Osteoporosis

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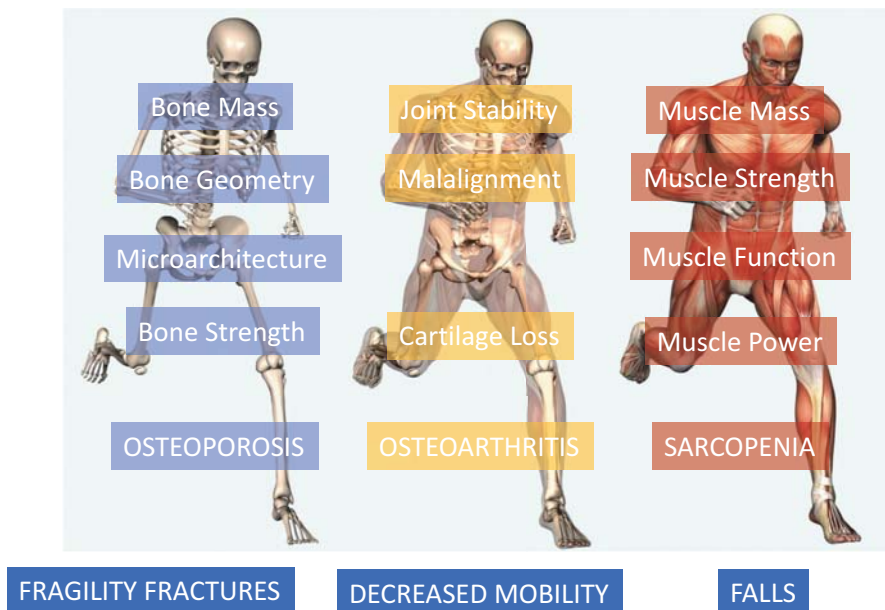
51st Annual Course in Drug Therapy, May 2021

Conflict of Interest

- Past Chair of Osteoporosis Canada Scientific Advisory Council
- Member of the International Osteoporosis Foundation Council of Scientific Advisors
- Member of the Advisory Board of CIHR Institute of Musculoskeletal Health and Arthritis

Learning Objectives

- Assess fracture risk
- List the considerations before initiating and during anti-osteoporosis treatment
- Implement the evidence to support a strategy towards optimal duration of therapy and drug holiday for patients on bisphosphonates
- Determine what to do if treatment fails

Bone Strength

Biomechanical, biological and genetic factors

| Bone Quality | + | Bone Density | + | Bone Geometry |

Bone mineral content

Bone turnover

Activation Frequency

Damage accumulation

Quality of material

Bone diameter

Cortical thickness

Limb alignment

Bone Strength

Musculoskeletal Health

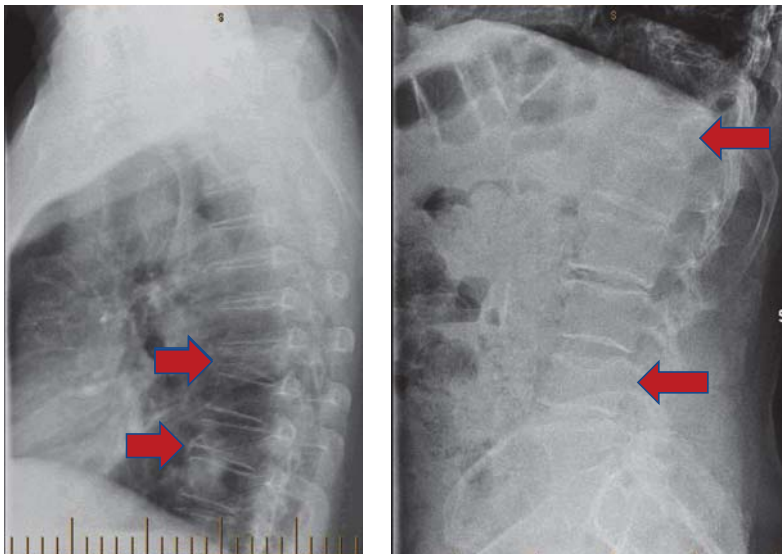| OSTEOPOROSIS | OSTEOARTHRITIS | SARCOPENIA |
Bone Mass	Joint Stability	Muscle Mass
Bone Geometry	Malalignment	Muscle Strength
Microarchitecture		Muscle Function
Bone Strength	Cartilage Loss	Muscle Power

