Sticks and Stones, Protect Their Bones!
Bone Health in Pediatric Patients with Intestinal Failure

Sivan Kinberg, MD MS MA
Director, Pediatric Intestinal Rehabilitation Center
Columbia University Irving Medical Center, New York, NY
Disclosures

- Takeda Pharmaceuticals, Speaker’s Bureau and Consultant
- Fresenius Kabi, Consultant
Learning Objectives

1. Understand the importance of monitoring bone health in children with intestinal failure (IF)
2. Identify factors which contribute to reduced bone mineral density in pediatric IF
3. Describe the evaluation of bone health in children
4. Determine the best approaches to managing bone health in pediatric IF
Case

- 3 year old girl with short bowel syndrome (SBS) on TPN since birth*
- Presents to Emergency Department with irritability and refusal to bear weight, afebrile
- Labs WNL

*Intestinal Failure: the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that IV supplementation is required to maintain health and/or growth

• Buckle fractures of the fibular diaphysis and distal tibial metadiaphysis
• Osteopenia
• Mild widening of the physis associated with mild splaying and fraying of the metaphysis, which may be compatible with rickets

*Real patient images, used with parental permission*
Metabolic Bone Disease in Intestinal Failure

- Definition: Alteration in skeletal homeostasis resulting in defective bone density (i.e. osteoporosis) and bone mineralization (i.e. Rickets)
- Major multifactorial complication in children with intestinal failure
- Several studies showed increased risk for low bone mineral density in children with intestinal failure on home parenteral nutrition
  - Defined by a z-score of $\leq -2.0$ on DEXA
  - Need to adjust for short stature (Ht-age Z-score $\leq -2.0$), seen in ~50% of children with IF
- Children
  - 45% Osteopenia
  - 16-25% Osteoporosis
- Adults
  - 57-88% Osteoporosis

DXA – Dual Energy X-ray Absorptiometry

- X-ray beams from 2 different sources of low energy levels aimed through patient’s body (lumbar spine, b/l hip, b/l femoral neck)

- Measures
  - Bone mineral content
  - Bone area
  - Bone mineral density (BMD)

- Advantages:
  - Rapid
  - Low radiation
  - Precise
  - Inexpensive
  - Measures several different bone sites

- DEXA should be performed in children and adolescents who may benefit from interventions to reduce their risk of a clinically significant fracture

2019 ISCD Pediatric Position Statement
Sample DXA Report

Lumbar spine  BMD (g/cm²) 0.483 Z-Score -5.2
Right total hip  BMD (g/cm²) 0.524 Z-Score -3.4
Left total hip  BMD (g/cm²) 0.440 Z-Score -4.2
Right fem neck  BMD (g/cm²) 0.401 Z-Score -4.1
Left fem neck  BMD (g/cm²) 0.33 Z-Score -4.3

IMPRESSION:

BASED ON Z-SCORES, YOUR PATIENT HAS DECREASED BONE DENSITY AT THE LUMBAR SPINE, RIGHT TOTAL HIP, LEFT TOTAL HIP, RIGHT FEMORAL NECK, AND LEFT FEMORAL NECK Bone measurements should be interpreted within the clinical context and other risk factors for metabolic bone disease.

*Real patient report, used with parental permission
Osteoporosis in Adults
Based on WHO criteria using bone density measurements

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>t-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;-1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>-1 to 2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
</tbody>
</table>

`t-score`: the number of standard deviations by which bone mass falls above or below the mean peak bone mass for a healthy young adult

`z-score`: compares bone density to age-matched population

2004 WHO Scientific Group On The Assessment Of Osteoporosis At Primary Health Care Level
Low BMD in Children ≠ Osteoporosis

- 2019 International Society for Clinical Densitometry (ISCD) Pediatric Position Statement on Fracture Prediction and Definition of Osteoporosis

- The diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of densitometry criteria alone

- The **diagnosis of osteoporosis in children** requires the presence of:
  1. **Clinically significant fracture history** (2+ long bone fractures by age 10 yrs, 3+ long bone fractures by age 19 yrs, vertebral compression fracture) **AND**
  1. **Low BMD Z-score ≤ -2.0**

Note: T-scores should not be used (only Z-scores)

