Osteoporosis in Premenopausal Women

Dr. Mahmoud Sajjadi

Associate Professor of Endocrinology and Metabolism

Endocrinology and Metabolism Research Institute

Tehran University of Medical Sciences

Case Presentation

- A healthy, **39-year-old premenopausal woman** insists on a **BMD** assessment, driven by the knowledge that **her mother** suffered a **hip fracture at age 78**. She is otherwise asymptomatic, reporting **regular menstrual cycles**, **no prior fragility fractures**, and **no chronic illnesses or medications**.
- Age of menarche: 14 year old
- BMI= 23 kg/m2
- Physical exams: NL

BMD screening for premenopausal women (ISCD)

- BMD screening is not routinely recommended for premenopausal women
  - History of a fragility fracture
  - Known secondary causes of osteoporosis
- FRAX algorithm for fracture risk assessment is validated only for individuals aged ≥40 years.

ISCD
The International Society For Clinical Densitometry

Case Presentation
Bone Mineral Density (BMD) Results

Site	BMD (g/cm²)	T-score	Z-score
Lumbar Spine (L1–L4)	0.845	-2.3	-2.1
Total Hip	0.820	-2.0	-1.9
Femoral Neck	0.780	-2.1	-2.0

BMD: Hologic

Definition of Osteoporosis in Premenopausal Women

- **Fragility Fracture:** Osteoporosis can apply to those with a history of low trauma fracture(s) , especially at major sites (spine, hip) or multiple fractures.
  - Low BMD is **not required** to make the diagnosis in this context.
  - Non-osteoporosis etiologies (e.g., bone lesions, osteomalacia) must be excluded.
- **Low BMD + Secondary Cause:**
  - Osteoporosis may also apply to premenopausal women with low BMD and an **active condition or medication exposure** (e.g., celiac disease, glucocorticoid therapy) known to confer high short-term risk of bone loss or fracture.
  - **BMD Criteria (Skeletally Mature Adults with Secondary Cause)**
    - Current recommendations support using either a **Z-score ≤-2.0 or T-score ≤-2.5** to define osteoporosis.
- Low BMD alone should not be used to define osteoporosis in a premenopausal woman

Primary and Secondary causes of osteoporosis in premenopausal women

Category	Causes / Examples
Primary Cause	A primary cause of osteoporosis is a **genetic or developmental bone disorder** that leads to bone fragility. Examples include: Osteogenesis Imperfecta (OI) and Ehlers Danlos syndrome
Secondary cause	Secondary causes comprise any acquired, underlying condition or medication exposure that contributes to bone loss or fragility
Nutritional / GI	Anorexia nervosa; Gastrointestinal malabsorption (e.g., celiac disease, postoperative states); Vitamin D and/or calcium deficiency
Endocrine / Metabolic	Hyperthyroidism; Hyperparathyroidism; Cushing syndrome; Hypogonadism (hypogonadotropic or hypergonadotropic); Hypercalciuria; Diabetes (type 1 and 2)
Autoimmune / Inflammatory	Rheumatoid arthritis; Other inflammatory conditions
Organ Disease	Kidney disease; Liver disease
Genetic / Rare Disorders	Homocystinuria; Hereditary hemochromatosis; Bone marrow processes (Systemic mastocytosis; Gaucher disease; Thalassemia major)
Infections	HIV infection and/or medications
Lifestyle	Alcoholism
Medications	Glucocorticoids; Immunosuppressants (e.g., cyclosporine); Antiseizure meds (esp. phenobarbital, phenytoin); GnRH agonists (when used to suppress ovulation); Heparin; Chemotherapy leading to amenorrhea; Thiazolidinediones; Depot medroxyprogesterone acetate
Possible Contributors	Excess thyroid hormone; Depression and/or SSRI use; Proton pump inhibitors

