# Premenopausal osteoporosis

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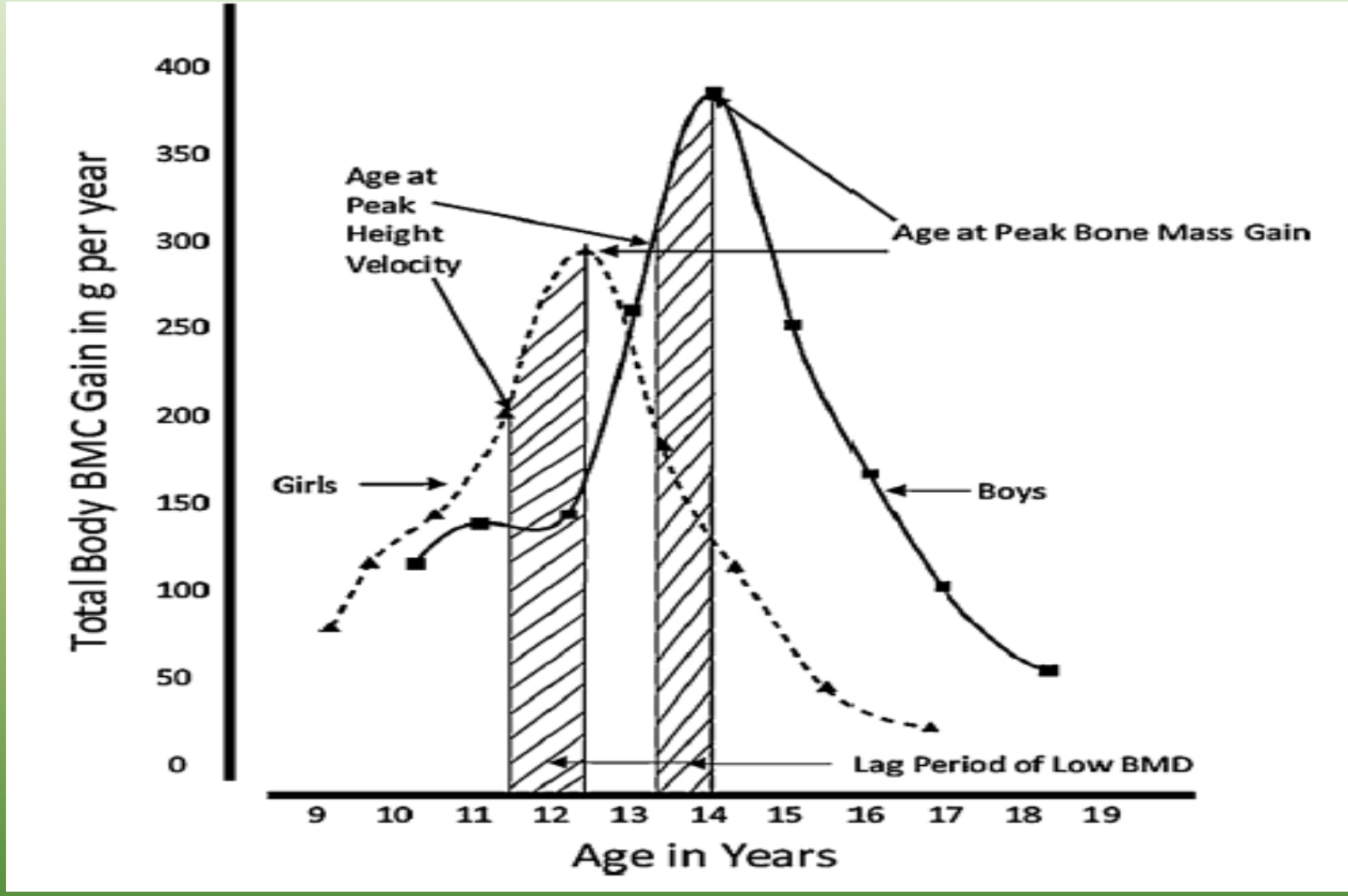
- Fragility fractures in PW **are rare** and mostly due **to secondary osteoporosis**, i.e. in presence of an underlying disease such as **hormonal, inflammatory** or **digestive disorders**. In absence of another disorder, **low bone density (BMD) together with fragility fractures qualifies as "idiopathic osteoporosis".** In contrast, low BMD alone does not necessarily represent osteoporosis in **absence of bone microarchitectural abnormalities**.

