<13 years)**
- **1/3 radius** (nondominant forearm) may be used in ambulatory children who cannot be scanned at other skeletal sites , exceed the weight , metal hardware, hyperparathyroidism

What predictions does Femur DXA scan make?

- lateral distal femur DXA scan .
- An alternate technique used in non-ambulatory children with spinal deformity or contractures, scoliosis, and positioning difficulties, CP
- A large cross-sectional study demonstrated an association of increased fracture risk (6–15%) in lower extremity with every one S.D. reduction in lateral distal femur BMD
- Proximal femur DXA measurements can be used for assessing children with reduced weight bearing

DXA ANALYSIS

BMD values for children are expressed as age- and sex-specific S.D. scores (Z-scores), but they also depend on body size, ethnicity, pubertal staging and skeletal maturity

- **As a result of DXA's two- dimensional measurement, BMD can be grossly under- estimated in children with short stature.**
- **Hence, in children with short stature, BMD requires adjustment for height or bone volume such as bone mineral apparent density (BMAD, in g/cm3) to avoid gross overestimation of osteoporosis**

The role of spine X-ray

A spine X-ray is recommended

- For pediatric patients with reduced mobility due to cerebral palsy or congenital myopathies
- **At 6–8 years of age**
- Or earlier in the event of back pain
- Then periodically until the end of growth

in a patient with suspected or confirmed bone fragility

- **Presence of VF**, which are frequently asymptomatic, should always be assessed by means of a simple **lateral full spine x-ray** or by DXA vertebral fracture assessment, if feasible

The role of spine X-ray

- For children with **suspected secondary osteoporosis**, it is recommended to extend the study with a **plain lateral thoracic and lumbar X-ray** to assess vertebral compression fractures, particularly if they **are receiving GCs**
- In the event of **low bone mass or risk factor persistence**, a second plain lateral thoracic and lumbar X-ray should be taken **after one year**

The American Academy of Pediatrics

DXA is recommended for children with

- **Primary bone disorders such as IJO, OI**
- **Secondary conditions known to increase fracture risk**
- **A history of clinically significant fracture**
- **Fractures out of proportion to the inciting trauma**
- **Multiple long bone fractures**
- **Systemic long-term corticosteroids**
- **Hypogonadism – primary or secondary**
- **Prolonged immobilization**
- **Apparent osteopenia on radiographs**

Published recommendations for bone density testing for specific disorders

Celiac disease

- No adequate dietary adherence
- irregular menstruation
- Anemia
- Other risk factors for fractures

Cerebral palsy

- Difficult lumbar spine X-ray interpretation in cases of severe scoliosis.
- Total-body or distal femur DXA only if there are fragility fractures

Published recommendations for bone density testing for specific disorders

Duchenne muscular dystrophy

- Baseline DXA and annual monitoring.
- Lateral spine x-ray: Baseline
- On GCs treatment: Repeat every 1–2 years.
- Not on GCs treatment: Repeat every 2–3 years.
- - If back pain or ≥ 0, 5 SD decline in spine BMD Z score on serial measurements over 12-month period: Repeat.
- Refer to osteoporosis specialist following the first fracture

Published recommendations for bone density testing for specific disorders

Epilepsy

- Consider DXA for epileptic patients receiving anti-epileptic drugs for a prolonged period

Thalassemia

- DXA every 2 years from adolescence

Juvenile idiopathic arthritis

- < 6 years: DXA in the presence of fragility fractures.
- > 6 years: DXA if not presenting rapid remission of JIA or in need of high doses of GCs

Published recommendations for bone density testing for specific disorders

Neoplasms

- Baseline DXA **two years after completing** chemotherapy with osteotoxic drugs., MTX, GCs or hematopoietic cells transplantation
- Secondary effects that favor osteoporosis development (growth hormone deficiency, hypogonadism,

Cystic fibrosis

- DXA in children ≥ age 8 if:
- weight < 90% ideal weight
- FEV1 < 50%
- Delayed puberty
- -High dosis of GCs > 90 days per year
- **At 18, all of them**

Published recommendations for bone density testing for specific disorders

Anorexia nervosa

- DXA in patients with amenorrhea for more than 6 months

Systemic lupus erythematosus

- DXA evaluation in patients with prolonged systemic GCs exposure **exceeding ≥0.15 mg/kg daily for ≥ 3 months**.
- Repeat on an annual basis if Z-score≤−2

Published recommendations for bone density testing for specific disorders

- DXA can be used to assess treatment response **after six months** in the event of **high doses of corticosteroids, chemotherapy, or in situations of malnutrition**

Contraindications DXA scan

- Recently administered gastrointestinal contrast or radionuclides.
- Pregnancy
- Severe degenerative changes or fracture deformity in the measurement area
- Implants, hardware, devices, or other foreign material in the measurement area
- The patient's inability to attain correct position and/or remain motionless for the measurement
- Extremes of high or low body mass index (BMI)

OPTIMAL TIMING FOR FOLLOW-UP STUDIES

- The optimal frequency for DXA performance is insufficiently defined
- **Our recommendation is to repeat DXA**
- After one year
- Then **every 1–2 year thereafter**
- According to the patient's trajectory, with a minimum interval between checks of 6–12 months

OPTIMAL TIMING FOR FOLLOW-UP STUDIES

- In cases who initially present normal densitometry,
- BUT risk factor(s) persist, the periodicity of densitometry must be individualized according to the risk factor associated and an **interval of one or two years** is advised until **peak bone mass is reached**

