OSTEOPENIA OF PREMATURITY

Presented by: Dr. Marjan Jafari

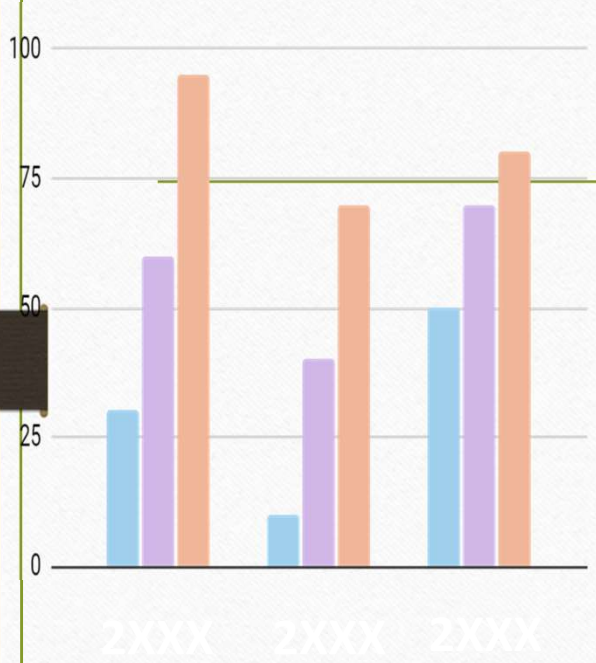
Introduction

- Premature babies are at increased risk for developing bone disease by reduced bone mineral content.
- Increased survival of infants with VLBW has been associated with an increased incidence of osteopenia of prematurity
- The incidence is inversely proportional to gestational age and birth weight, and two decades ago, it was estimated to be 50% in infants weighing less than 1000 g and 23%-32% in infants weighing less than 1500 g; however, the current incidence is difficult to estimate, because the nutritional strategy has changed.
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Etiology

- 1-mineral supplies
- 2- In utero mechanical stimulation
- 3- hormonal situation:
- Vitamin D deficiency Maternal vitamin D status

Additional risk factors for bone disease in preterm infants include



A) Prolonged parenteral nutrition

B) Feeding with unsupplemented human milk

C) Fluid restriction

D) Genetic polymorphisms

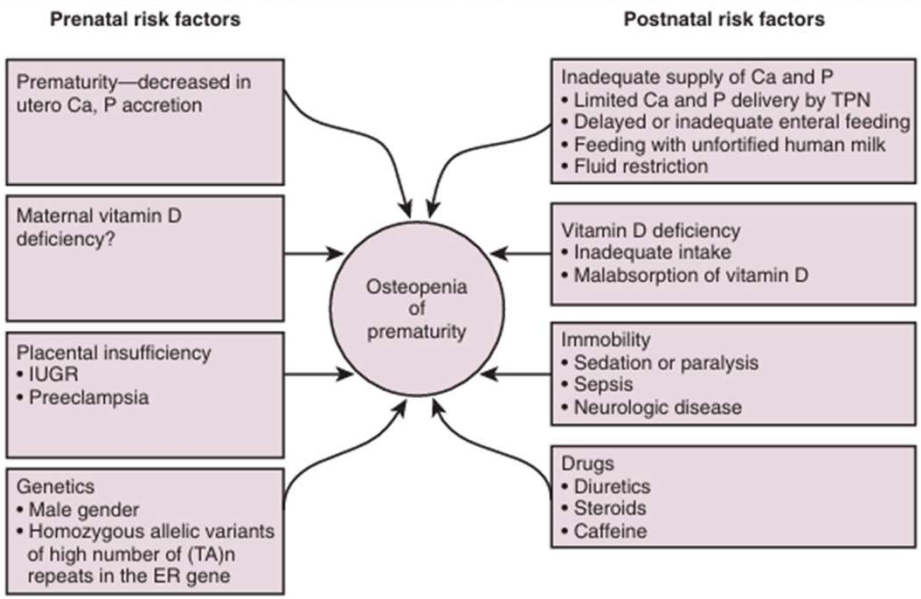
E) chronic illness

F) The use of hypercalciuric drugs such as furosemide for the treatment of bronchopulmonary dysplasia and methylxanthines for the treatment of apnea and bradycardia, both of which increase calcium loss

G) Immobility, especially for prolonged periods of sedation during mechanical ventilation, could enhance calcium loss and demineralization.