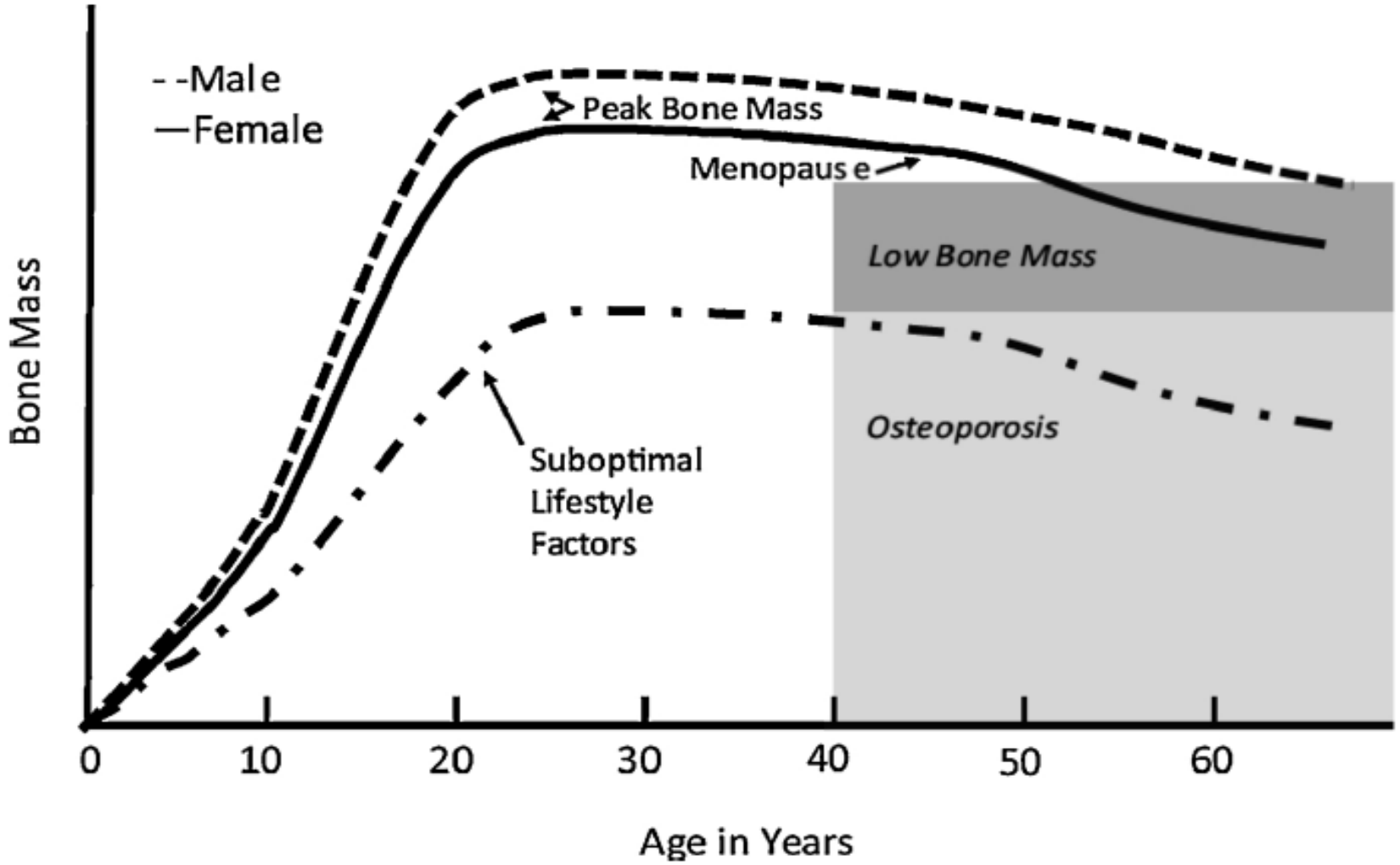
- The prevalence of “osteoporosis” in premenopausal women varies **from 0.5 to 50% depending on the population studied**, the definition of osteoporosis used, and the referral center involved.
- In premenopausal women with **known causes of secondary osteoporosis**, **the prevalence of low bone mass (defined as Z-score ≤ -2**) was recently reported as **17.3%** in patients affected by **systemic lupus erythematosus**, **7.3%** in **rheumatoid arthritis**, **44.5%** in **Cushing diseases**, **35%** in **HIV**, and **45%** in **cystic fibrosis**, and these disorders are associated with an **increased risk of fragility fractures.**
- A premenopausal woman with a **prior fracture has a 35 to 75% higher risk of** having a fracture in her postmenopausal years than a premenopausal woman without fracture.

