15.30-16.30 **VI sessione - Le patologie endocrine dell'età evolutiva: alterazioni scheletriche.**

Inquadramento clinico nell'adolescenza.
S. Palmieri

Aspetti assistenziali con particolare riferimento alle modalità e ai canali comunicativi nell'età evolutiva.
M. Bertolini

Agenda

- ✓ Paediatric osteoporosis definition
- ✓ Aetiology
- ✓ Diagnosis
- ✓ Nutritional Support

Pediatric Osteoporosis

Pediatric Osteoporosis Definition (ISCD 2013 Position Statement)

1) One or more vertebral fractures in the absence of local disease or high-energy trauma;

2) Low bone density (BMC or areal BMD Z-scores ≤ 2.0 SD) AND a significant fracture history:
   (a) Two or more long bone fractures by 10 years of age
   (b) Three or more long bone fractures at any age up to 19 years.

Bishop N, et al. J Clin Densitom 2014, 17 275-280

Pediatric Osteoporosis

- In patients with spontaneous vertebral fractures measuring BMD can add to the overall assessment of bone health but is not required as a diagnostic criterion.

- A BMD Z-score of > -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.

Bishop N, et al. J Clin Densitom 2014, 17 275-280

Agenda

- ✓ Paediatric osteoporosis definition
- ✓ Aetiology
- ✓ Diagnosis
- ✓ Nutritional Support

Agenda

- ✓ Aetiology

Primary Osteoporosis

Secondary Osteoporosis

Primary Osteoporosis

- Intrinsic skeletal defect of genetic or idiopathic origin.
- Heritable bone fragility may be suggested by the family history or typical physical stigmata.
- The diagnosis remains a possibility in any child with recurrent fractures once a secondary osteporosis cause has been ruled out.

Marrani E, et al. Drugs 2017

Primary Osteoporosis

	Condition	Genetic mutation or enzyme deficiency	Mechanism	Inheritance
(1)	Osteogenesis imperfecta	COL1A1, COL1A2 and other non-collagen mutations	Quantitative or qualitative defect in collagen, post-translational modification	AR/AD
(2)	Bruck syndrome	PLOD2	Impaired collagen cross-linking	AR
(3)	Osteoporosis pseudoglioma syndrome	LRP5	Impaired Wnt signalling and osteoblast functioning	AR
(4)	Ehlers-Danlos syndrome	COL5A1, COL5A2, TNXB, and COL3A1	Defects in connective tissue	AD
(5)	Marfan syndrome	FBN1 and TGBR2	Defects in connective tissue	AD
(6)	Cleido-cranial dysplasia	RUNX2	Impaired bone formation	AD
(7)	Calvarial doughnut lesions	Unknown	Unknown	AD
(8)	Spondylo-ocular syndrome	Unknown	Unknown	AR
(9)	Hajdu-Cheney syndrome	NOTCH2	Abnormal bone remodelling	AD
(10)	Primary osteoporosis	LRP5 and LRP6	Impaired Wnt signalling and osteoblast functioning	AD
(11)	Idiopathic juvenile osteoporosis	Unknown	Unknown	Unknown

AR = Autosomal recessive; AD = autosomal dominant.