FRAGILITY FRACTURES · DECREASED MOBILITY · FALLS

Fracture Risk Assessment

- 57 y old man with low back pain for a few weeks
- HBP, Left hip OA with recent THR
- Severe back pain while pushing a heavy object
- Vertebral fractures documented on XRay
- Seen in ortho 6 weeks after onset- Getting better in terms of pain; no neurological symptoms or signs. No surgery recommended
- No previous fractures
- Rx: irbersartan, vitamin D, naprosyn
- No ETOH; smoker 1 ppd during the summer

Osteoporotic Fractures: A Canadian Perspective-

Age-specific annual OP related fracture rates among people aged 40 years and older by fracture site and sex, Canada*, 2011/12

Public Health Agency of Canada,2020

Fracture Risk Assessment

WORK UP (Osteoporosis Canada Guidelines)

❖CBC, TSH, renal function, serum calcium and phosphorus, alkaline phosphatase

❖Serum protein electrophoresis in those with vertebral fractures

❖25 (OH) vitamin D in selected cases
  o Malabsorption
  o Obesity
  o Chronic kidney disease
  o Chronic liver disease
❖ Bone mineral density
❖ X-rays spine

Osteoporosis Canada Guidelines 2010, CMAJ

Fracture Risk Assessment

Fracture Risk Assessment


Calcium: Normal
Phosphorus Normal
S Creatinine elevated
Albumin: 33 g per liter
Protein: 117 g per liter
Serum protein electrophoresis: monoclonal peak IgG lambda
Bone marrow biopsy: almost complete replacement with plasma cells, compatible with multiple myeloma
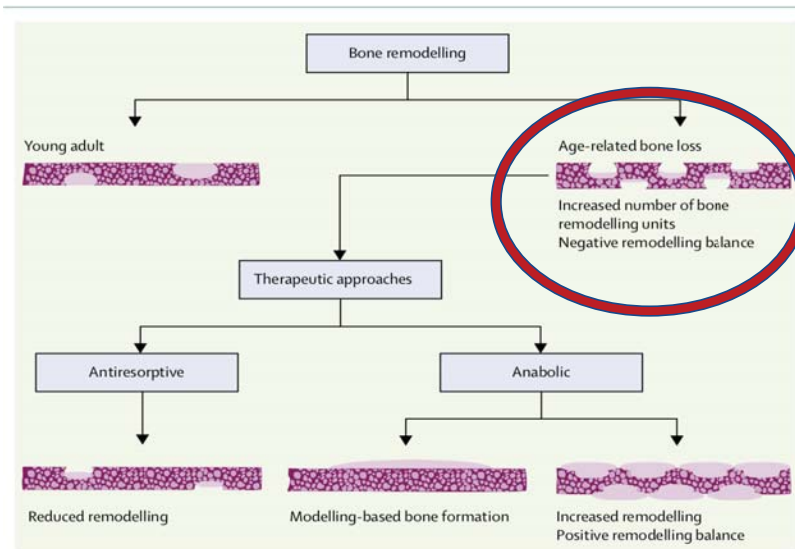
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                    ┌─────────────────────────────────┐
                    │      High Risk Fracture:        │  Yes
                    │  • Prior hip or spine fracture  │─────────────┐
                    │  • More than one fracture event │             │
                    └─────────────────────────────────┘             │
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High Risk Fracture:
- Prior hip or spine fracture
- More than one fracture event

→ **Yes** (to right branch)

→ **No**

Additional risk factors:
- Previous fracture
- Parent fractured hip
- Current smoking
- Glucocorticoids
- Rheumatoid arthritis
- Alcohol 3 or more units/day
- Secondary osteoporosis
- *Falls, 3 or more last year*

All men and women at age 65
Or
50 years and additional risk factor

Obtain BMD and
Calculate 10-year fracture risk with BMD

Low Risk for Fractures (10% or less)

