KAISER PERMANENTE®

Osteoporosis Screening, Diagnosis, and Treatment Guideline

Last guideline approval: March 2022

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Major Changes as of March 2022

- The list of lab tests recommended for ruling out secondary causes of osteoporosis has been updated.
- The list of populations that should be screened for osteoporosis has been updated (see Table 1).
- A new shared decision-making (SDM) tool for osteoporosis medication has been added: Osteoporosis and Osteopenia: Medication Options

Definitions

Fragility fracture is one caused by a degree of trauma not expected to cause a fracture; for example, a fall from standing height or lower. Fragility fractures, such as vertebral compression fractures and distal forearm fractures, are common in the elderly but can occur at any age. Exclusions: toes, fingers, face, skull, and ribs.

Major osteoporotic fracture is a fracture of the hip, spine (clinical), wrist, or humerus.

Osteoporosis is defined as a history of fragility fracture and/or a T-score of -2.5 or lower on dual energy X-ray absorptiometry (DEXA).

Osteopenia (or *low bone mass)* is defined as a T-score between -1.0 and -2.5 on DEXA.

Primary Prevention

The following are effective strategies for preventing osteoporosis:

Fall prevention

- For all adults, recommend regular weight bearing and muscle building exercises for prevention of osteoporosis and falls.
- Discuss fall prevention strategies with your patient. Tools include the Home Fall Prevention and Safety Checklist, Preventing falls in your home, and the KP Washington Health Research Institute article 10 things you can do to prevent devastating falls.
- Encourage patients to take their time when ambulating outside, especially around the curb and on rainy days.
- If a patient is unsteady, consider doing a fall risk assessment using the Timed Get Up and Go or other tool and/or referring the patient to Physical Therapy for fall risk assessment and walking aid recommendations.
- If appropriate, assess your patient for unhealthy alcohol use. Also assess for polypharmacy, including any medications that may cause sedation, dizziness or drowsiness
- If your patient has frequent falls, consider Physical Therapy referral to develop a personalized plan for improving balance and strength. Don't exclude patients who reside in a nursing home or similar setting, as they too can benefit from PT services; homebound patients can be referred to Home Health for PT.

Calcium and vitamin D

- Do not screen for vitamin D deficiency in adults aged 50 or over without osteoporosis.
- If the recommended daily allowance is not achieved through diet alone, consider over-the-counter supplementation with:
  - Calcium 1200 mg a day in two divided doses; the body can only absorb about 600–800 mg elemental calcium in one sitting. ***Note:*** **For patients on acid-reducing agents like PPI or antacid, calcium citrate is the preferred form,** as calcium carbonate needs acidity in the stomach to be absorbed. Calcium carbonate is best absorbed when taken after meals.
  - Vitamin D 1000–2000 IU a day (2000 IU a day in cloudier months) for maintenance dose.

Tobacco use

- For all adults who are current smokers, recommend smoking cessation.

Screening Recommendations and Tests

Table 1. Recommendations for osteoporosis screening with DEXA scan [1, 2]

Population	Preliminary FRAX?	DEXA Frequency [3]	Comments
Men and women of any age with **fragility fracture**	No	Every 2–10 years depending on initial T-score	History of fragility fracture is diagnostic for osteoporosis. Assess for secondary causes of osteoporosis (see p. 5).
Men and women of any age with **known secondary causes of osteoporosis** [4, 5]	No	Every 2–10 years depending on initial T-score	See p. 5 for secondary causes of osteoporosis.
Men and women aged ≥ 50 years **with history of long-term steroid medication** (≥ 5 mg/day prednisone for 3 consecutive months)	No	Every 2–10 years depending on initial T-score	See p. 11 for pharmacologic options for patients on long-term corticosteroid therapy
Postmenopausal women (those aged ≥ 50 years **or** aged ≥ 40 years with a postmenopausal code documented) [6] **with at least one of the following:** • Parent with history of hip fracture • Uses tobacco • Has > 3 alcoholic drinks/day • Last BMI < 21 • Body weight < 127 lbs • History of fracture since menopause	Yes If 10-year risk of major osteoporotic fracture 9.3% or higher, proceed to DEXA.	Every 2–10 years depending on initial T-score	
All women aged 65 years and older	No	Every 2–10 years depending on initial T-score	No upper age limit; use shared decision-making.
Men aged 70 years and older with at least one of the following: • Low body weight (use clinical judgment; no defined cutoff) • Daily alcohol consumption or more than 10 drinks per week • Current smoker • Sedentary lifestyle	No	Every 2–10 years depending on initial T-score	No upper age limit; use shared decision-making.

1 While there is limited direct evidence to support screening for osteoporosis to reduce fracture risk, DEXA is recommended for women aged 65 years and older because of strong evidence that bisphosphonates significantly reduce hip-fracture risk for older women who have met the diagnostic T-score criteria of -2.5 or lower.

2 KPWA recommends screening only those who will be willing to initiate treatment.

3 Because of limitations in the precision of DEXA testing, a minimum of 2 years may be needed to reliably measure a change in bone density; however, longer intervals may be adequate for repeated screening to identify new cases of osteoporosis.

4 While patients with CKD are at higher risk of osteoporosis, there are no evidence-based recommendations for screening this population earlier or more often than would be indicated by their other risk factors.

5 For transgender and gender diverse people, obtain a detailed medical history including past and present use of hormones and gonadal surgeries, and presence of traditional osteoporosis risk factors, to assess optimal age and necessity for osteoporosis screening.