H) There is evidence that placental insufficiency has a role in increasing the risk of low bone mass as well

I) The use of postnatal steroids can decrease bone formation



• **Fig. 87.9** Prenatal and postnatal risk factors for development of osteopenia of prematurity. Ca, Calcium; IUGR, intrauterine growth restriction; P, phosphorus; (TA)n, thymine-adenine repeat; TPN, total parenteral nutrition; VDR, vitamin D receptor.

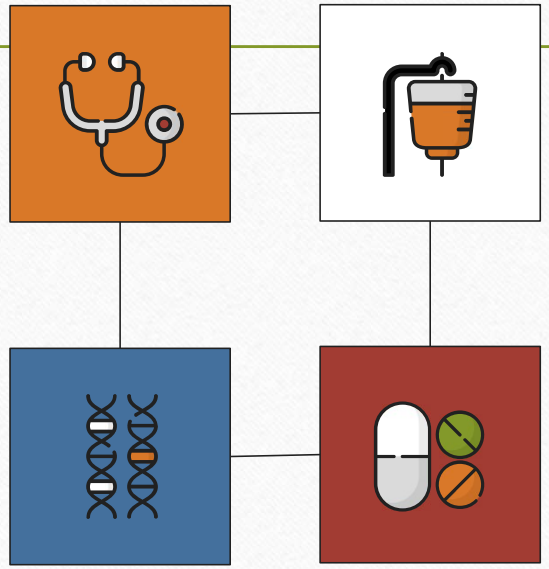
Diagnosis

01

Clinical Symptoms

02

Biochemical Features



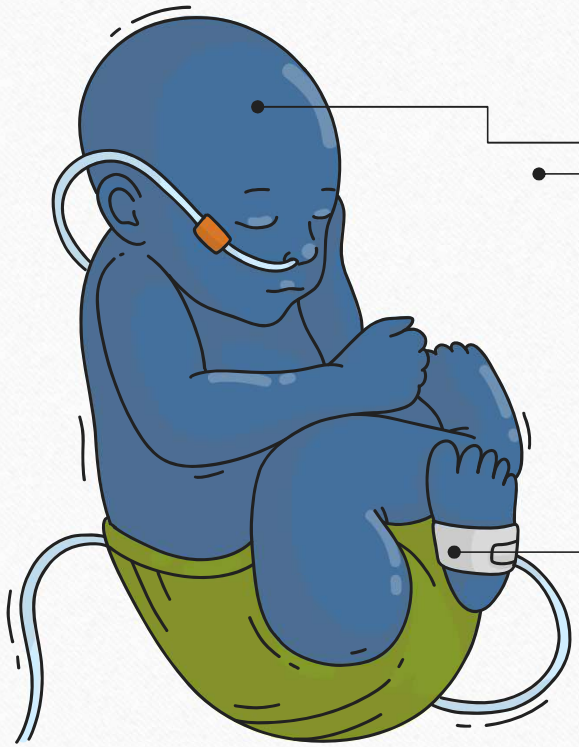
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Hormonal Features

04

Radiologic Features

Clinical Symptoms



01 Fractures

02 rickets

03 Decreased muscle tone
Delayed growth and poor weight gain

Biochemical Features

1-serum calcium (Nl range)

2-serum phosphorus (Nl or Low)