Treatment & Management

- **Management of osteoporosis requires multidisciplinary approach.**
- Geneticists
- Nurses
- Physiotherapists
- Occupational therapists
- Psychologists
- Social workers
- Dentists
- Audiologists
- Orthopaedic
- Spinal surgeons
- Neurosurgeons
- Pain management team

Treatment & Management

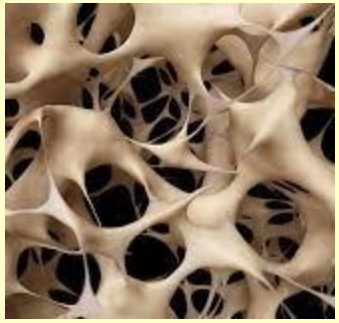
The primary goals of the management of osteoporosis are

- Medical management of the underlying condition
- General strategies for improving bone health

- prevention of vertebral fractures &Scoliosis
- improvement in function, mobility, and pain

Medical Management

- .. **Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society regarding**
- Bisphosphonates in the treatment of pediatric osteoporosis.



American Academy of Pediatrics

- Bisphosphonates are not first-line.
- Use of BPs reserved for children with **symptomatic or severe osteoporosis** that is refractory to supplementation and management of comorbid conditions

Bisphosphonates

- They selectively concentrate and increase BMD
- They are hydrophilic drugs with low intestinal absorption **< 1%** and high distribution volumes that are **excreted in urine**.
- Thus, dosages must be adjusted according GFR

- They are characterized by a very slow elimination from bone tissue, and remain in the body for **years after treatment**
- **Bisphosphonates are retained in the skeleton, with evidence of renal excretion 8 years after the cessation of a nitrogen-containing bisphosphonate, pamidronate, in young people**

Indication of treatment with Bisphosphonates

Pediatric patients with osteoporosis

- Z-score≤−2 + pathological fracture
- VF regardless of Z-score
- patients without osteoporosis, but a low BMD in early puberty Tanner 2

Indication of treatment with Bisphosphonates

When active risk factors are present

- patients with **Z≤–2. 5 SD** with a declining trajectory confirmed at least on two separate occasions **with one year apart** with a loss of ≥ 0.5 SD

When patients no longer present active risk factors

- patients with **Z ≤ -3DS with** a declining trajectory confirmed on at least on two separate occasions **with one year apart** with a loss of ≥ 0.5 SD

Indication of treatment with Bisphosphonates

- Moderate and severe forms of OI (type 111)
- **Oral bisphosphonates should only be considered for those with mild to moderate OI in the absence of vertebral compression fractures**
- Mild forms of OI or osteoporosis but should be relegated to well-designed clinical trials or used on compassionate grounds

Mechanism of Bisphosphonates in children with osteoporosis

Bisphosphonates come into close contact with osteoclasts, where they exert their therapeutic actions.

- since the **cortical surfaces of bone thicken** as the **interferes** with modeling, while skeletal resorption is blunted along endocortical surfaces.
- To inhibit bone resorption without as much impact on bone formation and mineralization
- **sizeable changes** in bone density and the **reshaping of vertebral bodies** in children

Bisphosphonates in children with OI

The mechanism of Bisphosphonates in children with OI.

therapeutic effects include improvement in

- Bone density
- Grip strength of bone
- Vertebral height
- Cortical thickness
- Trabecular number
- Quality of life and mobility
- Decreased bone pain
- Decrease bone turnover and fracture rate.

Use of bisphosphonates in conditions other than skeletal fragility

- Fibrous dysplasia
- Avascular necrosis of femoral head
- Bone cysts, bone tumor, skeletal metastases
- Inflammatory bone conditions
- Generalized arterial calcification of infancy
- Hypercalcemia

Bisphosphonates as preventative agents

- There are **insufficient data** on the use of bisphosphonates as **preventative agents** to recommend their administration to children with **asymptomatic reductions in bone mass or density alone**

Systemic illness& osteoporosis

The first step in treating children with osteoporosis caused by underlying disease

- Restoring the normal hormonal milieu
- Correcting vitamin D deficiency
- Rectifying underweight or overweight status
- physical deconditioning
- **. if these measures are insufficient, consideration of treatment with a bisphosphonate is warranted for those with low BMD or bone mineral content and bone fragility**.

Bisphosphonates &Neuromuscular diseases

- Most of the clinical studies examining the use of bisphosphonates in children with low BMD that is secondary to cerebral palsy.
- Both randomized clinical trials and small, uncontrolled studies have tested the efficacy of intravenous pamidronate in increasing BMD among nonambulatory children with cerebral palsy
- **Have noted**
- **skeletal gains at the spine, femoral neck, and/or total body**
- **Absence of serious adverse effects**

Bisphosphonates &Neuromuscular diseases

- They should be treated if they **sustain two low trauma long bone fractures** (not including hand, feet) **or VF**.
- Duration of treatment varies with a minimum of 12 months.
- Bisphosphonates should be used only after optimising vitamin D status, calcium intake, physical therapies to maximise mobility, and gonadal hormone treatment of absent, delayed or arrested puberty

idiopathic juvenile osteoporosis

- **We recommend consideration of the use of bisphosphonates in severe forms of idiopathic juvenile osteoporosis as evidenced by**
- **Two or more long-bone fragility fractures or vertebral fractures, consistent with the diagnosis of osteoporosis in pediatrics.**
- **There is no evidence to guide the duration of treatment**
- **we recommend that the dose of bisphosphonate should be reduced after 2 years if height-adjusted DXA scores are normalizing.**
- There is a lack of consensus regarding the use of bisphosphonates in mild **idiopathic juvenile osteoporosis**

How long after starting treatment is the maximum effect?