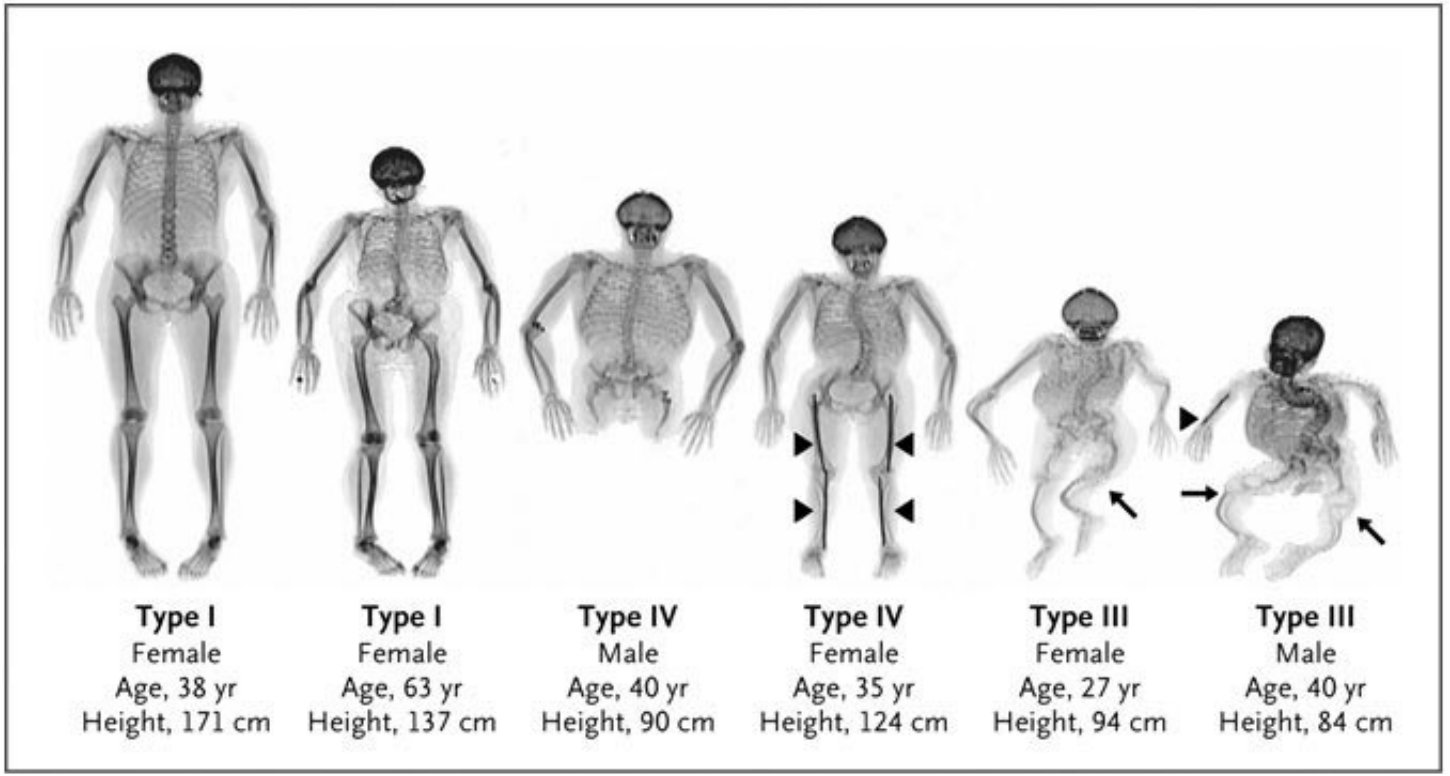
Korula S, et al. Endocr Dev 2015

Osteogenesis Imperfecta

- 1 in 25.000 births, M=F.
- Low bone mass, recurrent fracture, bone deformity, short stature.
- Approximately 90% of OI cases result from mutations in *COL1A1* or *COL1A2,* which produce type 1 collagen (quantitative or qualitative defects).
- Clinically heterogeneous (Sillence classification based on disease severity).

