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OSTEOPOROSIS

Updates to Management & New SOGC Guidelines

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UPDATES TO MENOPAUSE TREATMENT GUIDELINES DERZKO

DISCLOSURES

• Faculty: University of Toronto,

Associate Professor ,Department of Obstetrics & Gynecology and Department of Internal Medicine (Endocrinology)

- Relationships with for-profit and not-for-profit interests:
- --Advisory Boards (Not for Profit):
- SIGMA-CMS --Board of Directors & past Executive Member; Canadian Osteoporosis Society –Scientific Advisory Committee
 - --Advisory Board /Speakers Bureau/Consultant : Amgen, Allergan, Berlex, Biosyent, Duchesnay, Lupin, NovoNordisk, Pfizer

Grants/ Clinical Research Support: NovoNordisk

- Patents: None
- Other: None

OSTEOPOROSIS CANADA (www.osteoporosis.ca)

Over 2.3 Million

Canadians are Living with Osteoporosis



At least 1 IN 3 WOMEN and 1 IN 5 MEN will suffer from an osteoporotic fracture during their lifetime



OVER 80% OF ALL FRACTURES in people 50+ are caused by osteoporosis



Bone health is important at every age but expectally during childhoo and adolescence when bones are still growing. As most people react their maximum bone size and strength iknown as peak bone mass/i age 30, bone-healthy behaviours are important from an early sgirlir order to optimize bone health and reduce the risk of developing osteoporosis later in life.



OBJECTIVES

- To provide an overview of the 2022 SOGC OSTEOPOROSIS GUIDELINES
- To review screening, diagnosis & treatment options for osteoporosis in menopause patients
- To discuss strategies for management of menopause patients : consideration of their needs and individualization of their care



SOGC CLINICAL PRACTICE GUIDELINE

Guideline No. 422g: Menopause and Osteoporosis

Aliya A. Khan, Hajar Abu Alrob, Dalal S. Ali, Karel Dandurand, Wendy Wolfman, Michel Fortier

Background

- In Canada, postmenopausal osteoporosis is associated with significant morbidity, mortality, and health care costs.
- Prevention of fractures is inadequate, with treatment rates after a fracture ranging from 20% to 30%.?

Who to Screen- how can we optimize Fx prevention ?

eligibility criteria for study selection

•Population: general community women = 50 years, no history of fx or secondary causes of osteoporosis

•Intervention: validated risk assessment tool for fracture risk +/- BMD

- •Comparator (for control trials): no screening group
- •Outcome: fractures
- •Study design: RCT, systematic reviews

STUDY CRITERIA

Inclusion criteria - Majority of participants had no hx of low trauma fractures

- prospective cohort studies predicting fracture in adult women
- Screening tests included fracture risk prediction instruments, BMD testing, or combination of both
- Screening tools validated externally

• **Exclusion Criteria** - x-sectional, case control, retrospective cohort with fracture in the past, diseased population, endocrine disorders affecting fracture risk or drugs such as steroids

- Community based screening in older women could be effective in reducing hip fx
- No other significant benefit -mortality or other fx reduction
- No other harms

Whom to Screen to Prevent Osteoporotic Fractures

- Screening by clinical evaluation and DXA¹ assessment is only advised in postmenopausal women over the age of 65 years. (2,3,4, 5)
- In younger women, it is indicated *only* in patients who have:
 - Diseases associated with bone loss or
 - Drugs associated with bone loss, or
 - Previous fragility fracture, particularly if the fracture occurred in the previous 2 years.

¹ Dual-energy X-ray absorptiometry

² Viswanathan M et al. Screening to Prevent Osteoporotic Fractures. JAMA. 2018

3- Shepstone Lancet 2018 – SCOOP,

4-Rubin 2018- ROSE,

5- Merlijn -2019

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Recognizing the Signs & Symptoms of Osteoporosis

History & physical exam

Assess lifestyle behaviors Review medications for bone effects Review calcium and vitamin D intake Assess annually or when physical/mental status changes: Height and weight
Chronic back pain and kyphosis
Clinical risk factors

The SIGNS of OSTEOPOROSIS



Side Source: Contraception Online www.contraceptiononline.org

The SIGNS of OSTEOPOROSIS







COMPRESSION FRACTURES

Contraception Online www.contraceptiononi

The SYMPTOMS of OSTEOPOROSIS



Vertebral fractures

Side Source: Contraception Online www.contraceptiononline.org



Indications for BMD Testing in Older Adults (Age ≥ 65 Years)