6 If you have a postmenopausal patient who has risk factors but is younger than age 65 and you feel she does not clinically need a screening DEXA, you can postpone the HMT. If you are unsure, calculate a pre-DEXA FRAX score. Patients with a pre-DEXA FRAX score of > 9.3 should proceed with a screening DEXA.

The FRAX calculator

This tool estimates the 10-year probability of osteoporotic fracture for postmenopausal women and men aged 50 years and older who have **not** been previously treated for osteoporosis. Risk factors included in the FRAX are: age, gender, low body weight, height, previous fracture, parent with hip fracture, smoking status, glucocorticoid use, history of rheumatoid arthritis, menopausal status, and excessive alcohol consumption.

The FRAX calculator is available online at http://www.shef.ac.uk/FRAX/ . Use the drop-down list under "Calculation Tool."

Limitations: The FRAX calculator may over- or underestimate fracture risk in patients with a history of vertebral fracture, hip fracture, or multiple fractures, as well as in patients who are Black, Latino, or from other races or ethnicities. Some risk factors, such as frailty and dementia, cannot be readily quantified and are not included in the calculation.

Diagnosis

History of fragility fracture is diagnostic for osteoporosis.

For patients ***without*** **a fragility fracture,** interpret DEXA results as follows:

Table 2. Interpretation of bone density test results

Test	Results [2]	Interpretation [3]
Bone density by DEXA [1]	**T-score** [4]	
	T-score -2.5 and lower	Osteoporosis
	T-score between -1.0 and -2.5	Osteopenia
	T-score -1.0 and higher	Normal
	Z-score [5]	
	Z-score -2.0 and lower	Below expected range for age
	Z-score above -2.0	Within expected range for age

[1] May be measured and reported as a total hip score, the femoral neck score, and/or the L1 to L4 total lumbar score. Occasionally the distal radius is used if other sites are not practical or as an early indicator in hyperparathyroidism.

[2] DEXA result is based on the worst score of the individual scores of the spine, total hip, femoral neck, and when applicable, the one-third radius (forearm). Premenopausal women and men younger than 50 will only have Z-scores.

[3] Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

[4] The T-score represents the number of standard deviations a patient's bone density differs from the average bone density of a healthy 30-year-old of the same sex and ethnicity.

[5] The Z-score represents the number of standard deviations a patient's bone density is from the average bone density of people their same age, sex, and ethnicity.

Evaluation for Secondary Causes of Osteoporosis

For patients diagnosed with osteoporosis or osteopenia, assess for secondary causes as follows:

Initial lab testing

Order the following tests for all patients (can be done before office visit):

- Complete blood count
- 25-OH vitamin D
- TSH
- PTH
- Phosphorous
- CMP
- In men: Add 8 a.m. total testosterone.

Additional lab testing may be individualized as appropriate.

Table 3. Additional lab testing for secondary causes of osteoporosis

Indication	Test(s)
Recurrent renal stones or History of bariatric surgery	Consider 24-hour urine for calcium and creatinine.
Vitamin D deficiency (< 20) or Celiac symptoms	TTG and serum IgA
Vertebral compression fracture, or T-score ≤ -3.5, or Other clinical suspicion for multiple myeloma	Consider SPEP/UPEP
Cushingoid features	E-Consult with Endocrinology for appropriate work-up.

If any conditions emerge from testing, work up and treat findings appropriately.

Medical history and clinical exam

Assess the patient's medical history for the following conditions associated with osteoporosis:

Endocrine or metabolic disease (history, signs, or symptoms)

- Hyperparathyroidism/hypercalcemia
- Hypogonadism
- Hypopituitarism
- Hyperprolactinemia
- Cushing syndrome
- Hyperthyroidism
- Diabetes mellitus type 1
- Anorexia nervosa
- Acromegaly

Bone marrow–related disorders

- Multiple myeloma or myelodysplasia
- Thalassemia
- Systemic mastocytosis

Other conditions

- Rheumatoid arthritis
- History of organ transplantation
- Chronic kidney disease
- Secondary hyperparathyroidism due to renal disease
- Immobilization (paraplegia, quadriplegia, muscular dystrophy)
- Vitamin D deficiency
- Malabsorption (can be due to PPI therapy, celiac disease)
- Hypercalciuria
- Inadequate calcium intake

Medication review

Assess the patient's medication list for the following medications associated with osteoporosis.

Medications causing **bone loss:**

- Aromatase inhibitors
- Glucocorticoids > 3 months (See Pharmacologic options for patients on long-term corticosteroid therapy, p. 11.)
- Thyroid hormone in excess
- Immunosuppressive agents (e.g., cyclosporine)
- Gonadotropin-releasing hormone agonists or antagonists (e.g., androgen deprivation therapy, Lupron)
- Some anticonvulsants (e.g., phenytoin, phenobarbital)
- Cytotoxic agents
- Intramuscular medroxyprogesterone (Depo-Provera)

Medications associated with **increased fracture risk:**

- Thiazolidinediones
- SGLT-2 inhibitors
- Insulin with hypoglycemia
- Selective serotonin-reuptake inhibitors
- Selective norepinephrine-reuptake inhibitors
- Opioids
- Benzodiazepines/Z-drugs

Treatment Overview

Table 4. Recommendations for treatment of patients with osteoporosis or osteopenia [1]