Ward LM, et al. Osteoporos Int 2016

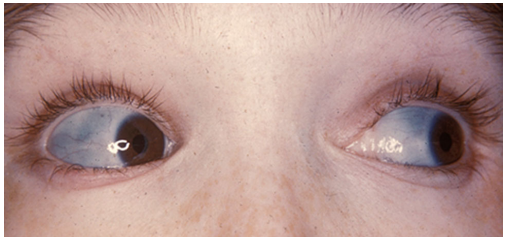
Osteogenesis Imperfecta

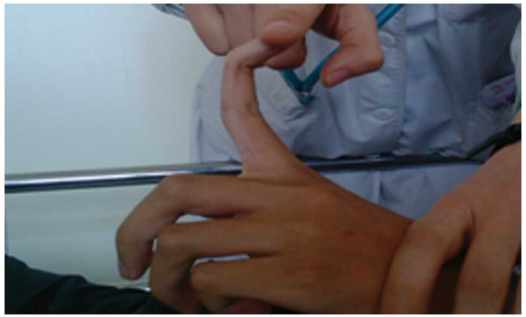


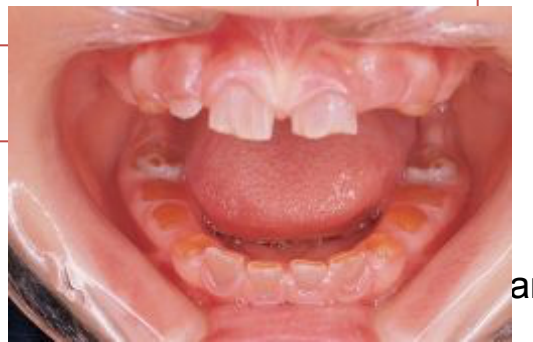
Reeder J, et al. N Engl J Med 2006

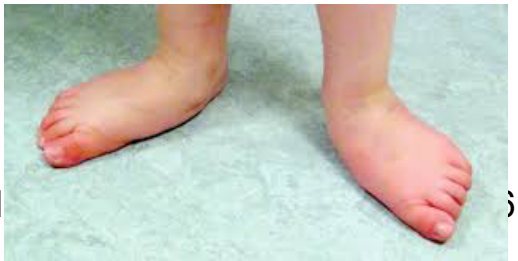
Osteogenesis Imperfecta

Extra-Skeletal Manifestations:
Blue sclera
Hypermobility
Flat feet
Abnormalities of the craniocervical junction
Dentinogenesis imperfecta
Hearing loss









Agenda

- ✓ Aetiology

Primary Osteoporosis

Secondary Osteoporosis

Secondary Osteoporosis

- Caused by chronic diseases and/or their treatment

Ward LM, et al. Osteoporos Int 2016

Secondary Osteoporosis

Genetic diseases

- Turner syndrome
- Klinefelter syndrome
- Lysinuric protein intolerance
- Glycogen storage disease
- Galactosemia
- Gaucher disease
- Hypophosphatemic rickets
- Hypophosphatasia
- Homocystinuria

Vierucci F, et al. Curr Opin Rheumatol 2017

Secondary Osteoporosis

Neuromuscular Disorders

Cerebral palsy

Rett syndrome

Duchenne muscular dystrophy, other myopathic diseases

Spina bifida

Spinal muscular atrophy

Other diseases associated with chronic immobilization

- Chronic Immobilization: Functional Muscle-Bone Unit
- Nutritional Deficits
- Drugs (Corticosteroid, Anti-epileptic)

Vierucci F, et al. Curr Opin Rheumatol 2017

Secondary Osteoporosis

Chronic Diseases

Malignancy (leukemia, lymphoma)

Reumatologic disorders

Cystic fibrosis

Inflammatory bowel disease

Malabsorption syndromes, celiac disease

Renal disease

Transplantation

Thalassemia

- Increased Inflammatory Cytokines
- Nutritional Deficits
- Reduced Physical Activity
- Exposure To Osteotoxic Drugs

Vierucci F, et al. Curr Opin Rheumatol 2017

Secondary Osteoporosis

Endocrine disorders

Cushing syndrome

Hyperthyroidism

Hypogonadism, anorexia nervosa, female athletes

Panhypopituitarism

Type 1 diabetes

- Glucocorticoid Excess
- Accelerated Bone Remodeling, Hypercalciuria, low PTH, Fecal Calcium Loss
- Nutritional Deficits, Sex Steroid or Growth Hormone Deficiency – Lower Peak Bone Mass
- Insulin deficiency, Cytokines, Increased risk of falls (hypoglicemia)

Vierucci F, et al. Curr Opin Rheumatol 2017

Secondary Osteoporosis

Iatrogenic

Glucocorticoids

Methotrexate

Cyclosporine

Heparin

Radiotherapy

GnRH agonist

Anticonvulsants (phenytoin, phenobarbital, carbamazepine)