- The bone mineral density (BMD) of premenopausal women depends primarily on their **bone accrual during childhood and adolescence** as the **final peak bone mass is reached around the age of 20 years, depending on the skeletal site.**
- However a recent retrospective case control study including 12.970 premenopausal women reported **a significant decrease of fracture risk with the use of combined oral contraceptives (COC).**




**Peak bone mineral accretion rate occurs at 12.5±0.9 years in girls and 14.1±0.9 years in boys.**

- In 2016, the National Osteoporosis Foundation (NOF) published a position statement **on peak bone mass and lifestyle**, **as lifestyle habits may contribute to 20–40% of the mean variance of adult peak bone mass**.
- For subjects **younger than 40 years old**, the International Society for Clinical Densitometry (ISCD) proposed us BMD **Z-scores below or equal to -2** (comparison to age and sex matched value) to **define "low bone mass", which is a value "below the expected range for age".**


- -Male
—Female
Peak Bone Mass
Menopause
Low Bone Mass
Osteoporosis
Suboptimal
Lifestyle
Factors
Bone Mass
0
10
20
30
40
50
60
Age in Years

*Risk factors for developing osteoporosis or osteopenia*

| | |
|---|---|
| **Unmodifiable** | Genetics |
| | Age |
| **Dietary and Lifestyle** | Calcium Deficiency |
| | Vitamin D Deficiency |
| | Protein Deficiency |
| | Anorexia Nervosa |
| **Medication** | Glucocorticoids |
| | Deport Medroxyprogesterone Acetate (DMPA) |
| | Antiepileptic Drugs (AEDs) |
| | Proton-Pump Inhibitors (PPI) |
| **Gastrointestinal Disorders** | Celiac Disease |
| | Irritable Bowel Syndrome |
| **Endocrine Disorders** | Hypogonadism |
| | Hperthyroidism |
| | Hyperparathyroidism |
| | Growth Hormone Deficiency |
| | Diabetes Melliitus Type-1 |
| **Inflammatory Disease** | Rheumatoid Arthritis |
| | System Lupus Erythematosus |
| **Other Considerations** | Depression |
| | Breastfeeding |

- The International Osteoporosis Foundation (IOF) also defines **low bone mass in the young as Z-scores below-2, however only before 20 yrs of age.** Thereafter, they kept the same definition as in post-menopausal women, namely a T score ≤ −2.5 for individuals older than 20 years and in the absence of delayed puberty.
- **Vertebral and/or multiple fragility fractures with low BMD** are a hallmark of osteoporosis for both societies. **Hence, for premenopausal women with low BMD (i.e. Z-score ≤ -2 or T-score ≤ -2.5) but without fractures, a diagnosis of low peak bone mass vs. osteoporosis may be difficult to ascertain**

## BMD changes during pregnancy[1]

Pregnancy and lactation may temporarily reduce BMD (longitudinal studies) and this must be considered when a single BMD measurement is interpreted:

- Lumbar spine BMD decreases 3-5% with pregnancy
- Lumbar spine BMD decreases 3-10% over a six-month lactation period (determined by duration of lactation and associated amenorrhoea)
- Recovery of BMD/return to baseline BMD expected after 6-18 months.

Some possible secondary causes of osteoporosis and bone fragility in young adults.

Gastrointestinal-related
- Inflammatory bowel disease (in particular Chron's disease)
- Malabsorption
- Coeliac disease
- Cystic fibrosis

Endocrine-related
- Hyperparathyroidism
- Hypovitaminosis D
- Turner syndrome
- Klinefelter's syndrome
- Anorexia nervosa
- Other hypogonadisms
- Cushing's syndrome
- Type 1 diabetes
- Pregnancy

Systemic-, hematologic- and inflammatory diseases
- Juvenile/rheumatoid arthritis
- Connective tissue diseases
- Leukemia
- Organ transplant
- Systemic mastocytosis
- Nephropathies
- Human immunodeficiency virus disease

Various genetic diseases
- Hemochromatosis
- Osteoporosis imperfecta
- Marfan syndrome
- Gaucher's disease
- Galactosemia
- Duchenne
- Thalassemia

Medications
- Glucocorticoids
- Anticonvulsants
- GnRH agonists/antagonists
- Aromatase inhibitors
- Cytotoxic chemotherapy
- Long-term Heparin
- Long-term Proton Pump Inhibitors

## [redacted]. Possible causes of low bone density in premenopausal women[3]

| Inherited | Nutritional | Endocrine | Medications | Other |
|---|---|---|---|---|
| Osteogenesis imperfecta<br>Homocystinuria<br>Marfan's syndrome | Malabsorption<br>Chronic liver disease<br>Alcoholism<br>Calcium deficiency<br>Vitamin D deficiency | Hypogonadism<br>Hyperthyroidism<br>Cushing's syndrome<br>Hyperpara-thyroidism<br>Anorexia nervosa | Glucocorticoids<br>Anticonvulsants<br>Heparin<br>Excess thyroid<br>GnRH agonists | Multiple myeloma<br>Rheumatoid arthritis<br>Mastocytosis<br>Immobilisation<br>Hypercalciuria |

GnRh – gonadotropin releasing hormone
Progesterone based contraception
Early initiation of oral contraception