Eligible population	Fragility fracture?	Secondary cause of osteoporosis?	FRAX score	Recommendation
Patients diagnosed with osteoporosis by DEXA (T-score of -2.5 or lower) or presence of fragility fracture	Yes	No	N/A	Offer pharmacologic treatment for primary osteoporosis.
	Yes	Yes	N/A	• Offer pharmacologic treatment for primary osteoporosis, **and** • Treat the secondary cause, **and** • Consider an E-Consult with Endocrinology.
	No	Yes	N/A	• Treat the secondary cause and re-check DEXA in 2–3 years, **and** • Consider an E-Consult with Endocrinology.
	No	No	N/A	Offer pharmacologic treatment for primary osteoporosis.
Patients diagnosed with osteopenia by DEXA (T-score between -1.0 and - 2.5)	N/A	No	High 10-year fracture risk [2]	Consider offering pharmacologic treatment.
	N/A	Yes	High 10-year fracture risk [2]	• Treat the secondary cause and re-check DEXA in 2–3 years, **and** • Consider an E-Consult with Endocrinology. • Consider offering pharmacologic treatment.
	N/A	Yes	Lower 10-year fracture risk [2]	• Treat the secondary cause and re-check DEXA in 2–3 years, **and** • Consider an E-Consult with Endocrinology.

[1] For patients with chronic kidney disease (CKD), E-Consult with Endocrinology, and/or consider consult with Nephrology.

[2] The FRAX tool recommends initiating therapy when 10-year probability of a hip fracture is 3% or higher and/or when 10-year probability of a major osteoporotic-related fracture is 20% or higher.

Goal

Prevent fracture by decreasing risk factors and improving bone density to a T-score higher than -2.5. (The T-score target may be higher or lower in high-risk patients.)

Lifestyle modifications/non-pharmacologic options

Consuming adequate calcium and vitamin D, taking fall prevention precautions, and performing weight-bearing exercise should be continued when initiating pharmacologic treatment for osteoporosis.

Pharmacologic Options for Osteoporosis

Shared decision-making: bisphosphonates

See shared decision-making tool Osteoporosis and Osteopenia: Medication Options (available on KP HealthConnect).

Key points

- Fractures can have a tremendous negative impact on a patient's quality of life.
- The benefits of bisphosphonates outweigh their potential risks.

Table 5. Adverse effects associated with bisphosphonates

Adverse effect	Symptoms	Risk	Counseling points
Gastrointestinal	Abdominal pain Dyspepsia Nausea Flatulence Gastritis	12.6%	• Take the medication in the morning at least 30 minutes before food with a full glass (8 oz.) of plain water. • Do not lie down for at least 30 minutes after taking the medication. • Zoledronic acid (IV bisphosphonate) is an alternative option for those who have difficulty tolerating the oral formulation.
Musculoskeletal pain	Bone, joint, and/or muscle pain	3.1%	• In those who develop severe pain, bisphosphonates should be discontinued.
Osteonecrosis of the jaw	Pain, swelling, or redness of gums Loose teeth Jaw numbness Visible bone in the mouth	0.001–0.01%	• Very **rare** and, if seen, typically in patients with cancer or compromised immune system who are treated with high doses of IV bisphosphonates.
Atypical femur fracture (AFF)	Dull or aching groin pain from minimal trauma that moves to the thigh over time Subtrochanteric or femoral shaft location Should be diagnosed by specialist following specific criteria	0.002–0.1%	• Very **rare.** Risk increases somewhat with prolonged use (> 5 years) but is still quite low, and can be mitigated by encouraging a drug holiday after 5 years.

Recommended pharmacologic options

Table 6. Recommended pharmacologic options for osteoporosis treatment
See prescribing notes – bisphosphates, following table.

Eligible population	Line	Medication	Initial dose	Therapeutic/goal dose/ duration of treatment
Patients with osteoporosis	1st	Alendronate	70 mg once weekly or 10 mg daily	5 years
	or	Risedronate [F/ST] [1] for intolerance to alendronate	35 mg once weekly or 5 mg daily or 150 mg once monthly	
	Or 1st	Zoledronic acid for GI **intolerance** to oral bisphosphonates	5 mg IV infused over at least 15 minutes every 12 months	3 years
	2nd	Denosumab [PA—consult with Endocrinology] [2]	60 mg as a single dose, once every 6 months	No studies have evaluated the optimal duration of treatment.

[1] F/ST = Formulary/specialty tier
[2] Denosumab may be considered only after failed trial of oral and IV bisphosphonates. See PA criteria.

Table 6 prescribing notes – bisphosphonates

- Use bisphosphonates with caution in patients with **chronic kidney disease and reduced glomerular filtration rate.** Current drug monographs state that an estimated GFR < 35 mL/min is a contraindication to bisphosphonate use.
- **Contraindications** to oral bisphosphonates include Barrett's esophagus and other esophageal disorders, gastric ulcer, gastric bypass, severe GERD, and malabsorption.
- If the patient has **GI intolerance with oral bisphosphonates,** try risedronate or switch to IV zoledronic acid. Some patients tolerate one better than the other. If the patient can't tolerate either option, refer to Endocrinology to discuss denosumab (Prolia).
- There is strong evidence for an **acute phase reaction within 3 days of zoledronic acid administration** (up to 25% increased risk over placebo of any of the following symptoms: pyrexia, myalgia, headache, arthralgia, chills). A 650 mg dose of acetaminophen initiated 45 minutes before zoledronic acid infusion and continuing every 6 hours for 3 days has been shown to reduce severity of symptoms. It is common practice also to ensure the patient is well hydrated prior to infusion.