<u>ALL women and men age > 65</u> should have BMD Test

Indications for BMD Testing in Older Adults (Age 50-65 years)

» Postmenopausal women, and men aged 50 – 64 with clinical risk factors for fracture:

- Fragility fracture after age 40
- Prolonged glucocorticoid use[†]
- Other high-risk medication use*
- Parental hip fracture
- Vertebral fracture or osteopenia identified on X-ray
- Current smoking
- High alcohol intake
- Low body weight (< 60 kg) or major weight loss
- Rheumatoid arthritis
- Other disorders strongly associated with osteoporosis



[↑]At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily; * e.g. aromatase inhibitors, androgen deprivation therapy.

Indications for BMD Testing for Individuals (Age <50 Years)

» Fragility fracture

- » Prolonged use of glucocorticoids*
- » Use of other high-risk medications[†]
- » Hypogonadism or premature menopause
- » Malabsorption syndrome
- » Primary hyperparathyroidism





» Other disorders strongly associated with rapid bone loss and/or fracture

[↑]At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily; ^{*} e.g. aromatase inhibitors, androgen deprivation therapy.

How to Screen for Osteoporosis Fracture Risk

1. FRAX screening tool with or without BMD

- Nord-Trondelag health study, Fx registry and Norwegian prescription database (1)
- 15,432 women and 13,585 men age 50-90
- FRAX without BMD calculated and hip Fx were observed for a median follow up of 5.2yrs
- Observed fractures compared to predicted fractures by FRAX
- AUC 0.81 (0.78-0.83) women (81% chance model will predict those who will have a hip Fx)
- BMD independent predictor of skeletal strength and Fx risk

2.TBS – analyzes the grey scale textural analysis of LS DXA image and assesses microarchitecture of trabecular bone (2, 3)

• FRAX adjusted for trabecular bone score [TBS] is a better predictor than FRAX alone.²

3. CAROC⁴ with BMD.⁵

3- Hans 2017

- ⁴ Canadian Association of Radiologists and Osteoporosis Canada
- ⁵ Leslie WD et al. Simplified 10-Year Absolute Fracture Risk Assessment: A Comparison of Men and Women. Journal of Clinical Densitometry. 2010 Khan et al JOGC 2022 Guidelines

¹ HUNT study Hoff et al 2017 2- Mccloskey EV, et al. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. Journal of Bone and Mineral Research. 2016

Fragility fracture: Definition

A fracture that occurs spontaneously or following a minor trauma such as:

- -Fall from standing height
- -Fall from sitting position

 -Fall from supine position (bed or reclining deck chair < 1 meter high)

-Fall after having missed 1 to 3 steps in a staircase

 After a movement outside of the typical plane of motion or coughing

<u>***Except</u>: Skull and face; Patella; Hand or finger; Toe ; Metatarsal; Cervical spine

≫.

Bessette L, et al. Contemp Clin Trials. 2008;29:194-210. Brown JP, et al. J Bone Miner Res. 2007;23 (suppl 1):M350.

There are Two Tools available for fracture Risk Assessment : 1. FRAX

Ostéoporose Canada	FRAX [®] WHO Fracture Risk Assessment Tool	
Year	Home Calculation Tool Paper Charts FAQ Calculation Tool	References English
Fracture	Please answer the questions below to calculate the ten year probability of fracture with BMD.	
Risk Assessment Tool	Country: Canada Name/ID: About the risk factors (i) Questionnaire: 10. Secondary osteoporosis • No · Yes	Weight Conversion
Calculator	1. Age (between 40-90 years) or Date of birth 11. Alcohol 3 or more units per day No Yes Yes Select DXA 2 Sex Male Female 1 Select DXA 2 Sex Male Female 1 Select DXA	Pounds • kg
2010 Guidelines	3. Weight (kg) 4. Height (cm)	Height Conversion
Initial Investigations	5. Previous fracture No Yes 6. Parent fractured hip No Yes	Convert
Factors Modifying Rx Choice	7. Current smoking No Yes	
Therapeutic Options	9. Rheumatoid arthritis No Yes	00052902 Individuals with fracture ri assessed since 1st June 2