Major causes of secondary osteoporosis in the young

| | | |
|---|---|---|
| Chronic and inflammatory | Inflammatory bowel disease | Malabsorption |
| | Coeliac disease | HIV |
| | Nephropathies | Organ transplant |
| | Cystic fibrosis | Connective tissue diseases |
| | (Juvenile) rheumatoid arthritis | Thalassemia |
| | Systemic mastocytosis | Leukemia |
| Endocrine | Diabetes type I | Cushing's syndrome |
| | Hypovitaminosis D | Hyperparathyroidism |
| | Hypogonadism (amenorrhea, Turner, anorexia nervosa) | |
| | Hyperthyroidism | Pregnancy |
| Neuromuscular and metabolic | Duchenne | Galactosemia |
| | Gaucher's disease | Glycogen storage disease |
| | Hemochromatosis | Marfan syndrome |
| Medications | Glucocorticoids | Glitazones |
| | PPIs (chronic use) | |
| | Anticonvulsants | Cyclosporine (tacrolimus) |
| | Aromatase inhibitors, depot MPA | GnRH inhibitors |
| | High-dose thyroxine | Heparin (long-term) |
| | Cytotoxic chemotherapy | HAART |

*HIV* human immunodeficiency virus, *MPA* medroxyprogesterone acetate (used as contraceptive), *HAART* highly active antiretroviral therapy, *PPIs* proton pump inhibitors

Major causes of amenorrhea due to abnormalities in the hypothalamic-pituitary-ovarian axis Adapted from Corrine K Welt, Robert L Barbieri, William F Crowley, Jr, Mitchell E Geffner, Kathryn A Martin, Uptodate 2019.

| Abnormality | Causes |
|---|---|
| Hypothalamic dysfunction | Isolated GnRH deficiency<br>Functional hypothalamic amenorrhea<br>- Weight loss, eating disorders<br>- Excessive exercise (including but not exclusively: running, ballet dancing, figure skating, gymnastics)<br>- Stress<br>- Severe or prolonged illness<br>Inflammatory or infiltrative diseases<br>Brain tumors – e.g., craniopharyngioma<br>Cranial irradiation<br>Traumatic brain injury<br>Other syndromes - Prader-Willi, Laurence-Moon-Biedl, leptin mutations |
| Pituitary dysfunction | Hyperprolactinemia, including lactotroph adenomas<br>Other pituitary tumors - acromegaly, corticotroph adenomas (Cushing's disease)<br>Other tumors - meningioma, germinoma, glioma<br>Genetic causes of hypopituitarism<br>Empty sella syndrome<br>Pituitary infarct or apoplexy |
| Ovarian dysfunction | Primary ovarian insufficiency (premature ovarian failure)<br>- Turner syndrome, fragile X permutation, chemotherapy and radiotherapy, somatic chromosomal defects, autoimmune, idiopathic |
| Other | Polycystic ovary syndrome<br>Hyperthyroidism<br>Hypothyroidism<br>Uncontrolled diabetes mellitus types 1 and 2<br>Exogenous androgen use |

HPO: hypothalamic-pituitary-ovarian; GnRH: gonadotropin-releasing hormone.

- **Premenopausal women with recent major fragility fractures (hip, vertebral, proximal humerus and distal forearm fractures) should be considered at high risk for further fractures in the short to medium term, and further assessment is recommended.**
- Osteoporosis in premenopausal women is more frequently caused by underlying diseases.
- The majority of the subjects were found to have a **cause of secondary osteoporosis at a range varying between 50% to 90% depending on the setting and time of diagnosis**.

## . Clinical scenarios of suboptimal bone health in premenopausal women

- Low bone mass with known secondary cause
- Idiopathic low bone mass (no fracture, no secondary cause)
- Secondary osteoporosis (glucocorticoid-induced osteoporosis)
- Idiopathic osteoporosis (prior fracture, no secondary cause)