Additional considerations for patients taking osteoporosis medication

- To **ensure absorption**, advise the patient to take oral bisphosphonates with water only and not with food or other medications.
- **Calcium supplementation:** Use calcium citrate in patients taking proton pump inhibitors (PPIs) or H2 blockers.
- **Vitamin D:** Optimize 25 OH vitamin D > 30 and ensure that hypocalcemia is not present.
- **Dental hygiene:** Educate patients starting a bisphosphonate about the importance of regular dental cleanings and good dental hygiene. For those patients who have a planned tooth extraction or dental implant surgery, consider delaying the start of bisphosphonate therapy until 3 months after completion of the dental procedure, or until maxillofacial bone healing is complete.

Pharmacologic options *not* recommended for osteoporosis

Tamoxifen, estrogen, nasal calcitonin

Stopping bisphosphonate therapy/drug holidays

Higher-risk patients

Patients with a history of fragility fracture or a T-score lower than -3.5 may benefit from up to 10 years of oral bisphosphonate or 6 years of IV bisphosphonate.

Lower-risk patients

Patients with mild to moderate osteoporosis and no fragility fracture while on therapy may be considered for a drug holiday after 5 years of therapy. There is insufficient evidence to guide treatment for more than 5 years.

If bone density is measured and:

- The patient has **achieved goal density,** the bisphosphonate may be stopped, and dietary and lifestyle modifications continued.
- The patient has a **T-score lower than -2.5,** explore adherence to treatment. If adherence is not an issue, consider one of the following:
  - Continue bisphosphonates for an additional 2–5 years. (The safety of long-term [more than 10-year] use of osteoporosis medications is not known.)
  - Recommend a "drug holiday" for 2 years, followed by 3 more years of therapy.
  - Consider switching to another class of medication.
  - Consider stopping bisphosphonate treatment and continuing dietary and lifestyle modifications.
- The patient has **decreased bone density from baseline,** consider E-Consult with an endocrinologist or rheumatologist.

Table 7. Additional considerations for drug holiday in patients at low risk for fragility fracture

	Factors favoring continuing therapy [1]	Factors favoring drug holiday with monitoring
Fall risk/fracture	Increased fall risk or history of osteoporotic fracture while on bisphosphonate therapy for 6 months or more	Not at high risk for falls
High-risk medications	Taking high-risk medications	Not taking high-risk medications
Thyroid, parathyroid, rheumatoid arthritis	Prolonged suppressed TSH or history of hyperparathyroidism or rheumatoid arthritis that is not reversed by treatment	Normal thyroid and parathyroid function, no history of rheumatoid arthritis
Change in bone density while consistently taking bisphosphonates	Absolute reduction of 5% or more between two successive BMD measurements at the same site	Absolute reduction of less than 5% between two successive BMD measurements at the same site
T-score/Z-score	T-score lower than -3.5 at any site or Z-score -2.0 or lower	T-score higher than -2.5

[1] If patient has one or more factors favoring continuing therapy, has been adherent to therapy, and **has a probable cause of malabsorption** (e.g., PPI therapy, celiac disease, Crohn's disease, gastric bypass, or bowel resection), **switch to IV zoledronate** and repeat DEXA after 2 more years of therapy.

If patient **does not have a probable cause of malabsorption,** has been adherent to therapy, and has one or more factors favoring continuing therapy, **evaluate for secondary causes of osteoporosis** (see p. 5).

During continuing therapy

Ensure adherence to bisphosphonate therapy and repeat DEXA after 2 years of therapy. E-Consult with Endocrinology if considering prolonged therapy for 5–10 years (oral) or > 5 years (IV).

During drug holiday

Measure bone density in 2 years or upon occurrence of new fragility fracture.

Pharmacologic options for patients on long-term corticosteroid therapy

Because long-term use of corticosteroids—defined as 5 mg/day prednisone for 3 consecutive months—is associated with increased risk of osteoporosis, it is reasonable to consider starting prophylactic therapy in patients on chronic steroids. The dose of steroid treatment for which the benefit of treatment with bisphosphonates is thought to outweigh the risk ranges from 5 to 7.5 mg/day.

To decrease the risk of developing osteoporosis, assess patients on corticosteroids to see if it would be appropriate to:

- Reduce the dose
- Switch to a topical or inhaled form
- Switch to an alternative drug

Prevention of steroid-induced osteoporosis

Medications for the prevention of steroid-induced osteoporosis are appropriate for men and women who are taking oral corticosteroid medication at a dose of ≥ 5 mg/day prednisone or equivalent for a duration of 3 months or more and have a FRAX 10-year risk of hip fracture ≥ 3%. Risedronate and zoledronic acid are FDA-approved for both the treatment and prevention of steroid-induced osteoporosis. Alendronate is not FDA-approved for the prevention of steroid-induced osteoporosis.

- First-line: oral risedronate (5 mg/day)
- Second-line: IV zoledronic acid (5 mg IV infused over at least 15 minutes every 12 months)

Treatment of steroid-induced osteoporosis

Follow the recommendations in Table 6, p. 9. **Monitoring/follow-up for patients with steroid-induced osteoporosis**

- A DEXA scan within the first 6 months of starting steroids is recommended, due to the rapid bone loss that occurs during the first 3–6 months.
- If steroid use is continued, a DEXA scan is recommended every 2–3 years after the initiation scan.