- **The majority of the gains from pamidronate therapy in childhood OI are realized in the first 2–4 years, raising the question as to the optimal duration of therapy in the pediatric setting .**
- **In patients with OI, gains in bone mass during therapy are maintained for at least 2 years after therapy has been stopped**

Outcome of bisphosphonates

- The majority of trials were small and not powered to show a statistically significant difference in many outcome measures, such as
- Mobility
- Fracture rate
- Quality of life.
- Studies on the effect of intravenous bisphosphonates on vertebral compression fractures, showed **that reshaping, which is growth dependent, is better the earlier they are started**

Bisphosphonates Discontinue

The BP dosage should be discontinued or progressively reduced in those patients

- **Not presenting fractures during preceding year**
- **And having reached a Z-score higher than -2**

Bisphosphonates Discontinue

- **Should continue on a long-term lower dose of bisphosphonate to preserve bone strength during growth.**
- **The annual dose of intravenous bisphosphonate can be halved once the height-adjusted BMD z score falls**
- **within the range of –2 to 0**

Bisphosphonates Discontinue

- **In children with less severe OI, it may be possible to stop bisphosphonate therapy during childhood without deterioration in clinical status or BMD.**
- **Once the BMD z score > 0, the dose can be reduced further and treatment continued at this lower dose until the cessation of growth**
- **Once a child with OI stops growing, it is recommended that therapy be suspended and the child monitored**

Bisphosphonates Discontinue

- In general, once the BMD adjusted height- z score is >0, therapy should be reduced to
- 0.025 mg/kg/year of zoledronic acid
- 1.5 mg/kg every 6 months of pamidronate until the end of growth.
- It may be possible to cease treatment in children with OI type 1.

Bisphosphonates Discontinue

- patients who have persistent risk factors for compromised bone health such as
- Collagenopathy
- Or who are still growing following a period of approximately 2–4 years of BP 'rescue therapy'
- 9 mg/kg pamidronate per year, one of the most common dosing regimens in OI may require treatment that is continued as close to the cessation of linear growth as possible

Adverse effects

- Rash
- Tachycardia
- Myalgia
- Bone pain
- Esophageal irritation
- Nephrotoxicity
- Anterior uveitis
- Atrial fibrillation
- iatrogenic osteopetrosis
- Esophageal cancer

Adverse effects

- **Hypocalcemia**
- **Hypophosphatemia**
- **Flu-like symptoms (fever, bone pains, myalgia, nausea/ vomiting**

- **Anterior uveitis**
- **Inflammation of the iris**
- **Teratogenic effects**

Adverse effects

- Radiographic metaphyseal bands
- Fractures after bisphosphonate discontinuation in growing children
- Osteonecrosis of the jaw.
- Delayed healing of osteotomy sites after intramedullary rodding procedure
- Delayed bone healing in children with OI
- Not delayed fracture healing

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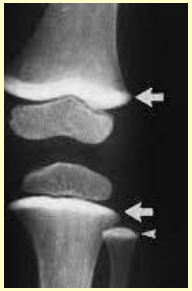

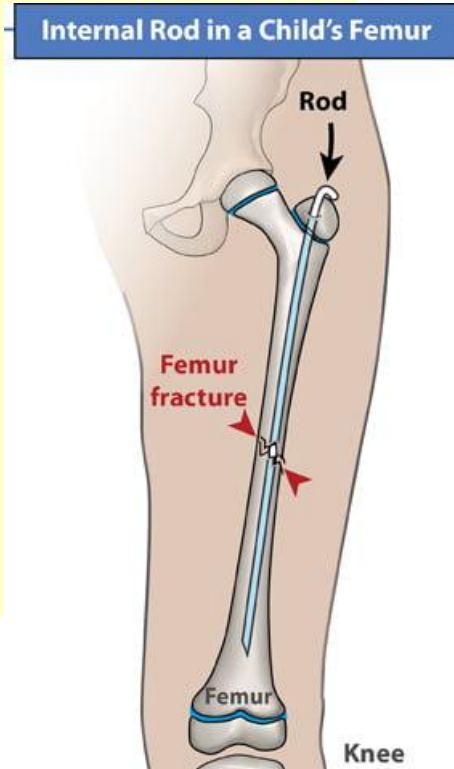

Adverse effects

- There is theoretical concern that bisphosphonates may impair **fracture healing because fracture healing requires callus remodeling and the coupled activity of osteoclasts and** osteoblasts.
- Thus, important questions are whether bisphosphonates can be **initiated in the immediate postfracture period**
- whether there is delayed fracture healing in patients who fracture while on therapy.
- There are few data to guide these clinical decisions
- We typically initiate bisphosphonates **two weeks post fracture**