## Management options

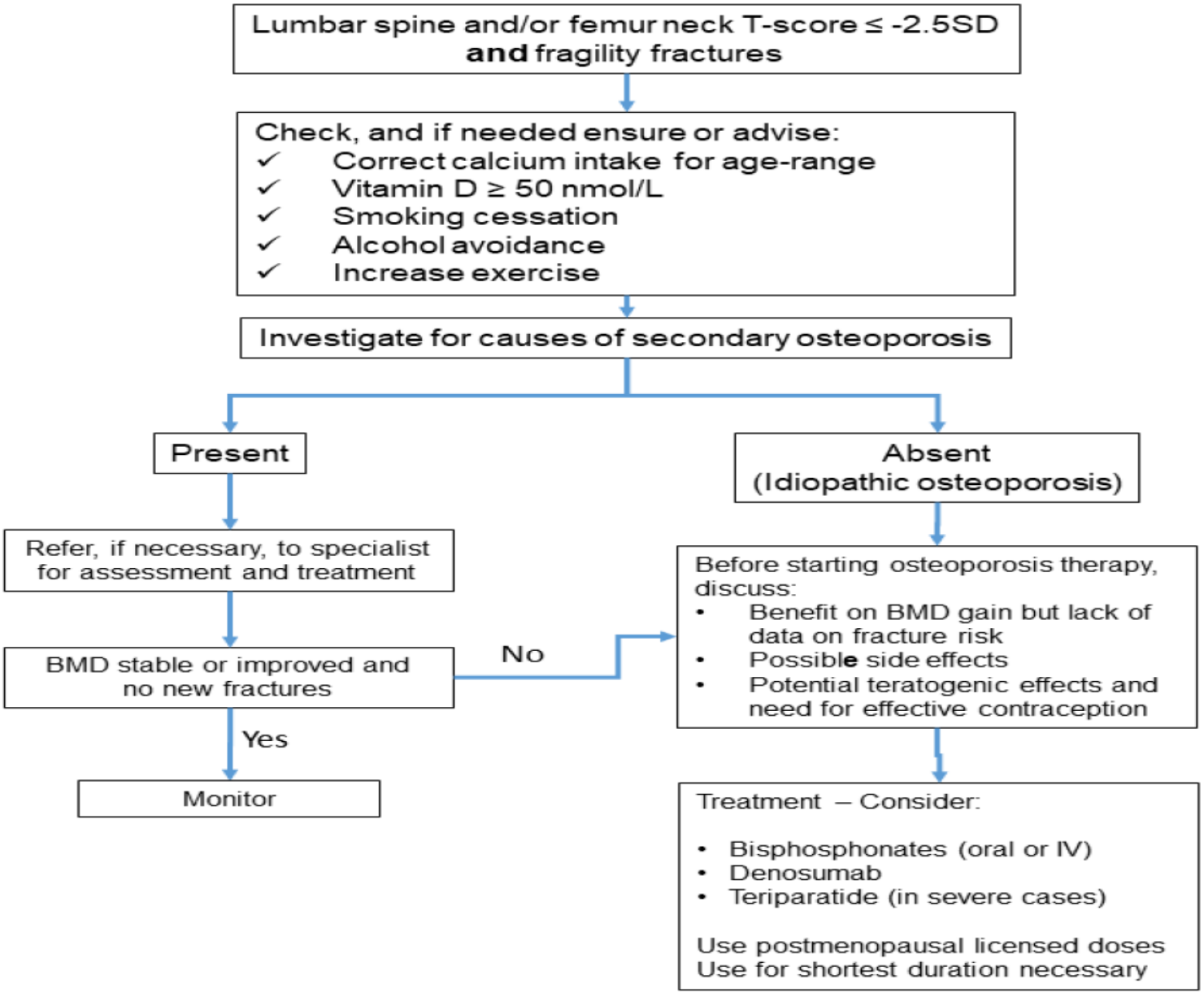
- Lifestyle modifications
- Address the underlying secondary cause
- Bone-specific therapy
  - Bisphosphonates
  - Teriparitide
  - Denosumab