Follow-up/Monitoring

Patients who have *not* sustained a fracture

Table 8. Recommended follow-up and monitoring for patients who have low bone density but have *not* sustained a fracture	
Baseline or most recent DEXA score and/or clinical circumstances	**Recommended screening interval**
Patients ***not* at high risk** due to medications or chronic conditions and with a T-score of:	
Higher than -1.5	Repeat DEXA scan only if the number of risk factors increases or there is a clinical concern regarding osteoporosis. May choose to repeat DEXA scan in 10 years, or sooner if number of risk factors increases or there is a clinical concern.
-1.5 to -1.9	Consider repeating DEXA scan in 5 years. [1]
-2.0 to -2.4	Consider repeating DEXA in 2 years. [1]
-2.5 or lower, choosing no treatment	Repeat DEXA scan as clinically indicated but no more frequently than every 2 years.
-2.5 or lower, choosing bisphosphonates	Consider repeating DEXA scan in 5 years. [1]
Patients **at high risk** due to comorbid conditions, and patients with fractures	Repeat DEXA scan after 2–3 years of treatment.
[1] Health Maintenance Topic (HMT) intervals for subsequent DEXAs are set based on the lowest T-score on the most recent DEXA result, in alignment with the table above. However, please use clinical judgment to manually adjust a patient's DEXA interval as needed based on their risk factors, considering age, comorbidities, fall risk, and preference for treatment. If you are still unsure about the appropriate screening/follow-up interval, E-Consult Endocrinology for further input.	

Medication monitoring

For all bisphosphonates, monitor the following at least annually:

- Creatinine
- Serum calcium
- Vitamin D

When to consult with Endocrinology

Consider an E-Consult with Endocrinology if:

- Patient has had 10 years of bisphosphonate and needs more therapy
- Patient with fragility fracture or osteoporosis has significant renal disease and may not be a candidate for bisphosphonate therapy
- Bisphosphonate therapy fails, as when a fracture occurs during active treatment
- Osteoporosis is unexplained, with no risk factors and negative workup
- Patient is intolerant to oral and IV bisphosphonate therapy after trial
- Patient needs or wants medication therapy other than bisphosphonate
- Provider/patient questions about drug holidays
- Pre-menopausal women and men under age 50 with low bone mass for age

Evidence Summary

The Osteoporosis Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

External guidelines meeting KPWA criteria for adaptation/adoption

To update the Osteoporosis Guideline, following externally developed evidence-based guidelines were reviewed, and the relevant recommendations were adopted or adapted as needed.

- 2021 Position statement of The North American Menopause Society (NAMS) Management of osteoporosis in postmenopausal women http://www.menopause.org/docs/default-source/professional/2021-osteoporosis-position-statement.pdf
- 2021 American College of Obstetricians and Gynecologists (ACOG) Osteoporosis Prevention, Screening, and Diagnosis https://www.acog.org/clinical/clinical-guidance/clinical-practice-guideline/articles/2021/09/osteoporosis-prevention-screening-and-diagnosis
- 2021 KP NATL Guideline Osteoporosis/Fracture Prevention Osteoporosis/Fracture Prevention Guideline - National | NATL Clinical Library (kp.org)
- 2020 American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update (Camacho 2020) https://www.endocrinepractice.org/article/S1530-891X(20)42827-7/fulltext
- 2019 Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline (Eastell 2019) https://academic.oup.com/jcem/article/104/5/1595/5418884
- 2019 European guidance for the diagnosis and management of osteoporosis in postmenopausal women (Kanis 2019)
- 2018 Screening for Osteoporosis to Prevent Fractures US Preventive Services Task Force Recommendation Statement https://jamanetwork.com/journals/jama/fullarticle/2685995
- 2017 American College of Rheumatology (ACR) Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (Buckley 2017)
- 2017 Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians (Qaseem 2017)
- 2017 KDIGO Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340919/
- 2017 National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. (Compston 2017) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5397452/
- 2012 Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline (Watts 2012)

Key questions addressed in the KPWA evidence review

1. **In postmenopausal women or men over the age of 50 years with a new diagnosis of osteoporosis on DXA (not fragility fracture) or osteopenia requiring treatment, what is the appropriate evaluation to rule out or detect a secondary cause of osteoporosis?**

   There is a lack of published evidence from large randomized controlled trials (RCTs) or prospective studies with valid methodology to determine the most appropriate tests needed to evaluate men and women >65 years of age diagnosed with osteoporosis before starting treatment. The recommendations of different published guidelines were based on low-quality evidence from very few earlier observational studies with methodological limitations.

   According to the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis guideline 2020 update (Camacho 2020), the following laboratory tests may be considered for all women with osteoporosis:

   - Complete blood count
   - Comprehensive metabolic panel
   - 25-hydroxyvitamin D (25[OH]D)
   - Intact parathyroid hormone (PTH)
   - Phosphate
   - 24-hour urine collection for calcium, sodium, and creatinine. The 24-hour urine calcium collection must occur after the patient is replete of vitamin D and has been on a reasonable calcium intake (1,000 to 1,200 mg/d) for at least 2 weeks.
   - If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be obtained.
   - Celiac antibodies or serum/urine protein electrophoresis could also be obtained.