3-Alkaline phosphatase

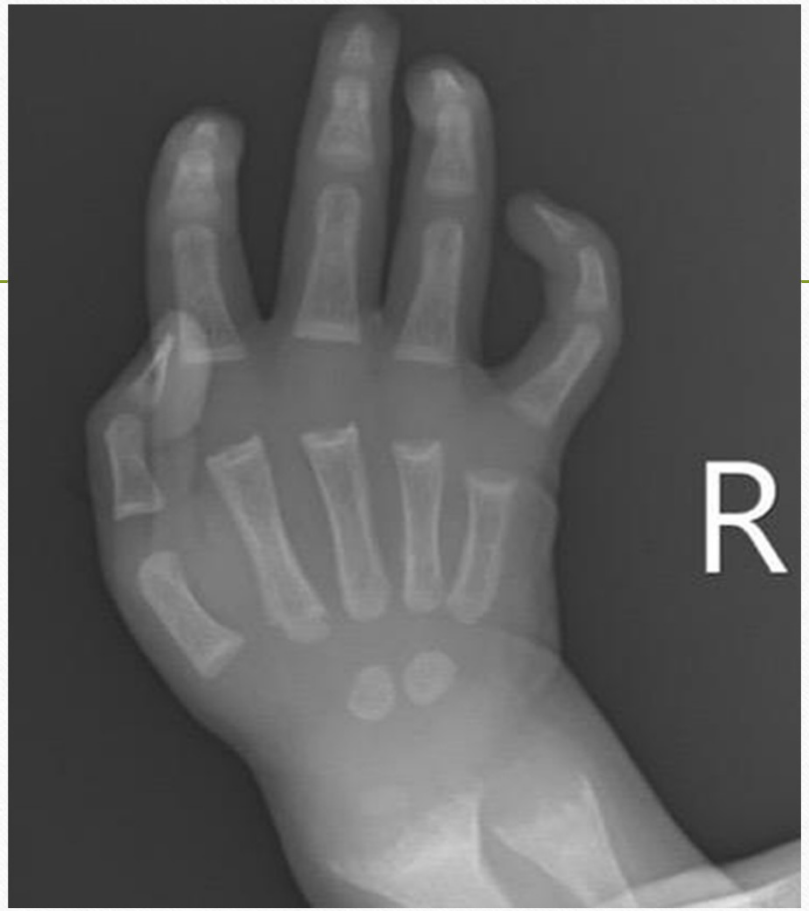
Hormonal Features

In preterm infants
1-the serum PTH,
2-serum 25(OH)D3, and
3-serum 1,25(OH)2D3
concentrations increase during the first month of life

Radiologic Features

Standard radiographs do not allow an accurate assessment of bone demineralization. Bone mineral density must decrease by 30% or more to be diagnosed by this method, and interobserver variability is considerable.
standard radiographs can detect fractures, and a wrist or knee radiograph at or after 4-5 weeks of age in a high-risk infant remains a practical assessment of the presence of overt rickets.
Currently, DEXA is the standard in whole-body mineral measurement, and normative data are available.




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Prevention and Treatment

• BOX 87.6 Management Approach for Enterally Fed Preterm Infants With Radiologic Evidence of Rickets

1. Maximize nutrient intake. Consider increasing human milk fortifier and/or feeding volume of preterm formula, as clinically indicated. If unable to tolerate human milk fortifier or preterm formula, then will likely need elemental minerals added as described below.
2. If no further increases in these can be made, add elemental calcium and phosphorus as tolerated. Usually beginning at 20 mg/kg per day of elemental calcium and 10-20 mg/kg per day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70-80 mg/kg per day of elemental calcium and 40-50 mg/kg per day elemental phosphorus.
3. Evaluate cholestasis and vitamin D status. May consider measuring 25-OH-D concentration, targeting serum 25-OH-D concentration of >20 ng/mL (50 nmol/L).
4. Follow serum phosphorus concentration and serum alkaline phosphatase weekly.
5. Recheck radiographs for evidence of rickets at 5- to 6-week intervals until resolved.
6. Advise caregiving team to be cautious in handling of infant.
7. Limit use of steroids and furosemide, as clinically feasible.

From Abrams SA, Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013;131:e1676-1683.

Parenteral Nutrition

Inadequate calcium and phosphorus intake has been associated with diminished bone mineralization in parenterally nourished premature infants.
This deficiency occurs when protein and energy are adequate for growth, but calcium and phosphorus are insufficient to sustain appropriate skeletal mineralization.
Calcium and phosphorus cannot be provided through parenteral solutions at the concentrations needed to support in utero accretion because of precipitation.

The solubility of calcium and phosphorus in parenteral solutions depends on:

1-the temperature, type, and concentration of amino acids;
2-dextrose concentrations;
3-pH of the calcium salt;
4-sequence of the addition of calcium and phosphorus to the solution;
5-calcium-to-phosphorus ratio; and
6-presence of lipids.