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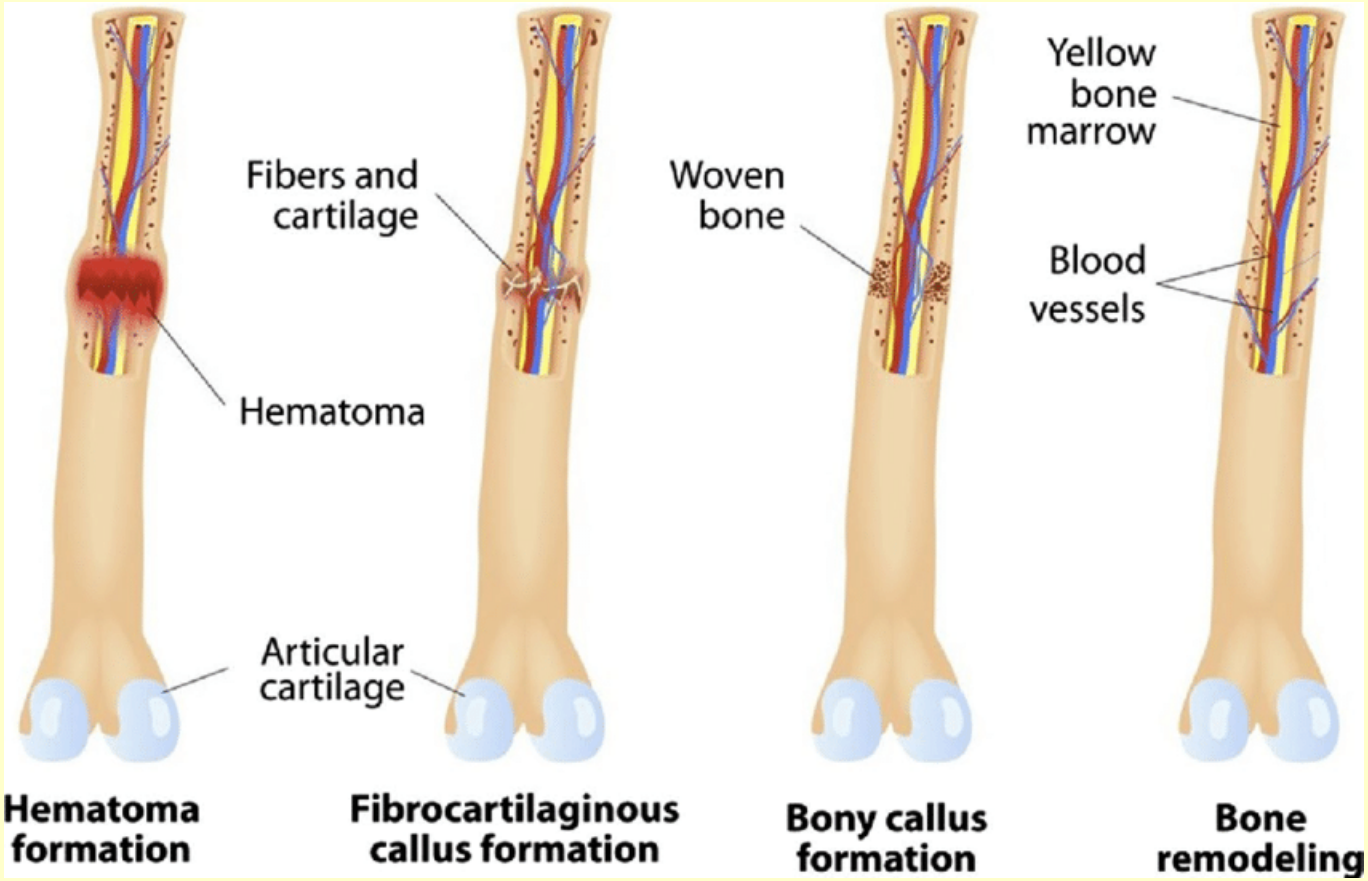
Callus remodeling



Bisphosphonates dose

- There is no consensus on the optimal agent, dosage, or duration of therapy.
- it is impossible to state whether one treatment protocol is more efficacious than another.
- The response **to intravenous therapy** seems to be more consistently positive than the response to oral agents.
- **Oral BPs can be used** in the absence of contraindications and VF, or during the de-escalation phase

Doses and dosing intervals for the most commonly used BPs in pediatrics

Drug	Administration	Dose
Pamidronate (2nd generation)	Intravenous (dilute in 100-250 ml physiological saline solution, in 3–4 hours)	< 1 year: 0. 5 mg/kg every 2 months 1–2 years: 0. 25-0. 5 mg/kg/day 3 days every 3 months 2–3 years: 0.375–0.75 mg/kg/day 3 days every 3 month > 3 years: 0. 5–1 mg/kg/day 3 days every 4 months Maximum dose: 60 mg/dose and 11. 5 mg/kg/year
Neridronate (3rd generation)	Intravenous (dilute in 200–250 ml physiological saline solution, in 3 hours)	1–2 mg/kg/day every 3–4 months
Zolendronate (3rd generation)	Intravenous (dilute in 50 ml physiological saline solution, in 30-45 min)	0.0125–0.05 mg/kg every 6–12 months (maximum dos
Alendronate (2nd generation)	Oral	1–2 mg/kg/week < 40 kg: 5 mg/day or 35 mg/week > 40 kg: 10 mg/day or 70 mg/week Maximum dose: 70 mg/week
Risendronate (3rd generation)	Oral	15 mg/week (< 40 kg); 30 mg/week (> 40 kg) Maximum dose: 30 mg/week

Approach for use of zoledronate in children with osteoporosis

Disuse osteoporosis secondary to CP, Retts and similar central neurological conditions