There are Two Tools available for fracture Risk Assessment : 2. CAROC

Calculating 10-Year Absolute Fracture Risk for Postmenopausal Women: CAROC

10-year absolute fracture risk in treatment naïve women combining femoral neck T-score and age¹



Lumbar spine or total hip T-score ≤ -2.5: consider the individual to be at least at moderate risk

Calibrated using Canadian fracture data and have been directly validated in Canadians²

*At least three months cumulative use during the preceding year at a prednisone-equivalent dose \geq 7.5 mg daily 1. Papaioannou A, et al. *CMAJ*. 2010;182:1864-1873. 2. Leslie WD, et al. *J Bone Miner Res*. 2009;24:353-360.

How Should We Evaluate Fracture Risk? Fracture Risk Evaluation Tools

CAROC Consider key fracture risk factors

Sex Age Low BMD(femoral neck) Fragility fracture after age 40 Systemic glucocorticoid therapy (>3 months' duration*) <u>FRAX</u>

Additional risk factors according to <u>Canadian</u> <u>FRAX®</u>

Low body mass index (BMI) Parental history of hip fracture Current smoking Alcohol intake ≥3 units daily Rheumatoid arthritis (RA) or other secondary causes of osteoporosis

*At least three months cumulative use during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily

CAROC = Canadian Association of Radiologists and Osteoporosis Canada FRAX = Fracture Risk Assessment Tool

Papaioannou A, Morin S. CMAJ. 2010.DOI:10.1503/cmaj.100771; Kanis JA, et al. (**FRAX risk can be calculated without FN BMD



Calculating 10-Year Absolute Fracture Risk for Postmenopausal Women:



^{1.} Papaioannou A, Morin S. CMAJ. 2010.DOI:10.1503/cmaj.100771 2. Leslie WE, et al. J Bone Miner Res. 2009;24:353

Whom to Treat



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How to Treat

- Non-pharmacologic interventions
 - Adequate calcium intake 1200 mg of elemental calcium from dietary sources or from supplements (if dietary intake is inadequate), in the form of calcium carbonate or calcium citrate is advised.??
 - Vitamin D supplementations with 800–2000 IU daily aiming for 25-hydroxyvitamin
 D level of 75–125 nmol/L.¹
 - Daily weight-bearing exercise²
 - Limited alcohol intake³
 - Smoke cessation⁴

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¹Weaver CM et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Ol. 2016 ²Kelley GA et al., Exercise and lumbar spine bone mineral density in postmenopausal women: a meta-analysis of individual patient data J Gerontol A Biol Sci Med Sci 2002. ³JA Kanis, et al., Alcohol intake as a risk factor for fracture, Osteoporos Int. 16, 2005 ⁴Kanis JA, et al., Smoking and fracture risk: a meta-analysis Osteoporos Int 2005

How to Treat

Pharmacologic Therapies

OC Releases Cat K, also release of growth factors from matrix TGFB, IGF1 inc OB differentiation



Adapted from Boyle WJ, et al. Nature. 2003;423:337

How to Treat

Anabolic therapy stimulates Wnt signalling in Osteoblasts new bone formation PTH/ PTHrP_ activate bone remodelling –scalloped cement line resorption –formation Romosozumab –Ab Sclerostin- modelling based-quiescent Estrogen- inhibits sclerostin



Pharmacological Interventions:

Bisphosphonates

Oral (alendronate or risedronate)

- Intermediate to high fracture risk under the following conditions:
- eGFR> 30-35 mL/min/1.73 m²
- Normal serum calcium and vitamin D
- Absence of GERD

Very high fracture risk as an alternative therapy •

IV (zoledronate)

- Intermediate, high or very high fracture risk
 - eGFR> 35 mL/min/1.73 m²
 - Normal serum calcium and vitamin D
 - Can be given in the presence of GERD

Following 3 years of annual IV zoledronate infusions or 5 years of oral bisphosphonate use, a "drug holiday" should be offered to those at an intermediate Khan et al JOGC 2022 Guidelines risk of fracture

Paggiosi MAet al. Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: The TRIO study. OI. 2014 Black DM et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the horizon-pivotal fracture trial (PFT). JBMR Res. 2012