Note: The term “osteopenia” should not appear in pediatric DXA reports

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

2019 ISCD Pediatric Position Statement
Causes of Metabolic Bone Disease in Pediatric IF

- Intestinal failure* and intestinal insufficiency** are risk factors for developing metabolic bone disease in children and adults
- High risk for micronutrient deficiencies, many of which are essential for growth and maintenance of skeletal mass
- Factors that contribute to the risk of metabolic bone disease
  - Malabsorption of essential micronutrients and minerals
  - Renal calcium wasting
  - Chronic metabolic acidosis due to high stool output and small intestinal bacterial overgrowth
  - Genetics
  - Minimal physical activity
  - Chronic inflammation
  - Longterm parenteral nutrition (PN)
- Data regarding the incidence of and risk factors for low BMD in children with IF remains sparse

* Intestinal failure: defined as dependence on Parenteral Nutrition/Intravenous Fluids
** Intestinal insufficiency: defined as dependence on enteral/oral nutritional supplements

Consequences of Metabolic Bone Disease

- Loss of BMD is significantly more detrimental in children with IF as the insult coincides with time of maximal bone mass accrual in a child's development.
- Failure to accrue bone mass in this critical period during childhood results in long-term osteopenia (and its attendant morbidity) in adulthood that may be difficult to reverse.
- Thus, ensuring optimal BMD in pediatric IF is essential.

## Causes of Metabolic Bone Disease in Pediatric IF

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Malabsorption in SBS, lack of sun exposure</td>
<td>High oral vitamin D3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Malabsorption in SBS or vitamin D deficiency, increased urinary Ca excretion</td>
<td>Vitamin D3, add oral calcium or calcium in PN</td>
</tr>
<tr>
<td>Vitamin C deficiency</td>
<td>Nutritional deficiency, MVI shortages</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Malabsorption, inadequate dietary intake, excessive oral calcium intake or parenteral iron</td>
<td>Increase phosphate in PN, use IV iron sucrose</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td>Cholestasis (limit copper), PN shortages</td>
<td>Copper supplementation, do not give Cu with Zinc</td>
</tr>
<tr>
<td>Aluminum toxicity</td>
<td>Aluminum contamination in PN (i.e. casein in PN protein, calcium gluconate, Kphos)</td>
<td>Change formulation</td>
</tr>
<tr>
<td>Fluoride toxicity</td>
<td>High levels in tea and certain bottles water</td>
<td>Use recognized isotonic drinks</td>
</tr>
<tr>
<td>Underlying inflammation</td>
<td>Inflammatory burden of disease (IBD)</td>
<td>Control inflammation</td>
</tr>
</tbody>
</table>

*Adapted from Allan P.J. & Lal S. *J Hum Nutr Diet*. 2020;33:423–430*
Vitamin D Deficiency

- **Vitamin D Deficiency**: 25-OH D <20 ng/dl, **Vitamin D Insufficiency**: 25-OH D 20-29 ng/dl
  - Higher incidence in SBS patients with < 50% residual bowel length
- Important for bone growth and skeletal development
  - Vitamin D increases calcium absorption from the gut which is then deposited in bone
- Sources
  - Ultraviolet B light–activated synthesis in the skin
  - Diet
  - PN: Adult MVI injection 200 IU (5 mcg), Pediatric MVI injection 400 IU (10 mcg)
- Monitoring
  - 25-OH D, serum calcium, PTH
- Treatment
  - Vitamin D2 (Ergocalciferol)
  - Vitamin D3 (Cholecalciferol), more effective than D2
  - Common starting dose is 50,000 IU (1.25 mg) weekly
  - 1000 - 100,000 IU daily (25 mcg – 2.5 mg)

Is there an association between vitamin D deficiency and low BMD in children with IF?
Vitamin D Deficiency & Low BMD

- Vitamin D deficiency by itself has not been shown to be associated with low bone mineral density

- Review by Ubesie et al. of Vitamin D status and DEXAs in 123 patients > 3 years of age

- Low BMD in 12.5%

- No association between low BMD and 25-OH vitamin D (p=0.31)

- Association with low BMD:
  - Exclusive TPN (p=0.03)
  - Age >10 years (p=0.02)

Logistic Regression: Vitamin D Deficiency & Low BMD with Age

\[
\begin{align*}
\text{logit (deficiency)} &= 0.87 - 0.10 \times \text{age} \\
\text{logit (abnormality)} &= 3.57 - 0.23 \times \text{age}
\end{align*}
\]