Idiopathic Low BMD and Idiopathic Osteoporosis

Term	Definition	Diagnostic Application
Idiopathic Low BMD (ILBMD)	Premenopausal women with **low BMD (Z-score ≤-2.0) but no history of fragility fracture** and **no** known **primary or secondary causes** of bone loss after extensive evaluation.	The term **osteoporosis should not be used**. The **relationship between low BMD and fracture risk** is **unknown** in this population.
Idiopathic Osteoporosis (IOP)	Premenopausal women with **low trauma fracture**(s) and **no identifiable etiology** after extensive evaluation for primary and secondary causes.	**Rare** condition; often linked to **genetic factors**. **Family history** and **childhood fractures (early onset)** common.
Note: ILBMD and IOP may reflect **resolved secondary causes**, **failure to attain peak bone mass**, or an **unknown/ongoing etiology**.		

Initial Evaluation

- **History & Physical:** age of menarche, history of oligo-/amenorrhea, prior pregnancy/lactation, medications, dietary/exercise patterns, tobacco and alcohol use, GI symptoms, kidney stone history, surgical history, and family history of osteoporosis/fracture.

- **Initial Laboratory Tests (For all premenopausal women with low BMD and/or fragility fracture):**
  - Serum calcium, phosphate, and creatinine levels
  - CBC
  - Liver function tests (alkaline phosphatase and aminotransferase levels)
  - Serum 25-hydroxyvitamin D level
  - TSH
  - 24-hour urine collection for calcium and creatinine

Additional Laboratory Tests (if indicated)

Women who have abnormalities on initial laboratory testing, certain findings on history and physical examination, or unexplained osteoporosis and fracture after the initial evaluation require additional laboratory tests

Test / Category	Examples or Notes
Hormonal evaluation	Estradiol, LH, FSH, prolactin
Parathyroid function	PTH
Vitamin D metabolism	1,25-dihydroxyvitamin D
Cortisol evaluation	24-hour urine for free cortisol (or dexamethasone suppression test)
Iron studies	Iron/TIBC, ferritin
Celiac disease screening	Celiac screen (serologies)
Protein disorders	Serum/urine protein electrophoresis
Inflammatory markers	Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
Autoimmune markers	Rheumatoid factor
Vitamin A status	Vitamin A/retinol level
Rare condition testing	Specific testing for mastocytosis, hemochromatosis, etc. (if clinically indicated)
Genetic evaluation	If primary forms of osteoporosis are suspected
Bone metabolism	Bone turnover markers
Histologic evaluation	Transiliac crest bone biopsy

Case Presentation, Laboratory Results

Test	Result	Units	Reference Range
Hemoglobin (Hb)	13.5	g/dL	12.0 – 15.5
White Blood Cells (WBC)	6.5	$\times 10^9$/L	4.0 – 10.0
Platelets (PLT)	280	$\times 10^9$/L	150 – 400
Mean Corpuscular Volume (MCV)	90	fL	80 – 100
Calcium (total)	9.4	mg/dL	8.5 – 10.5
Phosphate	3.41	mg/dL	2.5 – 4.5
PTH	43	Pg/ml	15-65
Creatinine	0.79	mg/dL	0.6 – 1.1
ALT	22	U/L	< 35
AST	24	U/L	< 35
ALP	75	U/L	30 – 120
25(OH) Vitamin D	34	ng/mL	30 – 50
TSH	2.0	mIU/L	0.4 – 4.0
Total T4	8.0	µg/dL	5.0 – 12.0
Total T3	120	ng/dL	80 – 180
24-hr Urine Calcium	200	mg/day	100 – 300
Celiac Serology	Negative	—	Negative
ESR	10	mm/hr	< 20

Imaging or other evaluation

- In the setting of unusual fracture(s) (eg, atypical site or type for osteoporotic fracture; antecedent, localized bone pain).

- Assess for pathologic fracture related to underlying malignancy or other bone lesion.