   The AACE/ACE 2020 was an update of the 2016 guideline (Camacho 2016) (this gave the recommendation a level 4 at the time) which in turn was an update of the guideline released in 2010 and earlier in 2006). The recommendation on the procedures/tests suggested for evaluation for secondary osteoporosis was based on 4 earlier published studies: An endemiological study (Barzel 2003), an economic study (Edwards 2007), a retrospective study among breast cancer patients (Camacho 2008), and a cross-sectional chart review study (Tannenbaum 2002). The guideline team judged the strength of evidence to be intermediate in 3 of these studies and low in one. However, due to the study design, all four studies provide only low-quality evidence.

2. **What medications or therapies pose higher risk for fragility fracture including glucocorticoids, antiepileptics, antiviral therapy, aromatase inhibitor (e.g., tenofovir and entecavir)?**

   Moderate-quality evidence from several observational studies and meta-analyses indicates that a large number of prescription and OTC drugs are associated with increased risk of fragility fractures. Among these drugs/classes are antidepressants, antiparkinsonian drugs antipsychotics, anxiolytics, benzodiazepines, Sedatives, systemic corticosteroids, HRT, thyroid hormones, thiazide diuretics, loop diuretics, antacid drugs (H_2 antagonists, and PPIs).

   Low- to moderate-strength evidence from one large observational study with a 9-year follow-up (Emeny 2019) that examined the association between the use of fracture-associated drugs (FADs) and hip fracture risk showed that:

   - Among women, significant risks associated with individual FADs ranged from an HR of 1.54 (95% CI, 1.05-2.24; P = .03) for first-generation antipsychotics to an HR of 3.26 (95% CI, 3.04-3.49;P < .001) for opioids and an HR of 3.29 (95% CI, 2.89-3.76; P < .001) for anti-Parkinson drug. 80 drug combinations exceeded the HR threshold of 3.00, 7 of which met the study's population-level impact:
     - Opioids plus sedative hypnotics (HR, 4.90; 95% CI, 3.98-6.02; P < .001)
     - Opioids plus loop diuretics (HR, 4.48; 95% CI, 3.96-5.07; P < .001)
     - Opioids plus PPIs (HR 4.00; 95% CI, 3.56-4.49; P < .001)

- SSRIs plus opioids (HR, 3.91; 95% CI, 3.46-4.43; P < .001)
- SSRIs plus benzodiazepines (HR, 4.50; 95% CI, 3.76-5.38; P < .001)
- SSRIs plus loop diuretics (HR 3.05; 95% CI, 2.75-3.37; P < .001)
- Nitrates plus loop diuretics (HR, 3.25; 95% CI, 2.84-3.72; P < .001)

- Among men, significant risks of single FADs ranged from HR of 1.51 (95% CI, 1.17-1.95; P=.002) for sedative hypnotics to an HR of 3.83 (95% CI, 3.36-4.36; P < .001) for opioids and an HR of 4.23 (95% CI 3.57-5.01; P < .001) for anti-Parkinson drugs. A total of 9 drug pairs met the population level impact criteria; 5 of which are similar to the women's high-risk pairs (opioids plus loop diuretics, opioids plus PPIs, SSRIs plus opioids, SSRIs plus loop diuretics, and nitrates plus loop diuretics). The riskiest drug pairs were opioids plus loop diuretics (HR, 6.93; 95% CI, 5.52-8.70; P < .001) and opioids plus SSRIs (HR, 6.26; 95% CI, 4.83-8.12; P < .001)
- The overall results suggest that the addition of a second and third FAD may be associated with a steep increase in hip fracture risk, and as the authors concluded many risky pairs of FADs included potentially avoidable drugs (e.g., sedatives and opioids).
- This was an observational study with a large population size and 9-year follow-up data. However, it had several limitations in addition to the study design that cannot determine a causal association; it may have residual confounders that were not adjusted such risk behavior, unrecorded diseases and comorbidities, or severity of known disease some of which may be associated with the risk of fracture. In addition, data on drug exposure was based on prescription fills which may not reflect the actual use of the drugs prescribed or the use of OTC drugs or others obtained from other sources. Moreover, the analysis did not take into consideration the doses, cumulative exposure, or individual drugs within each group, and evaluated the effect of the drugs only on hip fractures and not on other fragility fractures.

RCTs would be the ideal study design to determine the causal association between individual drugs and/or their combination with fragility fractures. However, RCTs may not always be feasible or ethical in several conditions when a group of drugs are known to effectively treat a certain disease or condition.

3. What are the benefits and harms of screening compared with no screening in preventing fragility fractures and related morbidity and mortality among adults < 65 years of age, seen in primary care?

The literature search did not identify any study that evaluated the benefits and harms of screening compared with no screening to prevent fragility fractures and related morbidity and mortality in primary care among adults < 65 years of age.

The recommendations for osteoporosis screening vary across organizations and societies. In general, the majority recommend DXA screening for women 65 years and older; and for younger postmenopausal women and men younger than 70 years if they have clinical risk factors for fractures, a fragility fracture, or a history of a prior fracture.

The recommendations on the benefits of screening and in turn treatment of men and women under the age of 65, who are at high risk for osteoporosis / osteoporotic fractures are mainly based on indirect evidence from studies evaluating the accuracy of screening approaches in identifying osteoporosis and predicting fractures. These studies were limited by several factors including their observational design, and variations between them in baseline risk factors among the participants, prior fractures, prior treatment, and duration of follow-up, and other limitations. In addition, none of the studies discussed potential harms associated with screening.