Probability vs. Age in years

- Odds ratio (deficiency) = 0.908
- Odds ratio (abnormality) = 0.798

Metabolic Bone Disease in Pediatric IF Patients: Prevalence and Risk Factors

- Retrospective review by Khan et al. of 65 children with IF with 99 DEXA scans 2004-2013
- Incidence of low BMD: 34%
  - BMD not corrected for short stature
- Incidence of Vitamin D deficiency (25-OH D<30): 41%, but no association with low BMD
- 29% patients had at least one fracture but no relationship with low BMD was seen
- Independent predictors of low BMD (multivariable logistic regression)
  - Low serum calcium (p=0.02)
  - Low weight-for-age z-score (p=0.03)
- Conclusion:
  - Overall nutritional well being is associated with improved skeletal health
  - Maintain adequate calcium reserves for optimal bone mineralization
  - Possible substantial risk for osteopenia in adulthood

PN and Low BMD

- Demehri et al. retrospective multivariate analysis of 36 Children with IF
- 50% with low BMD Z-score < -1
  - 69.4% had already weaned off PN by 1st DEXA
- Vitamin D deficiency: 64%
  - No association with BMD
  - Increasing vitamin D supplementation did not improve BMD Z-score
- The number of years on PN was the only significant predictor of decreased lumbar BMD (p = 0.006)
  - No patient with less than 16 months of PN had BMD Z-score of less than −2.0
- Pathologic fracture (11.1%) and bone pain (19.4%)
- Conclusion:
  - Need larger, controlled studies
  - Current supplement-based strategies are not effective in improving BMD
  - Promising approaches, such as bisphosphonate and GLP-2 therapy, should be investigated in the pediatric IF population—as both of these have been shown to improve BMD in adult patient at risk for MBD

Weaning Off PN and Low BMD

- Mutanen et al retrospective analysis of 41 pediatric IF patients
  - 27% on PN, 73% had weaned off PN years ago
- 70% had low femoral BMD Z-score \( \leq -1.0 \)
  - Both during and after weaning off PN
- Multivariate analysis predictors of decreased lumbar spine BMD
  - Time after weaning off PN (\( p=0.001 \))
  - Duration of PN (\( p=0.006 \))
  - Low calcium intake (\( p=0.035 \))
- No association with low BMD
  - Vitamin D 25-OH deficiency (41%)
  - Secondary hyperparathyroidism (44%)
- Conclusion: BMD, vitamin D, calcium and nutritional status should be closely monitored during and after weaning off PN to ensure sufficient vitamin D and mineral substitution for normal growth and bone mass attainment

Prevalence and Evolution of BMD on HPN

- Poinsot et al. reviewed 175 DXAs in 31 children on HPN
- **Aim:**
  - Determine prevalence of low BMD in children receiving HPN for IF
  - To evaluate the evolution of BMD and total bone mineral content (TBMC) during HPN with DEXA
- **Low BMD @ 1\textsuperscript{st} DEXA scan:** 45%
  - BMD not corrected for short stature
- **Per year of HPN:**
  - TBMC \textit{increased} by +0.1 ± 0.04 SD (P = .012)
  - The risk of low bone mass \textit{decreased} with OR 0.9 (95% confidence interval, 0.92–0.99; P = .018)
  - ?Due to adequate calcium content in HPN
- **Conclusion:** Low BMD is common in pediatric IF, but bone status could \textit{improve} during HPN in these children

Low BMD in Children with IF is Not Associated with Level of PN Dependency

- Nader et al. retrospective review of 40 IF children >5 years on PN >2 years
- High incidence of low BMD: 65%
  - BMD was corrected for short stature
  - Higher risk of low BMD with congenital enteropathy vs short bowel syndrome and pseudo-obstruction (p=0.01)
- Only 2 children with bone fractures (normal BMD and vit D 25-OH)
- Length of time on PN and higher dependence on PN did not impact BMD