- **2 years of full dose** every 6 months (year 1 and 2 of treatment
- Then: **1 year of half dose** every 6 months (year 3 of treatment
- Then: **one quarter of the dose** every 6 months after 3 years of treatment
- If BMAD (height adjusted BMD) is >+2 SDS, change **to 1/4 of the dose every 12 months**

Approach for use of zoledronate in children with osteoporosis

- **Primary bone fragility such as**
- **OI**
- **primary muscle disorders such as DMD, or CMD**
- **Haematological disorders such as Thalassaemia, Sickle Cell Anaemia**
- **Full dose every** 6 months until BMAD is **>0 SDS**
- If BMAD is >0 SDS, give **half dose** of zoledronate every 6 months
- If BMAD is >+2 SDS, give **one quarter dose** of zoledronate every 12 months

Approach for use of zoledronate in children with osteoporosis

Conditions where the underlying condition may be controlled or treated such as ALL—IBD—renal transplant

- If commenced, they should **have full dose every 6 months**, but the duration of treatment will be individualised based on
- **continuation of steroid treatment, their BMD, pubertal status and their underlying condition**

Full dose of zoledronate

- <2 years 0.025 mg/kg max dose: 2 mg **3 monthly**
- 2–5 years 0.035 mg/kg max dose: 2 mg if <3 years, 4 mg if >3 years **4 monthly**
- >5 years 0.05 mg/kg max dose: 4 mg **6 monthly**

Assessments during Bisphosphonate Use

- During treatment with intravenous BPs, assessments of laboratory parameters are recommended before each administration.
- For oral BPs, checks every six months are recommended

Assessments during Bisphosphonate Use

- Full blood count
- Urea and electrolytes
- Liver function test
- 25- hydroxy vitamin D
- Parathyroid hormone
- Calcium , magnesium, phosphate
- Dental review

Medical Management

Alendronate

- A large trial of low dose alendronate **did not show benefits** for children with OI
- The studies with higher doses have showed greater efficacy.
- **Risedronate is an aminobisphosphonate**.
- It inhibits bone resorption.
- . It has been demonstrated to have efficacy in children with **mild/moderate OI**

Contraindications for bisphosphonate therapy

- During pregnancy
- Renal impairment – Given the renal excretion of bisphosphonates, extreme caution should be taken
- Conditions where the underlying nature of the disorder means that an impairment of resorption will only further increase skeletal fragility, such as hypophosphatasia or with sclerotic lesions and high bone mass disorders
- Active rickets, where attention to the mineral deficits is required
- Not consider BPs systematic use in the absence of fragility fractures
- Esophageal disorders

REVIEW article

Front. Cell Dev. Biol., 04 June 2020 | https://doi.org/10.3389/fcell.2020.00433

Cathepsin K: The Action in and Beyond Bone

Rongchen Dai[1†], Zeting Wu[2†], Hang Yin Chu[1], Jun Lu[1,3], Aiping Lyu[1], Jin Liu[1*] and Ge Zhang[1*]

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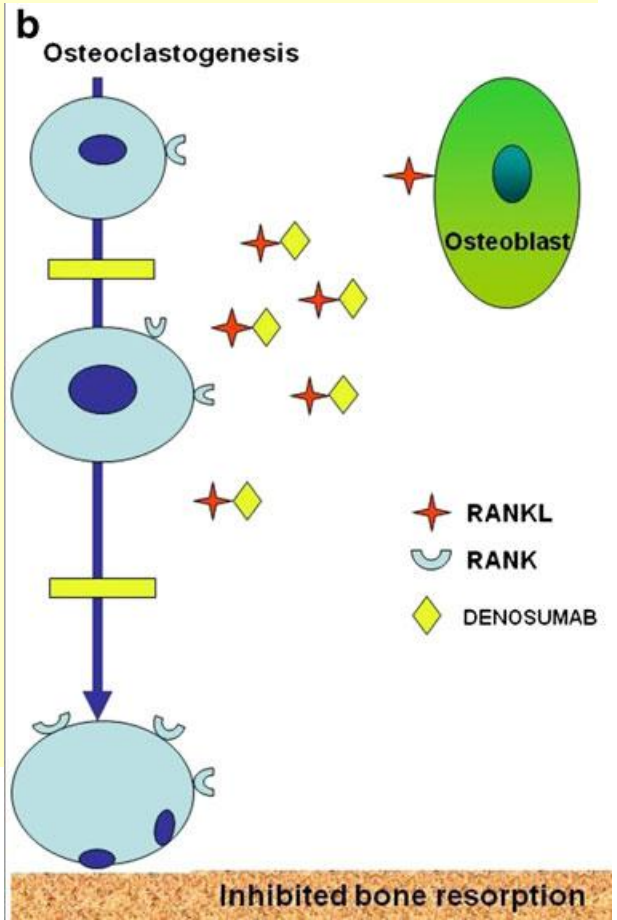
is one of the most potent proteases in lysosomal cysteine proteases family, of which main function is to mediate **bone resorption**. pharmacologic cathepsin K inhibition leads to continuous increases in bone mineral density for ≤5 years of treatment and improves bone strength at the spine and hip

Although many pharmaceutical companies are working on the development of selective inhibitors for CatK, **there is no FDA approved drug till now**