4.1. Does screening men with risk factors for osteoporosis reduce the risk of fractures?
4.2. What is the optimal age for screening men with or without risk factors for osteoporosis?

There is insufficient published direct evidence to determine the optimal age for screening men with or without risk factors for osteoporosis.

Currently there is no universally acceptable recommendation for screening men to identify individuals with osteoporosis or those at high risk of fracture.

Data on osteoporosis among men and the associated hip and vertebral fractures risk were mainly obtained from epidemiologic studies, analyses of national and international statistics, as well as one observational study.

Recommendations on screening men and/or optimal age for screening differed between national and international guidelines and scientific societies.

- The USPSTF (2018) concluded that the evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men However, it indicates that this recommendation applies to older adults without a history of low-trauma fractures, conditions that may cause secondary osteoporosis, conditions that may increase the risk of falls, and does not apply to persons who take long-term medications that may cause secondary osteoporosis.
- Other guideline and scientific societies recommendations on screening men differ by age as follows:

  Men > 65–70 years
  - The International Society for Clinical Densitometry, and the National Osteoporosis Foundation recommend assessment of risk factors for osteoporosis and DXA in men >65–70 years
  - The American College of Physicians suggests performing DXA in men >65 years only when risk factors are documented to increase the risk for osteoporosis and/or are candidates for drug therapy

  Men ≥ 50 years
  - The NOF suggest DXA for men 50-69 years with risk factors.
  - the 2010 Canadian guidelines indicate BMD testing for all men ≥65 years and men 50-64 years with clinical risk factors for fracture (listed earlier)

  Younger adults < 50 years
  - The 2010 the Canadian Practice Guidelines indicates screening for younger adults with fragility fracture, prolonged use of glucocorticoids or other high-risk medications, primary hyperparathyroidism, hypogonadism, malabsorption syndrome, and /or other disorders strongly associated with rapid bone loss and/or fracture.

- The International Society for Clinical Densitometry makes no age limitations for DXA screening in men with risk factors and recommends BMD testing in all men < 70 years who have a risk factor for low bone mass.
- The Endocrine Society Clinical Practice Guideline suggests testing men at increased risk (defined for age groups 70+, 50-69 and 50+) for osteoporosis by measurement of BMD).

5. In adult patients with chronic kidney disease (CKD), does early screening and treatment for osteoporosis prevent excessive bone loss and reduce the risk of fractures? If yes, at what stage of the disease?

In a recent systematic review (Hsu 2020) on osteoporosis in patients with CKD, the authors pointed out to the limitations of DXA that is commonly used for quantifying BMD in CKD patients. They explained that DXA evaluates the bone quantity and not the bone quality; it measures areal BMD, not volumetric BMD; it cannot discriminate between cortical and cancellous bone; and it cannot assess bone microarchitecture or bone turnover.

- The updated KDIGO 2017 guideline
  - Suggests BMD testing in patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis to assess fracture risk if results will impact treatment decisions (2C).
  - The updated guideline no longer recommends bone biopsy as mandatory before starting antiresorptive treatment in patients with CKD, but only suggests it for patients with CKD-MBD if the result will influence treatment decisions.
  - In patients with CKD G3a-G5D, the guideline Work Group suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).

- The 2021 European consensus statement indicates that
  - Routine DXA testing (screening) in all CKD G4-G5D patients is not supported by current evidence.
  - In patients with CKD G4-G5D, DXA may be considered in post-menopausal women, or men >50 years of age (opinion-based commendation)

- The literature search for studies on the association of bone mineral density with fractures in patients with chronic kidney disease did not identify any prospective US cohort study or meta-analysis that would change or add to the recommendation of the KDIGO guideline 2017 update.

The studies on the association between BMD or FRAX and fractures in patients with CKD were all observational retrospective studies. Two Canadian retrospective studies with methodological limitations were identified.

- One study (Prasad 2019) examined the relationship between BMD, biochemical markers of CKD-MBD, and fracture risk across KDIGO categories G3a–G5. Its results suggest that BMD may predict the risk of fracture and that the addition of other biochemical markers or clinical risk factors to BMD do not add to fracture prediction.
- The second study (Whitlock 2019) examined the ability of FRAX tool to predict fracture risk in patients with chronic kidney diseases. Its overall results indicate that FRAX score with or without BMD measurement significantly discriminated fracture risk in patients with non-dialysis CKD.

The search for studies on the benefits and harms of osteoporosis medications in patients with CKD identified two systematic reviews with meta-analyses:

- A Cochrane review (Hara 2021) on the effectiveness and safety of osteoporosis medications for fracture prevention in CKD provided
  - Low-quality evidence suggesting that in patients with CKD stages 3–4, anti-osteoporotic drugs may reduce the risk of vertebral fracture.
  - Moderate-quality evidence suggesting that in patients with CKD stages 3–4, antiosteoporosis drugs probably make little or no difference in the risk of clinical fracture and adverse events.
  - Insufficient evidence to determine that raloxifene has any effect on BMD at the femoral neck or on reducing the risk of clinical fracture and death in patients with CKD stages 5 and 5D.
  - Low-quality evidence suggesting that raloxifene may slightly improve the BMD at the lumbar spine in patients with CKD stages 5 and 5D.