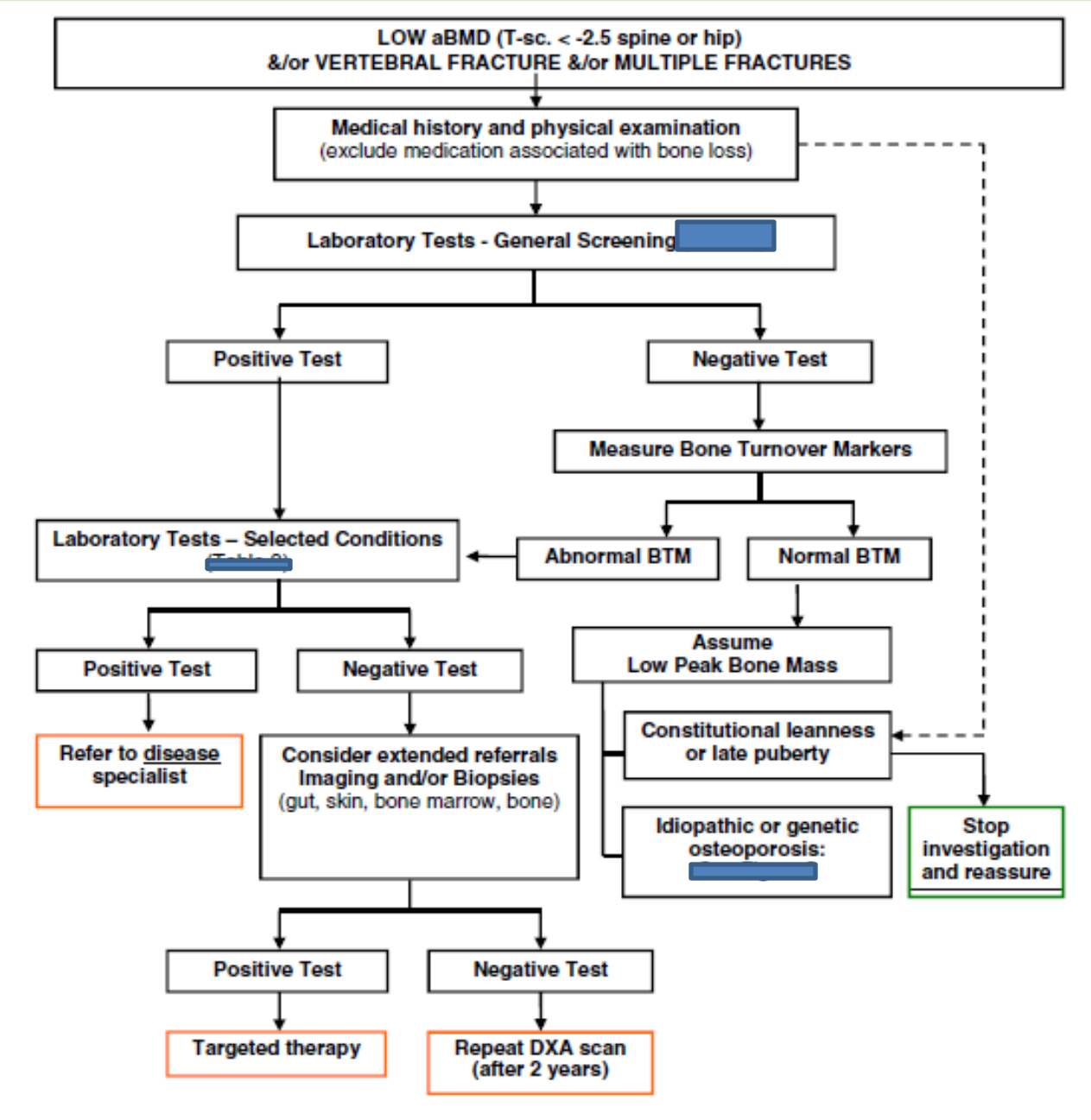
| Laboratory tests—general screening | |
|---|---|
| Mineral metabolism | Serum calcium (corrected for albumin) |
| | Serum phosphate |
| | Creatinine |
| | 25(OH)D |
| | iPTH |
| | ALP (bone specific) |
| | BTMs (for instance, s-CTX and s-PINP)[a] |
| Inflammation, hematopoietic disorder | Blood cell count |
| | ESR or CRP |
| Hepatic disease | GOT, GPT, γ-GT |
| Diabetes (primary or secondary) | Fasting glucose, Hba1C |
| Thyroid dysfunction | TSH |
| Hypogonadism (men) | Total testosterone |
| Malabsorption, Coeliac disease | 24-h urinary calcium |
| | Anti-endomysial, anti-transglutaminase |