Denosumab

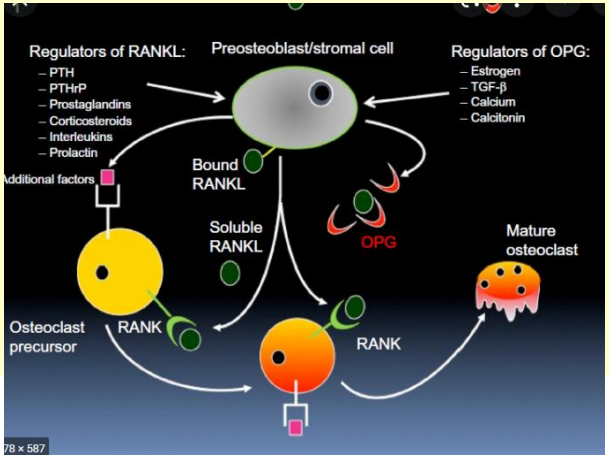
The follow up for 2 years of four children with OI type VI that were treated with Denosumab showed

- increase in BMD
- Normalisation of vertebral shape
- increase in mobility
- Reduced fracture rate.
- No new VF
- Improve vertebral shape



Denosumab

- **New potent antiresorptive drugs such as Denosumab**
- . It is an inhibitor of RANKL.
- It binds with high affinity and specificity to RANKL, mimicking the inhibitory effects of OPG and resulting in rapid suppression of bone resorption
- 1 mg/ kg BW (up to a maximum of 60 mg) SC every 6 months.



Case Report | Published: 13 May 2021

Denosumab for the treatment of primary pediatric osteoporosis

A.D. Anastasilakis, P. Makras, A. Doulgeraki, S.A. Polyzos, V. Guarnieri & S.E. Papapoulos

Osteoporosis International **32**, 2377–2381 (2021) | Cite this article

We studied a treatment-naïve 13.5-year-old boy with severe osteoporosis and multiple vertebral deformities who presented with back pain and difficulty in walking
Denosumab 60 mg subcutaneously every 3 months for 30 months, and he was pain-free within **6 weeks after the first injection.**

Bone Abstracts (2019) **7** P151 | DOI: 10.1530/boneabs.7.P151

(1)

The safety and efficacy of denosumab versus zoledronic acid in the treatment of pediatric osteoporosis: a randomized controlled pilot trial

Marie-Eve Robinson[1], Jinhui Ma[2], Nasrin Khan[3], Karine Khatchadourian[4], Marika Pagé[3], Victor Konji[3], Mary Ann Matzinger[5], Nazih Shenouda[5], Jacob L Jaremko[6], Caroline Zuijdwijk[4], Stefan Jackowski[3], David Saleh[7], Lynn MacLeay[3], Kerry Siminoski[8] & Leanne M Ward[4]

Ten children 4–16 years with low-trauma fractures due to osteoporosis were randomized 1:1 to receive ZA 0.025 mg/kg or Dmab 1 mg/kg every 6 months (total of 3 doses.)

Conclusion: In this pilot study, hypocalcemic episodes and side effects were fewer on Dmab compared to ZA, and vertebral fractures stabilized in both groups. These data support further study of Dmab in children with osteoporosi

Efficacy of Denosumab for Glucocorticoid-Induced Osteoporosis in an Adolescent Patient with Duchenne Muscular Dystrophy

A Case Report

Kumaki, Daiki MD[1]; Nakamura, Yukio MD, PhD[1,a]; Sakai, Noriko MD, PhD[2]; Kosho, Tomoki MD, PhD[1,3]; Nakamura, Akinori MD, PhD[1,4]; Hirabayashi, Shinichi MD, PhD[2]; Suzuki, Takako PhD[1]; Kamimura, Mikio MD, PhD[5]; Kato, Hiroyuki MD, PhD[1]

Author Information

JBJS Case Connector: June 2018 - Volume 8 - Issue 2 - p e22
doi: 10.2106/JBJS.CC.17.00190

We report the case of a 13-year-old boy with Duchenne muscular dystrophy who sustained bilateral femoral neck fractures associated with glucocorticoid-induced osteoporosis.

Denosumab therapy for 18 months markedly improved the lumbar bone mineral density and the bone turnover markers.

No fractures or complications were recorded during the treatment period

J Musculoskelet Neuronal Interact 2016; 16(1):24-32

Hylonome

Original Article

Safety and efficacy of denosumab in children with osteogenesis imperfecta - a first prospective trial

H. Hoyer-Kuhn[1], J. Franklin[3], G. Allo[1], M. Kron[1], C. Netzer[2], P. Eysel[4], B. Hero[1], E. Schoenau[1,5], O. Semler[1,5]

[1]Children's Hospital, University of Cologne, Germany; [2]University of Cologne, Institute of Human Genetics, Germany; [3]University of Cologne, Institute of Medical Statistics, Informatics and Epidemiology, Germany; [4]Center for Orthopedic and Trauma Surgery, University Medical Center, Cologne, Germany; [5]Cologne Centre for Musculoskeletal Biomechanics, Medical Faculty, University of Cologne, Germany

Abstract

Objectives: Osteogenesis imperfecta (OI) is a rare hereditary disease leading to bone fragility. Denosumab as a RANK ligand antibody inhibiting osteoclast maturation has been approved for osteoporosis treatment in adults. Aim of this study was a 48-week, open-label, pilot study of the safety and efficacy of denosumab in 10 children with OI. **Methods:** Ten patients (age range: 5.0-11.0 years; at least two years of prior bisphosphonate treatment) with genetically confirmed OI were studied. Denosumab was administered subcutaneously every 12 weeks with 1 mg/kg body weight. Primary endpoint was change of areal bone mineral density (aBMD) using dual energy x-ray absorptiometry of the lumbar spine after 48 weeks. Safety was assessed by bone metabolism markers and adverse event reporting. **Results:** Mean relative change of lumbar aBMD was +19 % (95%-CI: 7-31%). Lumbar spine aBMD Z-Scores increased from -2.23±2.03 (mean±SD) to -1.27±2.37 (p=0.0006). Mobility did not change (GMFM-88 +2.72±4.62% (p=0.16); one-minute walking test +11.00±15.82 m (p=0.15). No severe side effects occurred. **Conclusions:** On average, there was a significant increase in lumbar spine aBMD percent change after 48 weeks of denosumab. There was no change in mobility parameters and no serious adverse events. Further trials are necessary to assess long-term side effects and efficacy.

