OP for OsteoProtection in Pediatric rheumatology

Do children have osteoporosis?

Osteoporosis has been traditionally considered as a geriatric disease. Pediatricians are now acknowledging it with the increasing burden of chronic conditions impacting bone health with/without lifestyle factors. The continuous modeling & remodeling process in children leads to progressive bone mass increase till the maximum defined peak bone mass (PBM) is achieved. Several pathological conditions can compromise adequate PBM &/or cause bone loss & increase fracture risk.

Based on underlying etiology, osteoporosis is categorized into

Primary osteoporosis - Genetic disorders such as Osteogenesis imperfecta.
(Uncommon)

Secondary osteoporosis- Chronic diseases primarily affecting bone status
(Common) &/or drug related notably glucocorticoids.

How is bone health affected in chronic inflammatory diseases?

Children having systemic diseases with severe inflammation such as Systemic onset Juvenile Idiopathic Arthritis, Systemic Lupus Erythematosus, Juvenile Dermatomyositis & Systemic Sclerosis generally have impaired bone health. Multiple factors such as elevated inflammatory cytokines, low physical activity, altered body composition, malnutrition with calcium & Vitamin D deficiencies, malabsorption, pubertal delay, immobilization & glucocorticoid use contribute to reduction of bone strength in the above disorders.

Vertebral fractures are important but under-recognized (asymptomatic in 50%) manifestation of secondary osteoporosis with long bone involvement mainly of radius & femoral neck.

How is osteoporosis diagnosed in children?

Dual Energy X-ray Absorptiometry (DXA) is the preferred modality to ascertain bone mineral density (BMD) & bone mineral content in children. Lumbar spine (posterior-anterior) & total body less head -TBLH are the preferred, accurate & reproducible sites in children. DXA derived BMD is adjusted for age, sex & body size. The results are expressed as Z- score which is the number of Standard deviation (SD) below the age matched mean.

Most DXA software utilize pediatric reference databases for children older than 5 years. DXA whole body bone mineral content measurements for children <3 years are of limited clinical utility due to feasibility & lack of normative data.

Interpretation of BMD in pediatrics:

Osteoporosis

1) BMD Z- score </= -2.0
   With >/=2 long bone fracture in children < 10 years of age.
   >/=3 long bone fracture in children <19 years of age.
   OR
2) >/=1 Vertebral compression fracture, irrespective of BMD Z-score
   (in absence of local disease/ high energy trauma).

Low bone mass or low bone mineral density

BMD or Bone mineral content Z- score </= -2.0.

The term osteopenia is not used in children.

Vertebral fracture assessment (VFA) is assessed by Lateral X-ray of full spine. Findings atypical of an osteoporotic vertebral fracture (suspicion of destructive inflammatory or malignant processes, congenital malformations, misalignments, etc) mandate alternate imaging such as MRI. DXA VFA may be used as substitute for spine radiography to identify symptomatic & asymptomatic fractures.
The minimum interval between follow-up DXA scans is 6-12 months.

Basic Laboratory Tests for Osteoporosis

Laboratory test	*Variables to analyze*
Hematology	Complete Blood count
Blood chemistry	Serum Calcium, Ionized Calcium, Phosphorous, Magnesium, Total protein, Albumin, Urea, Creatinine, Glucose, Free T4,TSH, PTH, 25-OH Vitamin D3
24 hour urine chemistry	Calcium, Phosphorous, Creatinine, Tubular phosphorous reabsorption
Spot sample	Calcium/Creatinine
Bone turnover	Alkaline phosphatase

Age appropriate reference values to be considered while interpreting reports

How can osteoporosis be prevented in children with rheumatological disorders?

1) Calcium & Vitamin D supplementation in children with low BMD for treatment as well as prevention of fractures.

	Vitamin D(IU/day)		*Calcium(mg/day)*	
Age	*Prevention*	*Treatment*	*Prevention*	*Treatment*
1-12 months	400	2000 *	250-500	500
1-18 years	600	3000-6000*	600-800	600-800
At-risk groups	400-1000	as per age group	as per age group	as per age group

*For a minimum of 3 months; after treatment, daily maintenance doses need to be given.
25- OH Vitamin D3 needs to be monitored every 6- 12 monthly.
2) Exercise-swimming, cycling with avoidance of high impact sports; regular physical activity to maximize peak bone mass supplemented with diet containing adequate key nutrients.
3) Optimal control of the primary disease
4) Timely tapering of Glucocorticoids with introduction of disease modifying agents.

What medications are used to treat osteoporosis in children?