What about other micronutrient deficiencies?
Copper Deficiency and Bone Health

- Copper is absorbed in stomach and proximal small intestine and promotes osteogenesis
- Copper deficiency can lead to anemia, neutropenia and metabolic bone disease
  - Increased bone resorption, weakened bone formation and reduced bone mineralization
  - Adult study: Low serum copper associated with reduced BMD and total fractures
- Excreted through biliary tract, can accumulate in cholestasis
  - Cholestatic patients, decrease copper by 50%
  - Do not remove copper completely; shortages
- Check copper/ceruloplasmin q6 months, q3 months if abnormal
  - Calculate Free Copper = (Total Serum Copper in μg/dl) - (Ceruloplasmin in mg/dl x 3), Normal 1.6-2.4 μmol/L or 10-15μg/dL
  - Skeletal surveys should be obtained if chronic copper deficiency is suspected
- Treatment: Oral supplement or IV supplement
  - Competes with zinc for absorption

QU, X, He, Z et al. Jo of Ortho Trans. 2018;14:34-44
Vitamin K Deficiency and Bone Health

- Essential Cofactor for bone-related vitamin K-dependent proteins
- Deficiency in vitamin K can impact bone metabolism and decrease bone mineralization
- Vitamin K deficiency ?increased fracture risk
- Vitamin K supplementation in adult home PN: trend for higher BMD
- Monitor PT with INR
- Can supplement vitamin K in PN as IV additive

Rodriguez, CR and Cerrel, MD. J of Osteoporosis: 2019
Additional Vitamins and Minerals for Bone Health

- **Iron**
  - Component of Prolyl Hydroxylase converts proline to hydroxyproline for collagen crosslinking
  - Deficiency could lead to increased bone fragility

- **Zinc:**
  - Stimulator of overall growth as cofactor for enzymes activating DNA & RNA synthesis
  - Increases activity of osteoblasts, activates bone formation, promotes collagen synthesis & inhibits osteoclastic bone resorption

- **Selenium**
  - Affects cartilage integrity

- **Vitamin C:**
  - Scurvy (can present as lower leg pain and refusal to bear weight in children)
  - Needed in formation of mature collagen
  - Causes subperiosteal hemorrhage as a result of collage defects
  - Increased deficiency risk with current MVI shortage

How do we monitor bone health in children with intestinal failure and insufficiency?
Monitoring Bone Health in Pediatric IF

■ History and Physical Exam
  - Most patients with low BMD are asymptomatic
  - History of bone fractures from minor trauma
  - Bone pain, refusal to bear weight
  - Ensure daily DRI met for calcium: enteral and parenteral
  - Review medications (i.e. steroids, loop diuretics can impact BMD)
  - Signs of vitamin and mineral deficiencies
  - Growth charts, growth velocity

■ Labs
  - BMP, Mg, Ph, ionized calcium
  - Alkaline phosphatase and isoenzymes
  - Vitamin D 25-OH
  - Parathyroid hormone
  - Vitamin C
  - Zinc, copper/ceruloplasmin, selenium
  - INR
  - Urine Calcium: Creatinine (0.1–0.6) to check for excess urinary calcium excretion

■ General X-rays
  - Bone Age
  - DXA
    - Baseline at age 4-5 years
    - Repeat every 1-2 years

How do we manage low BMD?
Management of Low BMD

- If pediatric IF patient has radiographic bone demineralization, low BMD or unexplained bone fracture:
  - Check vitamin 25-OH D, calcium, Phos, alkaline phosphatase isoenzymes, PTH
  - Maximize calcium, phosphorus and vitamin D intake
  - Minimize medications that have negative impact on bone health (i.e. corticosteroids)
  - DXA scan
  - Consult endocrinology
    - Bisphosphonates (decrease bone resorption)
  - Weight bearing exercises, Physical Therapy
    - Exercises that make bones work against gravity, such as walking or climbing stairs
    - Encourage child to participate in weight bearing exercise as much as possible. Aim for 30 minutes a day, 5 to 7 days a week

Weight Bearing Exercises (By Age)

Pre-school age

**Hop Scotch:** Start with feet shoulder-width apart. Alternate by jumping off both feet at the same time and landing on only one foot, then back to landing on two feet.

**Jumping Jacks:** Start with feet together and arms at your sides. Jump off the ground to bring your feet shoulder-width apart and hands above your head. Jump again to bring yourself back to the starting position. Repeat.

Elementary school age

**Shuttle Run:** Set up two cones about 15 yards apart. Sprint from cone 1 to cone 2 and back as quickly as possible, repeat 3 times.