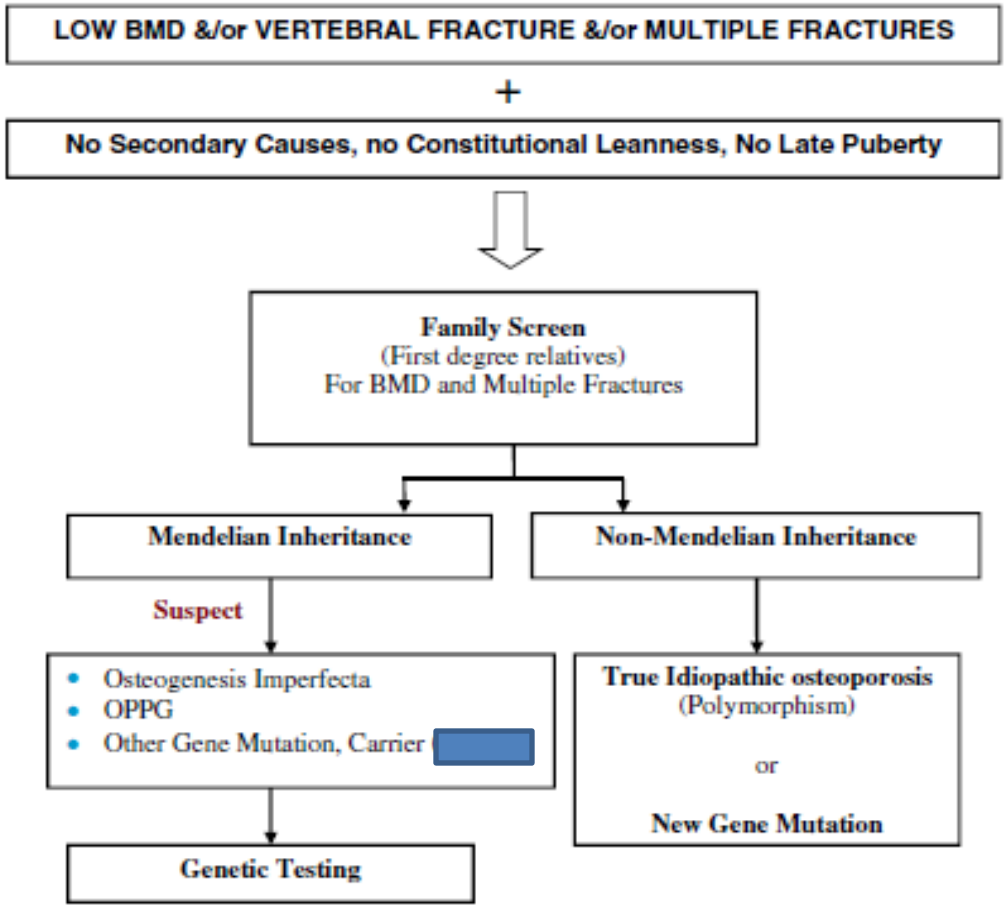
Laboratory tests—selected conditions

| Background | Test |
|---|---|
| TSH alterations | Free T4 |
| Altered glucose, Cushing's syndrome | 24-h free urinary cortisol |
| Altered testosterone (men) | LH/SHBG (free testosterone) |
| Amenorrhea, hypogonadism (women) | FSH/estradiol |
| Altered renal function (CRF) | $1,25(OH)_2D_3$ |
| Hemochromatosis | Ferritin |
| Hypophosphatasia | ALP, BALP, urinary phosphoethanolamine |
| Mastocytosis | Tryptase, IgE |
| Gaucher's disease | Glucocerebrosidase |

*TSH* thyroid-stimulating hormone, *LH/SHBG* luteinizing hormone/sex hormone-binding globulin, *FSH* follicle-stimulating hormone, *CRF* chronic renal failure, *BALP* bone-specific alkaline phosphatase, *IgE* immunoglobulin E


Lumbar spine and/or femur neck T-score ≤ -2.5SD
and fragility fractures
Check, and if needed ensure or advise:
✓ Correct calcium intake for age-range
✓ Vitamin D ≥ 50 nmol/L
✓ Smoking cessation
✓ Alcohol avoidance
✓ Increase exercise
Investigate for causes of secondary osteoporosis
Present
Absent
(Idiopathic osteoporosis)
Refer, if necessary, to specialist for assessment and treatment
BMD stable or improved and no new fractures
No
Yes
Monitor
Before starting osteoporosis therapy, discuss:
• Benefit on BMD gain but lack of data on fracture risk
• Possible side effects
• Potential teratogenic effects and need for effective contraception
Treatment – Consider:
• Bisphosphonates (oral or IV)
• Denosumab
• Teriparatide (in severe cases)
Use postmenopausal licensed doses
Use for shortest duration necessary


LOW aBMD (T-sc. < -2.5 spine or hip)
&/or VERTEBRAL FRACTURE &/or MULTIPLE FRACTURES
Medical history and physical examination
(exclude medication associated with bone loss)
Laboratory Tests - General Screening
Positive Test
Negative Test
Measure Bone Turnover Markers
Laboratory Tests – Selected Conditions
Abnormal BTM
Normal BTM
Positive Test
Negative Test
Assume
Low Peak Bone Mass
Refer to disease specialist
Consider extended referrals
Imaging and/or Biopsies
(gut, skin, bone marrow, bone)
Constitutional leanness
or late puberty
Idiopathic or genetic
osteoporosis:
Stop
investigation
and reassure
Positive Test
Negative Test
Targeted therapy
Repeat DXA scan
(after 2 years)




Clinical pathway for young adults, with either low BMD and/or vertebral fracture, and/or multiple fractures, where no secondary causes of osteoporosis (including constitutional leanness and delayed puberty) were found

**Table 4** Main monogenic disorders primarily manifest as bone fragility

| Monogenic disorders | Gene mutations | Familial pattern of inheritance | Description and main clinical outcome | Incidence |
|---|---|---|---|---|
| Osteogenesis imperfecta | Col I α1 and Col I α2 | Autosomal dominant (types I–V) | Fragility fractures, bone deformity, and low BMD | Estimated at 6 to 7 per 100,000 people worldwide |
| | LEPRE1 and CRTAP (some OI types II, III, and VII) | Autosomal recessive (some types II, III, VII, and IX) | Dentinogenesis imperfecta | Types I and IV are the most common forms, affecting 4 to 5 per 100,000 people |
| | PPIB in type IX | | Mild forms may be manifest as low aBMD only | |
| Hypophosphatasia | ALPL | Autosomal dominant (adult form) | Defective mineralization, leading to softening of the bones (osteomalacia) | Severe forms affect an estimated 1 in 100,000 newborns. Milder cases, such as those that appear in adulthood, probably occur more frequently |
| | | Autosomal recessive (perinatal) | Recurrent fractures in the foot and thigh bones inducing chronic pain | |
| | | | Loss of adult teeth prematurely | |
| | | | Joint pain and inflammation | |
| Osteoporosis-pseudoglioma syndrome (OPPG) | LRP5 (11q13.4) | Recessive | Fragility fractures, bone deformity, low BMD and partial blindness | Unknown |
| | | | Carrier state may be manifest as bone fragility only | |