Bisphosphonates (BP)s notably Pamidronate have been used extensively in management of osteogenesis imperfecta; this safety & efficacy data has been extended to treat childhood osteoporosis.
Bisphosphonates are pyrophosphate analogs that inhibit osteoclast activity, recruitment & apoptosis suppressing bone turnover, by disrupting the mevalonate pathway of osteoclastogenesis.
Commonly used BPs in Pediatric Osteoporosis

Drug	Administration	Dose	Frequency	Remarks
Pamidronate (2^{nd} generation)	Intravenous Dilute in 100-250 cc Normal saline Over 3- 4 hours	< 1 year :0.5mg/kg/day 1-2 year:0.25-0.5 mg/kg/day 2-3 years:0.375- 0.75mg/kg/day >3 years : 0.5-1.5 mg/kg/day Over 3 consecutive days. Maximum dose: 60 mg/dose,11.5mg/kg/year	2 months 3 months 3 months 4 months	Widely used
Zolendronate (3^{rd} generation)	Intravenous Dilute in 50 -100 cc Normal saline Over 30- 60 minutes	<2 year : 0.015-0.025 mg/kg 2-5 years: 0.035mg/kg > 5 year : 0.05 mg/kg/day Maximum dose: 4 mg Annual dose not > 0.1 mg/kg/body weight	3 months 4 months 6 months	
Alendronate (2^{nd} generation)	Oral	1-2 mg/kg/ week <40 kg 5mg/day or 35mg/week >40 kg 10 mg /day or 70 mg/week Maximum dose :70 mg/week		Sit upright at least 30 minutes after taking medicine. Not to suck/chew medicine. Take with at least 180 cc water.

Bisphosphonates

- Used off label in childhood osteoporosis requiring informed consent.
- Used for secondary prevention-once the first fracture occurs, preventing new fragility fractures with no prophylactic role.
- Pre infusion testing- CBC, Calcium, Phosphorous, Magnesium, Urea, Creatinine, Electrolytes.
- Generally well tolerated.
  Most cases, infusion-related side effects within 24-48 hours such as fever, malaise, abdominal pain, nausea/vomiting, myalgia & bone pain which can last for several days.
  BPs are relatively contraindicated in renal failure warranting dose adjustment.
- Oral BP can cause dyspepsia, esophagitis, esophageal reflux & gastritis; occasionally severe enough to discontinue medication.
- Osteonecrosis of jaw reported in adults. Elective invasive dental procedures to be completed prior to BP start.
- Major teratogenic risks not reported, however pregnancy to be avoided for 12 months after bisphosphonate dose.

How does one follow up patients on Bisphosphonate therapy?

- Clinical assessment with dental examination 6-12 monthly.
- Biochemical assessment with CBC, Electrolytes, Alkaline phosphatase, Renal & Liver function, PTH, Urine routine & Urinary Calcium/Creatinine ratio annually. If an increase in calciuria then renal ultrasound to be performed.
- 25 -OH Vitamin D3 every 6-12 months or 3-6 months after dose change.
- Repeat DXA after 1 year, thereafter 1-2 years case based, minimum interval between checks 6-12months
- Vertebral fractures to be evaluated individualized to the patient's risk factors, with minimum interval period of 6 months & maximum period of 2 years.
- Follow up to be continued as long as risk factors persist for osteoporosis or on BP.

What is duration of Bisphosphonate therapy?

- Discontinue or progressively decrease dose for patients with no fractures in preceding year & whose Z-score is > -2.
- Discontinue if severe side effects occur.

When should DXA be done in children on glucocorticoids with rheumatological disorders?

- Once during the initial 6 months of glucocorticoid therapy & repeat every 9-12 months if treatment continues.
- Juvenile idiopathic arthritis < 6 years DXA: In presence of fragility fractures
  Above 6 years DXA: if not presenting rapid remission/needing high dose of steroids.
- Systemic lupus erythematosus: prolonged systemic steroids >0.15mg/kg/day for >/=3 months.

Learning points

- DXA preferred modality to ascertain BMD & expressed as Z-score representing the Standard Deviation below age matched mean.
- Unlike adults, diagnosis of osteoporosis in pediatric age group is not solely made on DXA findings, but also presence of fractures.
- The term osteopenia is not used in children.
- Prophylactic therapy with BPs is not indicated in children with low BMD without fragility fractures.

Suggested Reading:

- Galindo-Zavala et al. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. Pediatr Rheumatol Online J.(2020);18(1):20
- ISCD (The International Society for Clinical Densitometry) Positions Pediatric. 2019
- Khadilkar A et al. Prevention and Treatment of Vitamin D and Calcium deficiency in children & adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatrics 2017:54:567-73

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Coming next P for Pain Amplification Syndrome.