DO NOT RECOMMEND PHARMACOTHERAPY

Reassess BMD and fracture risk:
- 10 years if fracture risk < 10%
- 5 years if fracture risk 10-15%
- 3 years if fracture risk > 15%

If not treated

10-year fracture risk 10-20%

Lateral spine imaging
Assess for other risk factors

Vertebral fracture

No vertebral fracture

SUGGEST PHARMACOTHERAPY
Intermediate Benefit

- 10-year fracture risk ≥ 20%
- Prior hip or spine fracture
- More than one fracture event

RECOMMEND PHARMACOTHERAPY
Largest Benefit

The Bone Cells and Modeling vs Remodeling

	Modeling	Remodeling
Function	Shape bone, increase bone mass	Renew bone
Cells involved	Osteoclasts or osteoblasts	Osteoclasts and osteoblast
Mechanism	Activation-formation Activation- resorption	Activation –Resorption-Formation
Timing	Throughout life	
Effect on bone mass	Increase	Maintain or slight decrease

osteoblasts 4-6 %   osteoclasts 1-2 %

osteocytes > 90-95 %

Modeling changes bone shape
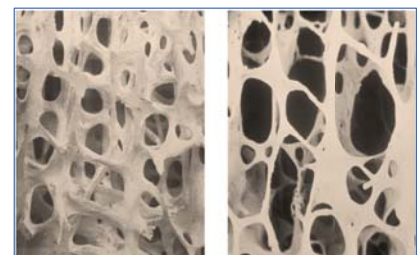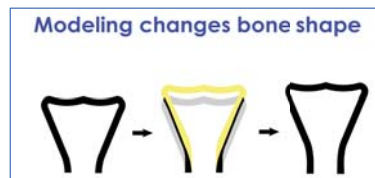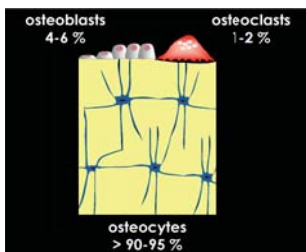
Antiresorptive and anabolic effect of Rx on bone remodelling

Antiresorptive Agents

Drug	Effect of remodeling	Effect on Fracture	Offset	Adverse events
Bisphosphonate ALN, RIS, ZOL	↓ to ↓↓	↓↓ to ↓↓↓	slow	GI, acute phase reaction, AFF, ONJ
RANKL inhibitor DMAB	↓↓↓	↓↓↓	rapid	Hypocalcemia, AFF, ONJ
SERMs Raloxifene	↓	↓	rapid	Thromboembolic ds

	Contraindications
Bisphosphonates Denosumab (MS 153) Raloxifene	Upper GI, eGFR < 35 ml/min Hypocalcemia, eGFR <15 ml/min Thromboembolic disease

Anabolic Agents

Drug	Effect on bone formation	Effect on fractures	offset	Adverse events
PTH receptor agonist Teriparatide	Increased -remodeling-	↓↓ to ↓↓↓	Rapid	*osteosarcoma
Anti Sclerostin antibody Romozumab	Increased transiently -Modeling-	↓↓ to ↓↓↓	Rapid	*cardiovascular

Compston J, McCLung and Leslie *Lancet* 2019

Duration of Bisphosphonate Therapy

Harms	RCTs	Cohort studies
Osteonecrosis Jaw	rare	1 per 100,000 p-years of Tx
Atypical Femur Fx	rare	110 per 100,000 p- years of Tx

| Drug: Continuation vs Discontinuation	Fracture outcome	Relative Risk (95% CI)	Absolute Risk Difference	Strength of Evidence
Alendronate (N=1099) (**10 y** vs **5y** + 5y PBO)	Clinical	0.93 (0.71-1.21)	-1% (-6- 4%)	moderate
	Non-vertebral	1.00 (0.76-1.32)	-1% (-5 - 5%)	moderate
	Clinical Vertebral	**0.45 (0.24-0.85)**	**-3% (-5- -0.5%)**	moderate
	R Vertebral	0.86 (0.60-1.22)	-1% (-5- 2%)	moderate
Zoledronic Acid (N=1233) (**6 y** vs **3y** +3y PBO)	Clinical	1.04 (0.71-1.54)	NA	moderate
	Non-vertebral	0.99 (0.7- 1.5)	-0.3% (-3- 35)	moderate
	Clinical Vertebral	1.81 (0.53-6.2)	NA	insufficient
	R Vertebral	**0.51 (0.26-0.95)**	**- 3% (-6---1%)**	low