Genetic testing

- **Considered in patients with any of the following:**
- A family history of early onset osteoporosis
- Fractures beginning in childhood
- Notable disease severity
- A history of joint injuries or hypermobility
- Dental abnormalities

Management: Nonpharmacologic Approaches

- **Nonpharmacologic strategies for all women (low BMD or osteoporosis)**
- **Calcium and vitamin D intake**
  - Calcium: 1000 mg total from diet plus supplements if needed
  - Vitamin D: 600 IU vitamin D3 daily
- **Exercise (regular weightbearing exercise and physical activity):** Recommendations must be individualized.
- **Lifestyle Modification:** Address tobacco and excessive alcohol use
- **Avoidance of undernutrition** and wide fluctuations in body weight
- **Management for Secondary Causes**:
  - When a secondary cause is identified, interventions should be **targeted to address the specific cause**.
  - Subsequent monitoring is needed for improvement.

Indications for Concomitant Pharmacologic Treatment

- **Fracture History:** History of fracture at **major sites** (e.g., spine or hip) or **multiple fragility fractures.**
- **Documented Ongoing Bone Loss:** Evidence of accelerated, ongoing bone loss (**≥3 to 5 percent BMD loss per year**).
- **High risk for short-term bone loss: Low BMD and/or fragility fracture with an active secondary cause** that cannot be readily mitigated and confers high risk for short-term bone loss.
  - **Examples:** Glucocorticoid therapy; Chemotherapy/hormonal therapy

Idiopathic Low BMD (ILBMD) – Treatment

- **General Approach**
  - No pharmacologic treatment if **no fractures** or **secondary causes**.
  - Ensure **adequate calcium & vitamin D**.
  - **Repeat BMD** in **1–2 years**.
- **Stable BMD on Repeat Measurement**
  - Continue **nonpharmacologic interventions** (nutrition, exercise, etc.).
  - **Remeasure BMD at least once more in two years to ensure stability.**
  - These women typically maintain **stable BMD** over time, even though BMD is low.
- **Evidence of Ongoing Bone Loss**
  - **Uncommon** in ILBMD.
  - Suggests **ongoing or undiagnosed secondary cause** → requires further workup.
  - If **Z-score ≤ -3.0** or **progressive bone loss**, consider **pharmacologic therapy**.

Idiopathic Osteoporosis (IOP)

Pharmacologic Therapy – When to Treat

- Limited data; treat **selected cases** with fragility fractures:
  - Major site fracture (**spine, hip**)
  - Other fracture (e.g., **forearm, rib**) **+ very low BMD (Z-score ≤ -3.0)**
  - Multiple fragility fractures

Idiopathic Osteoporosis (IOP)
Pharmacologic Therapy – When to Treat

- Women Not Meeting Criteria for Drug Therapy
  - Implement **nonpharmacologic measures** (calcium, vitamin D, lifestyle).
  - **Repeat BMD in 1 year** to assess trajectory.
  - A **single low BMD may reflect low peak bone mass**—not active bone loss.
  - **Serial BMD testing** needed to confirm stability or progression.

- Stable BMD on repeat measurement
  - **Continue nonpharmacologic** interventions
  - **Remeasure BMD at least once more** in two years to ensure stability
- Ongoing Bone Loss:
  - Rare—may indicate **undiagnosed secondary cause**.
  - **Further evaluation** recommended.
  - **Pharmacologic therapy** or change in medication often warranted.

Choice of Pharmacologic Therapy

Initial Choices

- Antiresorptive therapy (e.g., **Bisphosphonates**).

- Bone-anabolic therapy (**Teriparatide** is the most studied anabolic agent in this context).

Choice of Pharmacologic Therapy

Bisphosphonates (Antiresorptive)

- Although bisphosphonates have been **shown to prevent bone loss in young women with various conditions**, long-term efficacy, safety, and fracture **data are scarce** in premenopausal women.
- The **decision to initiate** treatment with bisphosphonates in any premenopausal woman should be made on a **case-by-case**
- Used with **caution in reproductive-age women** due to long half-life in bone. **Oral bisphosphonates are preferred over IV** zoledronic acid in this group.
- **Most case reports** of bisphosphonate use during pregnancy **do not report adverse maternal or fetal outcomes**
- Goal should be for the **shortest possible duration of use**.
- Rare potential **risks of long-term use**: **ONJ** and **atypical femoral fractures**

Choice of Pharmacologic Therapy

Anabolic Therapy (Teriparatide) Preferred for Selected Women

We opt for initial anabolic therapy (eg, teriparatide) prior to bisphosphonate therapy for selected women with any of the following:

- **History of vertebral or other major (e.g., hip) fracture(s).**
- **Very low BMD (Z-score ≤-3.0) with** a history of **fragility fracture**.
- **Desire for pregnancy in the short term** (due to long half-life of bisphosphonates in bone).