Teriparatide

- **Synthetic parathyroid hormone (teriparatide) used in adults to directly stimulate bone formation**
- **is contraindicated in children due to the risk of osteosarcoma reported in rodent models .**

Anabolic steroids

- Anabolic steroids, testosterone, oxandrolone
- Consider the risks of premature closure of the epiphyses, short stature, and hirsutism.
- increased risk of **tumor development**
- No epiphyseal closure was demonstrated for oxandrolone
- Testosterone is associated positively with lean mass, **lumbar and whole-body bone area, trabecular and cortical area, and periosteal circumference at the radius**.

Growth Hormone Treatment

- **Growth hormone is another anabolic agent, known to increase cortical thickness and improve muscle mass.&BMC, increased lumbar spine BMD**
- **When growth hormone is combined with BP treatment in children with severe OI, greater BMD and height velocity can be achieved compared to BP therapy alone.**
- **However, no difference in fracture incidence was reported .**
- **Larger and well-designed multicenter trials are required to confirm these beneficial effects**

Growth Hormone Treatment

- Benefits for others with low bone density have not been extensively studied
- . It does improve BMC in children with burn injury **if given for a year**
- But the need for repeated injections and the cost limit its use

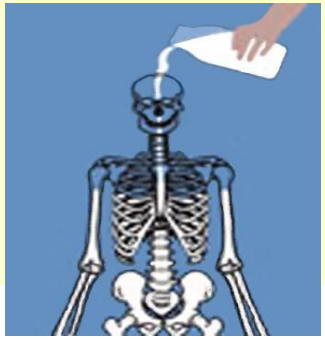
Surgical Care

- **surgery is unlikely to play a role in treatment**.
- In most cases, the cause is systemic and results in widespread disease.
- Surgery may be necessary for rod placement or for stabilization of fracture

Dietary Measures

. **AAP**

- A diet rich in dairy products is recommended to help provide the calcium and vitamin D required.
- Tobacco, caffeine and alcohol use must be avoided in children and adolescents
- Recommend **exposure to sunlight on** the hands, face and arms between six to eight minutes/day in the summer and 30 min/day during the coldest months of the year



Follow-up

- Calcium, phosphorus, alkaline phosphatase, iPTH and 25-hydroxyvitamin D3 should be evaluated on **an annual basis**
- During treatment with vitamin D ,recommended to monitor 25-hydroxyvitamin D3 **every 6 to 12 months**, unless the dosage is changed. In such cases, patients should be monitored at 3–6 months
- Calcium/creatinine levels in urine should be monitored once a year.
- **Renal ultrasounds** for nephrocalcinosis in the event of calciuria increase

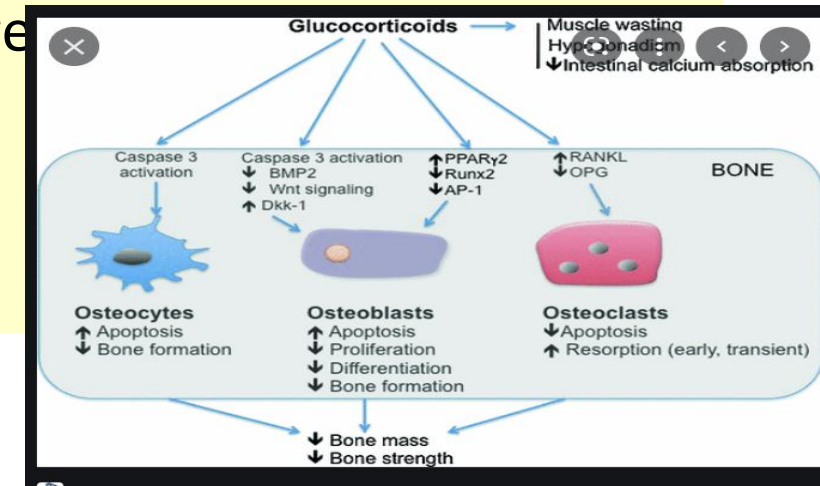
End of treatment

- The optimal treatment duration is not clearly defined and is currently based on expert recommendations
- We propose discontinuing or progressively decreasing BPs dosing for those patients who
- Have not presented **fractures during the preceding year**
- Have attained a **Z-score higher than -2**

Glucocorticoid induce osteoporosis

Increase in bone resorption

- Cause an initial increase in osteoblast production of the receptor activator of nuclear transcription factor kappa B ligand (RANKL)
- which stimulates marrow to produce osteoclastic cells increasing bone resorption.
- stimulate RANK ligand synthesis
- suppressing synthesis of osteoprotege