Pharmacological Interventions: Denosumab

Very high and high fracture risk under the following conditions:

- Normal serum calcium (adjusted for albumin or ionized)
- Normal vitamin D
- eGFR> 15 mL/min/1.73 m²

Can be used for up to 10 years

If denosumab is discontinued, it should be replaced with an alternative treatment option

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Cummings SR et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-co FREEDOM trial and its extension. J Bone Miner Res. 2018 Bone HG et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: Results from the phase 3 rando FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017

Pharmacological Interventions: Romosozumab

Very high and high fracture risk

Can be used for up to 1 year

Should be followed by an antiresorptive agent to prevent declines in BMD Contraindications: Recent myocardial infarction or stroke or in the presence of a high risk for major adverse cardiovascular events

Saag KG et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. NEJM. 2017 Khan et al JOGC 2022 Guidelines

Pharmacological Interventions: Teriparatide and Abaloparatide

Very high and high fracture risk

Can be used for up to 2 years

Should be followed by an

antiresorptive agent to prevent

declines in BMD

Contraindications: Previous cancer Previous radiation exposure Hypercalcemia High PTH level Unexplained elevation in ALP

Kendler DL et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): A multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2018

Miller PD et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis. JAMA. 2016 Khan et al. IOGC 2022 Guidelines

Pharmacological Interventions: Menopausal Hormone Therapy

Low, intermediate and high fracture risk under the following conditions:

- Women under the age of 60 years
- Experiencing menopausal symptoms

Contraindications: History of breast cancer or thromboembolic disease Increased risk of cardiovascular or cerebrovascular disease

Manson JE et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA. 2013

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Pharmacological Interventions: Selective Estrogen Receptor Modulators Raloxifene or bazedoxifene

Intermediate fracture risk under the following conditions:

- Increased risk of breast cancer
- Low risk of thromboembolic disease

Contraindications: **History of thromboembolic disease**

Silverman SL et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: Results of a 5-year, randomized, placebo-controlled study. Osteoporosis Int. 2012 Ettinger B et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA. 1999

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Special Circumstances

Atypical Femoral Fractures (AFF)

- Incidence of 1 AFF in 1000 patient-years of use following 10 years of bisphosphonate therapy.
- Incidence of 2 AFF per approximately 6000 treated patients with long-term denosumab use (up to 10 years)

Radiographic features

- stress fractures of the femoral shaft
- short oblique or transverse fracture line
- cortical thickening

Khan AA et al. Atypical femoral fracture. CMAJ. 2017

Khan et al .IOGC 2022 Guidelines

Atypical (Subtrochanteric) Fx a ssociated with prolonged Antiresorptive Therapy:2005

- Fx associated with minimal or no trauma
- Fx line originates at lateral cortex , is substantially transverse , may become oblique as progresses medially across femur
- Complete fxs extend through both cortices, may be a medial spike; incomplete fxs involve only lateral cortex
- non-comminuted or minimally comminuted
- Localized periosteal or endosteal thickening lateral cortex present at Fx site ("beaking" or "flaring")
- ASBMR major criteria for atypical fx
- Need 4/5



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Special Circumstances **Approach to AFF**

- Ask all patients on bisphosphonate or denosumab therapy about thigh or groin pain
- If thigh or groin pain is present, proceed to bilateral full femur Xrays and/or a bone scan if necessary.
- In the presence of an AFF, bisphosphonate or denosumab therapy should be **stopped**
 - Teriparatide may be offered to affected patients, in the absence of contraindications

Khan et al JOGC 2022 Guidelines Khan AA et al CMAJ 3017

Watts et al Responses to treatment with teriparatide in patients with atypical femur fractures previously treated with bisphosphonates, JBMR 2017 Miyakoshi et al., Healing of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: A comparison between treatment with and without teriparatide, JBMR 2015

Special Circumstances Osteonecrosis of the Jaw (ONJ)

- Exposed bone in the oral cavity that has not healed and has persisted for>= 8 weeks.
- Incidence with low doses of antiresorptive therapy used in osteoporosis
 1 in 10 000 to 1 in 100 000 patient-years

• Other risk factors

• Diabetes, steroid therapy, periodontal disease, denture use, smoking, and antiangiogenic agents

Prevention of ONJ

• Antiresorptive therapy can be withheld following a dental procedure until the surgical site has healed (usually within 6 to 8 weeks)