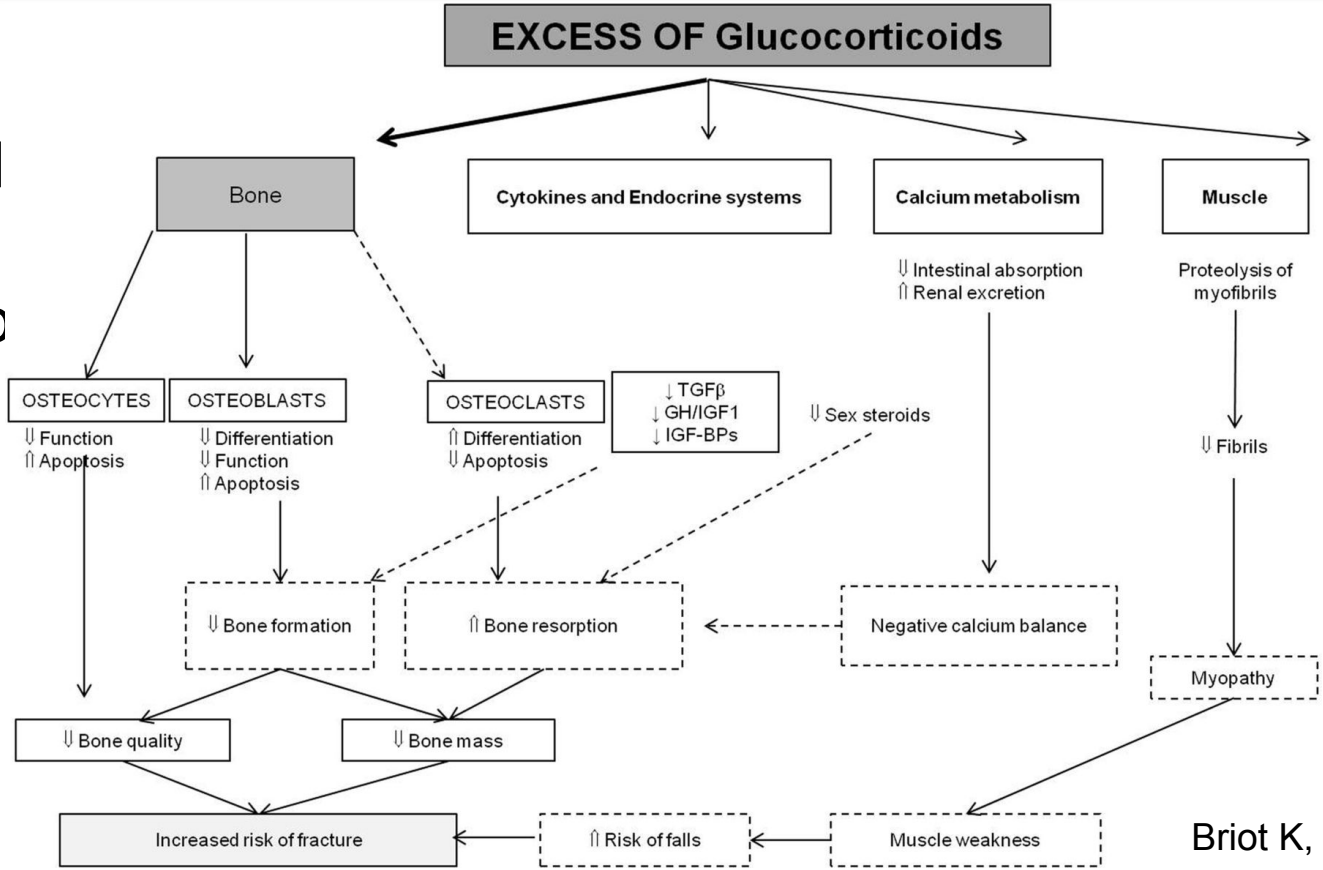
Vierucci F, et al. Curr Opin Rheumatol 2017

Glucocorticoid – Induced Osteoporosis

- GIO
  child
- GCs
  seric

ts and

many



Briot K, et al. RMD 2014

Glucocorticoid – Induced Osteoporosis

- A “safe” lower threshold has not yet been established
- GC therapy adversely impact the trabecular-rich spine
- Vertebral fractures occur within months of initiating GCs and at a relative better BMD
- Fracture risk returned to normal once GCs were stopped
- Negative skeletal effects of GCs are added to those of the underlying disease

Grover M, et al. Curr Osteoporos Rep 2017

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Skeletal Health Screening

- Patient and family fracture history
- Disease severity
- Medication exposure
- Back and bone pain
- Review of nutrition (protein and calcium)
- Physical activity
- Pubertal stage

Grover M, et al. Curr Osteoporos Rep 2017

Biochemical Workup

Routine	II Level Exams
- Creatinine - Complete Blood Count - Calcium - Phosphorous - Magnesium - Alkaline Phosphatase - 25-Hydroxyvitamin D - PTH - Anti-Tranglutaminase Ab - Urinary Calcium	- TSH, FT4 - Sex Steroids - IGF1 - Ionized calcium - Cortisol after 1 mg overnight DST suppression - Bone alkaline phophatase - Osteocalcin - Telopeptide

Grover M, et al. Curr Osteoporos Rep 2017

Dual - Energy Radiograph Adsorptiometry (DXA)

- Gold standard method for bone mass measurement
- Low exposure to ionizing radiation
- Robust pediatric reference data

- Identify patients at greatest risk of skeletal fragility fractures
- Guide decisions regarding treatment
- Monitor responses to therapy