**Balance and Hop:** Balance on left foot. Bend left knee and hip to lower down. As you come up, stand up tall and hop off the left foot and land back on the left foot. Repeat 10 times on left foot and then switch to right foot.

Age 12 and over

**Assisted Squats:** Hold a counter top or sink for stability. Keep arms straight and stand at arm's length from the counter. Feet parallel to hips, toes facing forward. Holding on, slowly lower hips down and back as if you're about to sit. Go as far as you feel comfortable ideally until thighs are almost parallel to floor. Slowly push up to stand. Repeat 8 - 10 times.

**Curb Jumps or Squat Jumps:** Stand with feet shoulder-width apart at the bottom of the curb. Go down into a squat and as you come up, jump off both feet simultaneously and land on top of the curb. Step or jump back down to the bottom of the curb and repeat. If you don't have a curb, pretend to jump up and onto something and then jump back.

**Push-ups:** Begin with hands underneath shoulders and feet together in plank position. (Start on your knees for an easier version). Keep your body straight and slowly lower toward the floor and then push back up.

**Biceps Curls:** Use a set of free weights or flexible band with a moderate resistance. With weights or band in your hands, start with your arms at your sides. Bend elbows to bring weights toward the shoulder. Slowly lower arms back down to your sides.
Bisphosphonates

- Antiresorptive agents
  - Slow bone resorption by reducing osteoclast function
  - Oral: alendronate, risedronate, ibandronate
  - IV: pamidronate, zoledronic acid, etidronate

- Used extensively in adults to treat postmenopausal and glucocorticoid-induced osteoporosis, malignancy-induced hypercalcemia and Paget's disease

- The potential adverse effects of bisphosphonates on the growing skeleton have been the main limiting factor to their use in pediatric patients
  - The use of bisphosphonates in pediatric patients should be carefully weighed to ensure that the potential benefits to bone health outweigh any potential risks
  - There is insufficient evidence for the routine use of bisphosphonates in clinical care
  - Therefore bisphosphonate treatment should be regulated by endocrinologists experienced in the management of bone disease in pediatric patients

What about GLP-2?

• Glucagon like peptide-2 (GLP-2) is an intestinotrophic hormone produced by L cells in the distal ileum and proximal colon that increases absorption

• Data implicate GLP-2 as a mediator of the effects of nutrition on bone metabolism, particularly on the suppression of bone reabsorption

• GLP-2’s role on bone remodeling has been studied in adults
  • Postmenopausal women
    • Double-blind placebo-controlled dose-ranging trial comparing three different doses of GLP-2 (0.4 mg, 1.6 mg and 3.2 mg GLP-2, administered nightly) against a saline control injection
    • Treatment with GLP-2 resulted in a significant dose-dependent increase in total hip BMD over the course of the study that for the 3.2 mg GLP-2 group reached 1.1% (P=0.007) from baseline
  • Short bowel syndrome
    • Measured bone resorption marker C-terminal telopeptide (CTX) in response to a meal and compared with plasma concentrations of GLP-2
    • SBS patients without a colon did not have a reduction in serum concentration of CTX when compared to normal controls, suggesting that bone resorption is decreased postprandially by intestinal factors and GLP-2 is a possible candidate
    • Subsequent pilot study in 8 SBS adult patients did not show decrease in bone resorption with GLP-2 treatment

Take Home Messages

- Patients with intestinal failure and intestinal insufficiency should be routinely monitored for metabolic bone disease
  - Patients should be monitored even after PN weaned
- Bone health assessments should be done frequently (H+P, assessing risk, monitoring labs)
- DXA scans should be a part of a comprehensive skeletal health assessment in patients on long term PN
  - Lack of evidence indicates how often DXA scans should be performed
- Optimize calcium intake and serum calcium, weight for age Z-scores, ?Vitamin D
- PN does not seem to be a risk factor for MBD
  - Optimize the PN formulation to minimize hypercalcuria by providing adequate calcium, phosphorus, magnesium, and acetate, and avoiding excessive protein and aluminum contamination
- Consider referral of patients with low BMD and osteoporosis to Endocrinology
- Physical therapy, weight bearing exercises
- ?Role of intestinal growth hormones on BMD (i.e. GLP-2)
- Additional prospective, large scale multicenter studies are needed to identify risk factors for low BMD and determine optimal monitoring of bone health