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Khan AA et al., Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus, JBMR 2015 Khan AA, et al., Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ, J Clin Densitom 2017

Osteonecrosis of the Jaw (ONJ)

- Exposed bone in maxillofacial area for 8 weeks or more in absence of radiation therapy to area
- May be associated with pain, swelling and infection
- Most cases in patients with cancer on high dose IV bisphosphonates often in combination with glucocorticoids or chemotherapy



Photo Courtesy of M Kraenzlin

- Risk in oral BP users of 1:10,000 to 1:100,000 patient years
- ? Causal relationship with BP use not clearly established
- Unclear if stopping therapy prior to invasive dental procedures is helpful, but reasonable if elective procedure and appropriate to wait

Khosla S et al. ASBMR Task Force Report J Bone Miner Res. 2007;22:1479

7 Khan et al JBMR 2015 Khan et al JOGC 2022 Guidelines

International Task Force on ONJ recommendations for prevention:

Evaluate Key Risk Factors for ONJ:

- Invasive dental procedure
- Diabetes
- Glucocorticoid therapy
- Periodontal disease
- Denture use
- Smoking
- Anti-angiogenic agents

Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus

Khan A et al, J Bone Miner Res. 2015 Jan;30(1):3-23.

HRT

(Menopausal Hormone Therapy : MHT)

- WHI 5yr RCT in PMF aged 50-79 yrs N =16,608
- EPT -0.625mg CE + 2.5mg MPA
- Increased LS and TH BMD by 4.5% and 3.7% relative to pbo –Cauley 2003
- Vfx, hip fx, total fx reduced by 34% vs placebo in a low risk population
- Meta-analysis and SR -5-7 yrs of HT reduced risk of spine, hip and nonvfx
- -Barrionuevo JCEM 2019, Fink 2019
- HT and effect on fracture risk has not been evaluated in women with osteoporosis
- Estrogen has not been approved as a treatment for postmenopausal osteoporosis

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women¹

Based on GRADE A evidence as assessed in the Osteoporosis Canada 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada^{1*}

Type of Fracture	ANTIRESORPTIVE THERAPY						BONE FORMATION THERAPY
	Bisphosphonates			Denosumab	Raloxifene	Estrogen ** (Hormone	Teriparatide
	Alendronate	Risedronate	Zoledronic Acid			Therapy)	
Vertebral	~	~	~	~	~	~	~
Hip	~	~	~	~	-	~	-
Non- Vertebral	~	~	~	~	-	~	-

*For postmenopausal women, windicates first line therapies and Grade A recommendation.

- **Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.
- In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

Premature Menopause & Osteoporosis

Malmo Study 2012

Malmo Study 2012

34 year f/u of 3<u>90 Swedish ♀:</u>

2 groups

- (Group A) =early menopause (<47yo mean 42yo) 61 ♀</p>
- (Group B)= N Menopause (>47yo *mean 51yo) --* 329 ♀

RESULTS at age 77 yo:

<u>Group A</u>: 56% = OP (cf Group B : 30% = OP) <u>Group A</u>: fragility # 68% > Group B Consequences of Premature (<47 yo) Menopause

OP - 83% 1 Mortality - 59% 1

BJOG Apr 25, 2012

HT & Osteoporosis

WHI HT reduced the risk for fracture (eg, hip,

2

- spine, nonspine) in postmenopausal women in the Women's Health Initiative (WHI) who were not selected on basis of osteoporosis
 - Many systemic HT products are approved for *preventing* postmenopausal osteoporosis
 - No HT product is approved for *treating* osteoporosis

- Extended use of HT is option for women at high risk of osteoporotic fracture when alternate therapies aren't appropriate
- Risks of long-term HT use should be considered
- Benefits of HT on bone mass dissipate quickly after discontinuation

*** Premature Menopause/ Premature Ovarian Insufficiency

- Data regarding HT in women over age 50 should not be extrapolated to younger postmenopausal women
- Likely that risks attributable to HT are smaller and benefits greater in these younger women
- Use of HT or oral contraceptives until median age of menopause is recommended at which time decision can be reevaluated

SOGC/OP GUIDELINE 2022

TREATMENT ALGORITHM







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THANK YOU



THANK YOU FOR YOUR ATTENTION !