- The other identified systemic review with meta-analysis (Wilson 2017) examined the benefits and harms of osteoporosis medications (bisphosphonates, teriparatide, raloxifene, and denosumab) compared with placebo, usual care, or active control in terms of bone mineral density (BMD), fractures, and safety in patients with CKD. The overall pooled results provide
  - Moderate-strength evidence suggesting that bisphosphonates may slow loss of BMD of the lumbar spine in kidney transplant recipients, but its effects on BMD of the femoral neck and other areas in these patients were less clear.

- Conflicting or insufficient evidence of the effectiveness of bisphosphonates on BMD among patients with CKD who had not received a transplant.
- Limited evidence on fracture risk reduction and the safety profile of bisphosphonates among patients with CKD and transplant recipients.
- Limited evidence on the effectiveness of other osteoporosis medications, including raloxifene, teriparatide, and denosumab.
- Low-strength evidence suggesting that raloxifene may not be more effective than placebo at increasing BMD but may reduce risk for fractures. However, the evidence is limited to patients with stage 3–5D CKD. None of the studies evaluating raloxifene adequately reported on safety.

Overall, there is insufficient published evidence to determine with certainty the effectiveness and safety of osteoporosis medication on BMD and fracture risk in patients with CKD.

6. What is the comparative accuracy of US FRAX tool in predicting the risk of fractures among white, Black, and Latino individuals, and individuals from other races and ethnicities?

The Fracture Risk Assessment Tool (FRAX) was developed by the WHO in 2008 to predict the 10-year probability of hip fracture or major osteoporotic fractures (hip, spine, wrist, shoulder). The tool was derived from 9 cohorts and validated in 11 independent cohorts (230,486 participants including men and women) around the world. FRAX uses age, sex, weight, height, prior fracture, parental history of fracture, five other clinical risk factors. It also includes bone mineral density at the femoral neck when available. It has then been calibrated for use in different countries using country-specific fracture incidence and mortality data. For the US non-Hispanic white population, the FRAX model was calibrated using national mortality data and fracture incidence rates from the Rochester Epidemiology Project* cohort (a largely a white community of Olmsted County, Minnesota between 1989 and 1991).

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The model was calibrated** to other races by assuming a ratio to the sex-specific hip fracture incidence rates for white women and men based on race-specific hip fracture incidence rates and race-specific mortality rates obtained from epidemiological studies published three decades ago and may not reflect the current fracture rates.

*** The US FRAX calculator returns a lower fracture risk by a factor of 0.43 for African American women and 0.53 for AA men; 0.53 for f Hispanics women and 0.58 for Hispanics men; and for those of Asian ancestry:0.50 for women and 0.64 for men. These correction factors were derived from cohort studies conducted in the 1980s and 1990s, which showed a differential fracture risk by race and ethnicity but have not been updated since. The adjustment was not empirically based, and racial/ethnic differences that influence fracture risk were not adequately considered (Wu 2020, Reid 2021) BMD is greater in non-Hispanic black (NHB) men and women and lower in Asian populations compared with non-Hispanic whites (NHW). Race/ethnicity does not represent biological difference, but a complex relationship comprised of socioeconomic, political, geographic, and environmental factors. Many socioeconomic and environmental factors influence BMD and fracture risk. FRAX also does not account for disparities in medical comorbidities that contribute to fracture risk among minority patients e.g., DM) (Reid 2021)*

Several investigators reported that FRAX underestimated the probability of fractures in African Americans and Hispanics, and in turn decreases the likelihood of osteoporosis treatment in minority groups. However, there is insufficient evidence from large valid prospective studies to support that observation.

The best published studies to date analyzed data from the Women's Health Initiative observational and controlled sub-studies (Crandall 2019, Wu 2020).

- One observational study (Crandall 2019) evaluated and compared the accuracy of the FRAX and Garvan tools in predicting hip fracture risk in postmenopausal women aged 50–64 years during 10 years of follow-up. The results of the analysis showed that at the maximal AUC for FRAX of 0.65, the sensitivity of the tool for identifying incident hip fracture was 16.0% for white women and 0.0 for African American women and Hispanics.
- Another observational study (Wu 2020) also used data from the four Women's Health Initiative (WHI) sub-studies to examine the performance of FRAX in the prediction of fractures among minorities in the US. The results suggest that FRAX overestimates the risk of major osteoporotic fracture and hip fracture in women 50–79 years old across all racial groups, but especially in Asian, African American, and Hispanic women. The authors explained that the observed probability of major osteoporotic fracture and hip fracture, was significantly lower than the risk estimated by FRAX, indicating that the FRAX did not adequately consider racial and ethnic differences of fracture risk.
- The two studies had the advantage of including a large number of women participating in the WHI RCTs and observational studies with long-term follow-up. However, WHI only included women 50–79 years of age, the great majority of whom were Caucasians ≈9% were black,≈4% Hispanic, and a very small number of Asian and American Indian women (≈2% for each) which would limit generalization of the results. In addition, the studies only evaluated FRAX without BMD which was unavailable for most of the participants.

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Guideline Development Process and Team

Development process

The Osteoporosis Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

This edition of the guideline was approved for publication by the Guideline Oversight Group in March 2022.

Team

The Osteoporosis Guideline development process included representatives from the following specialties: endocrinology, family medicine, geriatrics, pharmacy, radiology, rheumatology, and sports medicine.

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