Glucocorticoid induce osteoporosis

Decreased bone formation

- interference with vitaminD metabolism
- Decreased calcium absorption
- increase renal calcium excretion
- Decreased sex hormone production

Glucocorticoid induce osteoporosis

Decreased bone formation

- inhibition of osteoblast proliferation and differentiation
- Promote **osteoblast apoptosis**
- Alter PTH secretory dynamics
- Antagonize the anabolic action of PTH
- Inhibit production of IGF-1 and testosterone
- Decreased serum and urine biochemical markers of bone formation
- Reduce marrow cell osteoblast differentiation, eventually leading to a **low-turnover bone loss or adynamic bone**

incidence rate of osteoporosis in patients receiving GC

- Any patient taking **any dose of** glucocorticoid with an anticipated duration of ≥3 months requires an evaluation

- Patients treated with systemic GCs **lose bone mass more** markedly during the **first 3–6 months of treatment**, mainly trabecular bone
- Incidence rate of VF **around 10% during the first year**, with nearly 50% of such cases being asymptomatic

What dose of corticosteroids increase the risk of osteoporosis?

The Spanish Rheumatology Society Consensus holds

- prevention of GIOP must begin as early as possible for all patients receiving doses higher than **5 mg/day of prednisone for more than three months**
- Fracture risk have been reported to persist with prednisone **doses of 2. 5 a 7. 5 mg/ day**

OPTIMAL TIMING FOR FOLLOW-UP STUDIES

- Lateral spine x-ray is recommended in order to detect VF at **the beginning of treatment with GCs and an annual or biannual**
- since they are frequently **asymptomatic** and can appear even in patients **with Z-scores higher than -2**
- It is recommended to carry out **lumbar spine or TBLH DXA** within the **first six months** after the beginning of treatment with GCs, and then **every 9 to 12 months if treatment continues**

Preventive actions Follow-up

American College of Rheumatology

- prescribing the lowest possible dose of GCs to control the underlying disease
- To encouraging physical exercise
- Avoiding toxic products, such as tobacco and alcohol
- It is recommended to start simultaneous treatment and/ or optimize calcium intake **(500–1000 mg/day) and vitamin D 400-600 IU/day** for patients to receive systemic GCs **for three months or more**

Preventive actions Follow-up

GIOP

- Our group recommends maintaining calcium and vitamin D supplementation **for three months after discontinuation of GCs treatment** since its effect on bone continues even after treatment has be same dose recommended.

Vitamin D & calcium supplementation

prescribed for patients with chronic pathologies presenting

- **levels lower than 20 ng/mL**
- Or between **20-30 ng/mL** who **present Z-score≤−2** or any data showing low bone fragility
- vitamin D3 should be keep higher than 30 ng/dL
- Treatment can be modified according to plasmatic D3, iPTH and calciuria which **monitored every six to twelve months**

The NIH Consensus Conference on Osteoporosis

Recommended that preadolescent and young adolescent children have a calcium intake that is 50% more than the intake suggested for younger children and older adults

1300-1500mg/day

Recommended a daily dosage of 2,000 IU for at least six weeks to achieve a blood level of 25(OH)D above 30 ng/ml.

- The recommended maintenance therapy thereafter is 600–1,000 IU daily, aiming at blood levels of 25(OH)D between 30 and 50 ng/ml.

Oxford Centre for Evidence-Based Medicine

Recommendations

- For children and adolescents receiving GCs chronically and presenting **low BMD (Z-score≤−2) and pathological fractures**
- it is recommended to use BPs associated with calcium and vitamin D

Oxford Centre for Evidence-Based Medicine

- Recommends the **use of BPs** for preventive purposes despite the lack of any comprehensive data
- . Our own working group does not consider its systematic use in the absence of fragility fractures.

its effectiveness is proven

- when GIOP has been established
- when pathological fractures are clearly

inhaled GCs&osteoporosis

- The dose lower than the **equivalent of 800 mcg/day** of budesonide has only a minimum effect on fracture risk
- **While higher doses** are associated with an accelerated decrease in BMD and a higher risk of fractures
- **it is not advisable to** routinely carry out such procedures as **lateral spine x-rays or DXAs**, unless these patients have other risk factors

Preventive actions for inhaled GCs

- Role of calcium and vitamin D supplementation **has not yet been established**
- Although some groups recommend supplementation for higher risk populations

Exercise

- Activity plays a role in the prevention of osteoporotic fractures.
- improves **bone mass &BMC in children** and adolescent
- Lack of locomotion reduces mobility, muscle force, and subsequently bone strength.
- High frequency, low amplitude whole body vibration is a non-drug therapy to increase muscle force and mobility in children.

References

- A Contemporary View of the Definition and Diagnosis of Osteoporosis in Children and Adolescents
  J Clin Endocrinol Metab 2020
- Uptodate 2021
- Management of primary and secondary osteoporosis in children

  Ther Adv Musculoskel Dis 2020
- Pediatric Osteoporosis *Pediatrics in Review 2019*
- Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children
- Pediatric Rheumatology 2020

References

- Mughal MZ. Curr Osteoporos Rep. 2014;12(3):313–318
- Halton J; J Bone Miner Res. 2009
- Cummings EA,. J Clin Endocrinol Metab.2015
- **Zoledronic acid in pediatric metabolic bone disorders.**
- Transl Pediatr. 2017
- Diagnosis of Osteoporosis in Children and Adolescents
  Touch MEdical MEdia 2013

از توجه اساتید و همکاران محترم
سپاسگزارم