Teriparatide Should be avoided in those at increased risk of osteosarcoma (including those with Paget disease, hereditary disorders predisposing to osteosarcoma, prior radiation, growing bones [open epiphyses], or unexplained elevation in alkaline phosphatase).

Special Considerations and Monitoring

- **Consolidation Therapy After Teriparatide**
- For **postmenopausal women**, **anabolic therapy** is typically **followed by antiresorptive** therapy.
- For premenopausal women with **IOP**, **consolidation therapy with bisphosphonates** is usually favored after teriparatide to prevent bone loss.
- **BMD gain** in premenopausal women who **resumed menses after cessation** of both **long-acting GnRH analog and teriparatide therapy** (One study)
- Women with **idiopathic pregnancy and lactation-associated osteoporosis** who regain normal menstrual cycles may be **able to maintain BMD without subsequent antiresorptive** therapy.

Other Agents (less available evidence) and Contraindications

Denosumab:

- May be **an option for severe osteoporosis** in premenopausal women **either as** part of a **sequential approach after anabolic therapy or as initial** therapy.
  - Fracture affecting a major site
  - Multiple fragility fractures
  - Fragility fracture in the setting of very low BMD [Z-score ≤-3.0]
- **Effects of discontinuation** in premenopausal women are **unclear**
  - **Postmenopausal pattern** of bone loss/fracture risk **not yet confirmed**
  - May require **consolidation therapy** after stopping
- **Clinical Implications:**
  - Sequential treatment (including consolidation) → **longer therapy duration**
  - May be **less suitable for younger women** or those **planning pregnancy**
  - Effective plan for pregnancy prevention during therapy and for at least five months after the last dose

Other Agents (less available evidence) and Contraindications

There are no clinical trial data on the efficacy or safety

- Abaloparatide
- Romosozumab

Avoid in Premenopausal Women:

- SERMs (e.g., raloxifene): Block estrogen action on bone, leading to further bone loss.
- Calcitonin: calcitonin did not confer improvement in BMD

Monitoring

BMD should be **remeasured annually** after pharmacologic or nonpharmacologic intervention.

Bone loss (≥3 to 5 percent BMD loss per year) can be considered an indication for change in or initiation of medical treatment.

Case Presentation

Bone Mineral Density (BMD) Results after 2 year

Site	Previous BMD (g/cm^2)	Follow-up BMD (g/cm^2)	Change in BMD (%)
Lumbar Spine (L1–L4)	0.845	0.840	-0.59
Total Hip	0.820	0.825	+0.61
Femoral Neck	0.780	0.771	-1.15

The "Change in BMD (%)" is calculated as:

$$\text{Change}(\%) = \left(\frac{\text{Follow-up BMD} - \text{Previous BMD}}{\text{Previous BMD}} \right) \times 100$$

BMD: Hologic

Case Presentation (Management Plan)

- Nonpharmacologic interventions:
  - Calcium 1000 mg/day, Vitamin D 600 IU/day
  - Regular weight-bearing and resistance exercises
  - Avoid smoking, excess alcohol, undernutrition

- Follow-up:
  - BMD stable at 2 years (<3-5 percent % change)
  - No fractures; continues nonpharmacologic care

Summary

- Diagnosis: Idiopathic Low Bone Mineral Density (ILBMD)
- No secondary cause identified after full evaluation
- Stable BMD on serial follow-up (2 years)
- Nonpharmacologic management effective
- Pharmacotherapy not indicated