With a range of fluid intake of 120-130 mL/kg per day, it is advisable to supply a calcium content of 1.5-2.0 mmol/dL and a calcium-to phosphorus ratio of 1.3 : 1 by weight and 1 : 1 by molar ratio in the total hyperalimentation solution.
This quantity of calcium provided by the parenteral route is about 60%-80% of that deposited by the fetus during the last trimester of gestation.

Enteral Nutrition

The exclusive use of human milk without phosphorus and mineral fortification promotes the occurrence of osteopenia and rickets in infants with VLBW.
Both liquid and powdered human milk fortifiers are commercially available.
Their use has dramatically reduced the incidence of fractures and radiographically diagnosed osteopenia.
A similar reduction has also been observed in preterm infants fed preterm formulas.

TABLE 87.5 **Approximate Calcium Balance in a Typical Infant Receiving 120 kcal/kg per Day Intake***

	Calcium Concentration (mg/dL)	Intake (mg/kg per Day)	Absorption %	Total Absorption (mg/kg per Day)	Approximate Retention (mg/kg per Day)
Human milk	25	38	60	25	15-20
Preterm formula/fortified human milk	145	220	50-60	120-130	100-120

*Human milk assumed to be 20 kcal/oz, and preterm formula and fortified human milk assumed to be 24 kcal/oz.
Data from Abrams SA, and the Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013;131:e1676-1683.

An ideal approach to assess the adequacy of mineral intake in VLBW or other very high-risk infants may involve the following recommendations:

1-Preterm infants, especially those less than 27 weeks' gestation or with birth weight less than 1000 g with a history of multiple medical problems, are at high risk of rickets.

2-Routine evaluation of bone mineral status using biochemical testing is indicated for infants with birth weight less than 1500 g but not those with birth weight greater than 1500 g.

Biochemical testing should usually be started 4-5 weeks after birth.

3-Serum alkaline phosphatase greater than 800-1000 IU/L or clinical evidence of fractures should lead to a radiographic evaluation for rickets and management focusing on maximizing calcium and phosphorus intake and minimizing factors leading to bone mineral loss.

4-A persistent serum phosphorus concentration less than approximately 4.0 mg/dL should be followed, and consideration should be given for phosphorus supplementation.

5-Routine management of preterm infants, especially those with birth weight less than 1800-2000 g, should include human milk fortified with minerals or formulas designed for preterm infants.

6-At the time of discharge from the hospital, VLBW infants will often be provided higher intakes of minerals than are provided by human milk or formulas intended for term infants through the use of transitional formulas. If exclusively breastfed, a follow-up serum alkaline phosphatase at 2-4 weeks after discharge from the hospital may be considered.

7-When infants reach a body weight greater than 1500 g and tolerate full enteral feeds, vitamin D intake should generally be approximately 400 IU/day, up to a maximum of 1000 IU/day.

Best Practices

What is the current practice?

Metabolic bone disease of the preterm infant

Nutritional practices vary widely by institution across the country and world. Many clinicians are wary about early provision of adequate protein because of fears of hyperammonemia, acidosis, and uremia and, thus, limit mineral content in parenteral nutrition. Concerns for potential NEC often delays fortification of HM or moving to full-strength preterm formula.

What changes in current practice are likely to improve outcomes?

Major recommendations

Provision of early aggressive PN in the first days after birth

- At least 3.5 to 4.0 g/kg/d protein, 150 to 200 mg/kg/d calcium, 75 to 90 mg/kg/d phosphorus
- Move to fully fortified HM or full-strength preterm formula as soon as feasible
- Screening calcium, phosphorus, and ALP every 1 to 2 weeks
- Consider long bone and chest films to screen for fractures if ALP greater than 500 to 700 IU/L
- Continue fortified HM or preterm formula until infant is 1800 g to 2000 g

Rating for the strength of the evidence: strong

Bibliographic sources: see reference section

Summary statement

Most mineral accretion occurs in the last trimester of gestation, placing preterm infants at particular risk for MBD. Early, aggressive nutrition is key to the prevention and treatment of MBD.

Thanks for your attention