*Assessment of conditions and management strategies*

| Background | Assessment | Management |
|---|---|---|
| Calcium Deficiency | 3-day food journal, serum calcium corrected for albumin | 1000 mg/day for prevention<br>Food: broccoli, kale, leafy greens, nuts, legumes |
| Vitamin D Deficiency | Serum 1,25(OH)D | >30 ng/mL: 800-1000 IU/day<br><20 ng/mL: 50,000 IU/week for 8 weeks<br>Foods: egg yolk, salmon, mackerel, cod liver oil |
| Protein Deficiency | Food Frequency Questionnaire | Animal and non-animal protein comprimising all essential amino acids |
| Anorexia Nervosa | Blood laboratory markers related with malnutrition and bone health; serum 1,25(OH)D, ALP, serum calcium, serum phosphate, iPTH, TSH, PSH, estradiol | Refer to mental health and nutrition specialists |
| Glucocorticoids | Serum calcium corrected for albumni, FSH, estrogen, estradiol | See appropriate management of calcium deficiency |
| Depot Medroxyprogesterone Acetate | FSH, estradiol | Refer to endocrinologist or gynecologist to discuss other options for birth control |
| Antiepileptic Drugs | Serum 1,25(OH)D | See appropriate management for vitamin D deficiency |
| Proton-Pump Inhibitors | 3-day foor journal to assess dietary calcium, serum calcium corrected for albumin | See appropriate management for calcium deficiency |

| | | |
|---|---|---|
| Celiac Disease | Anti-tissue tranglutaminase, antigliadin antibodies, antienomysial antibodies | Refer to gastroenterologist for upper-GI biopsy Education on a gluten-free diet and assessment for nutrient deficiencies due to malabsorption |
| Irritable Bowel Syndrome | Anti-saccharomyces cerevisiae antibody (Crohn's), perinuclear anti-neutrophil cyctoplasmic antibody (UC), serum 1,25(OH)D | Refer to gastroenterologust and assessment of nutrient deficiencies due to malabsorption |
| Hypogonadism | FSH, Estradiol, Serum calcium corrected for albumin | Refer to endocrinologist |
| Hyperthyroidism | TSH, Total T4, Total T3, Free T4, Free T3 | Refer to endocrinologist and address appropriate nutrient deficiences through diet or supplementation |
| Hyperparathyroidism | Serum calcium corrected for albumin, serum phosphate | Refer to endocrinologist and see appropriate management for calcium deficiency |
| Growth Hormone Deficiency | Growth hormone | Refer to endocrinologist |
| Diabetes Mellitus Type-1 | HbA1c | Refer to endocrinologist or primary care provider and provide education on dietary approaches to reduce sugar intake |
| Rheumatoid Arthritis | Rheumatoid Factor, antibuclear antibodies (ANA), serum calcium corrected for albumin, serum magnesium, serum vitamin K | Refer to rheumatologist and address appropriate nutrient deficiencies through diet or supplementation |
| Systemic Lupus Erythematosus | ANA, serum 1,25(OH)D, dietary protein | Refer to rheumatologist, and address nutritional support for deficiencies. Refer for or provide strength training program. |
| Depression | Serum 1,25(OH)D, serum calcium corrected for albumni, PTH, 8am plasma ACTH | Refer to mental health professional Address appropriate nutrient deficiencies through diet or supplementation |
| Breastfeeding | Serum calcium corrected for albumin | See appropriate management for calcium deficiency<br>Those with stablished osteoporosis may be advised to avoid breastfeeding |

## Key learnings

- Low bone mass and idiopathic osteoporosis are uncommon in younger women
- The predictive relationship between BMD and fracture risk is unclear in otherwise healthy premenopausal women
- Extent of bone loss in premenopausal women is defined by DXA Z-score
- The initial diagnostic approach should attempt to identify secondary causes, of which there are many, and to distinguish between low peak bone mass and active bone loss
- Biochemical bone markers may be useful if only a single BMD scan is available
- Oral bisphosphonates and teriparatide, specifically in the setting of glucocorticoid-induced osteoporosis, are the only FDA-approved bone-specific therapies in young adult women.