Messina C, et al. EJR 2018

DXA

Skeletal Sites For DXA Assessment:

- Lumbar Spine (L1-L4, trabecular bone)
- Total Body Less Head (whole body scan, cortical bone, body composition)
- Lateral Distal Femur Scans (contractures, metal implants)
- Forearm (obesity > 135 kg, metal implants)

Messina C, et al. EJR 2018

DXA

Limits and pitfalls:

- Motion artefacts
- Use of T-score
- Short stature
- Delayed puberty (BMC and BMD adjustment by Tanner stage)
- Fractures are not always associated with a reduced BMD

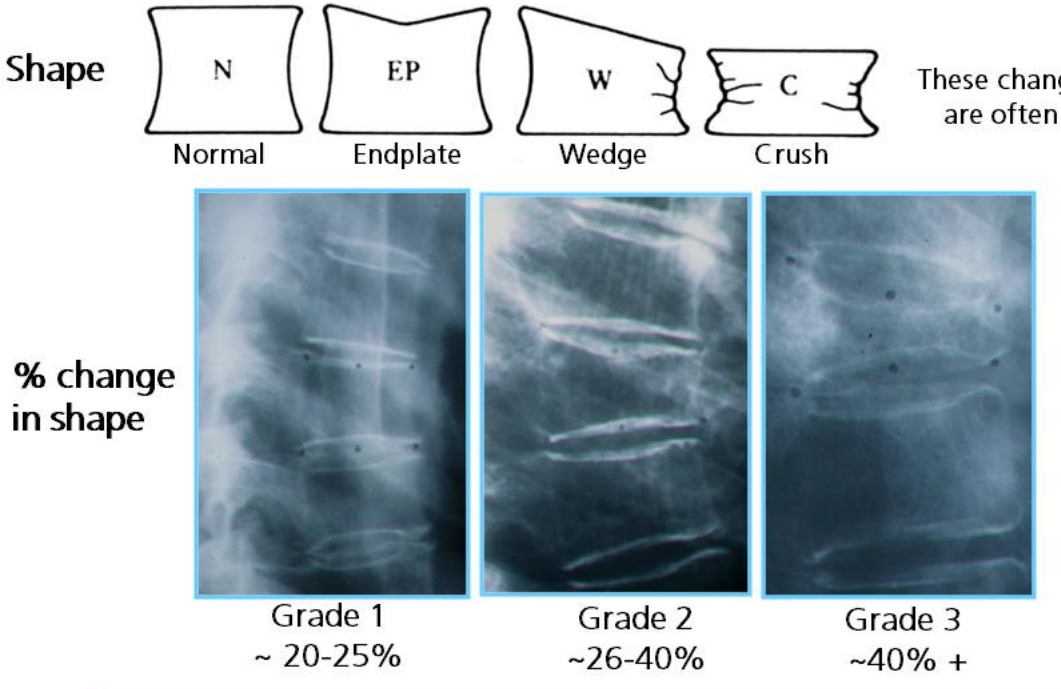
Messina C, et al. EJR 2018

Vertebral Fractures

- VFs are an important yet under-recognized manifestation of osteoporosis in children
- VFs (even severe) can be asymptomatic
- Lateral thoracolumbar spine radiographs (or vertebral fracture analysis by DXA)

Genant Method

Vertebral shapes and grading



Genant HK, et al. J Bone Miner Res 1993

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Nutritional Support

- Healthy body mass index
- Optmal intake of calories, protein, calcium and vitamin D

Recommended daily calcium intake:

Age (years)	Calcium (mg)
1-3	500 mg
4-8	800 mg
9-18	1300 mg

Grover M, et al. Curr Osteoporos Rep 2017

Nutritional Support

Recommended 25-hydroxivitamin D concentrations:

Healty children	> 20 ng/ml
Children with increased risk of fracture	> 30 ng/ml

➢Higher doses of vitamin D may be needed in patients with obesity, cystic fibrosis other malabsorption disorders

Grover M, et al. Curr Osteoporos Rep 2017

Physical Activity

- Weight – bearing activity
- Short period of high – intensity exercise
- Physical therapy or vibrating platforms in patients with immobilization disorders

Grover M, et al. Curr Osteoporos Rep 2017

Take Home Messages

- Osteoporosis is an under-recognized complication of chronic ilness in evolutive age
- Increased attention to risk factors and early intervention to reduce the frequence of fragility fractures

GRAZIE PER L'ATTENZIONE