Duration of Therapy with Bisphosphonates
The efficacy of bisphosphonates beyond 5 years is unclear

- Osteoporosis Canada (2010): 3 to 5 years, but continue in those at high risk
- The ACP guidelines (2017) 5 years but suggest that high risk patients may benefit from longer treatment
- The NOF guidelines (2014) 3 to 5 years and those at high risk should continue treatment
- An ASBMR task force (2016) recommends an initial 5 years of oral therapy or 3 years of iv therapy followed by continued therapy up to 10 years (oral) or 6 years (IV) in those at high risk

Those at high risk?

- Very low Femoral Neck BMD
- Recent fracture (hip, spine, humerus and wrist)
- FRAX probability of 25% or more
- High frailty score, falls++

- Consider continuing bisphosphonate for longer (up to 7 years) or switching to another molecule (denosumab)

Denosumab: Increased Risk of Vertebral Fractures after Stopping Therapy

Lumbar Spine BMD
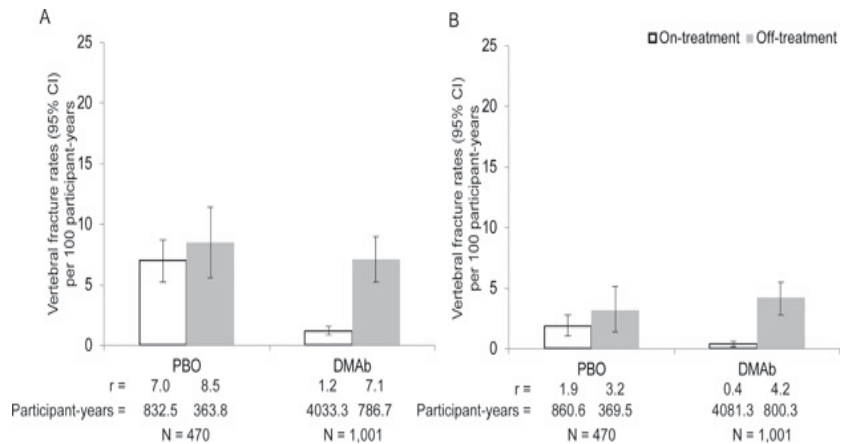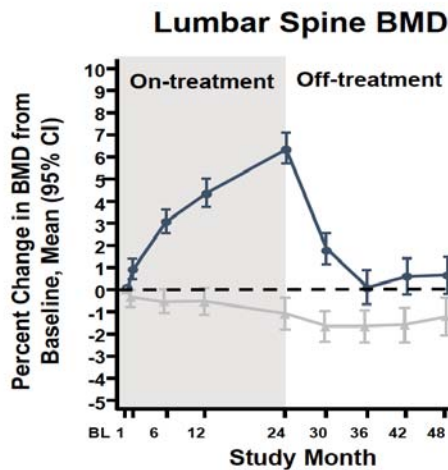
When prescribing denosumab, clinicians should counsel patients against discontinuation without medical consultation. Patient should be transitioned on a bisphosphonate (iv) if treatment is to be interrupted.

# Treatment Failure: BMD is decreasing

- **BMD**: It is suggested to monitor BMD 2- 3 years after starting or changing antiresorptive pharmacotherapy to prevent fractures

Table 5. Estimated Fracture Risk Reduction Associated With BMD Improvement

|	Vertebral fracture	Hip fracture	Nonvertebral fracture
Δ Total hip BMD			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
Δ Femoral neck BMD			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
Δ Lumbar spine BMD			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%

BMD = bone mineral density.

Figure 1. Cumulative fracture risk, by change in total hip BMD.
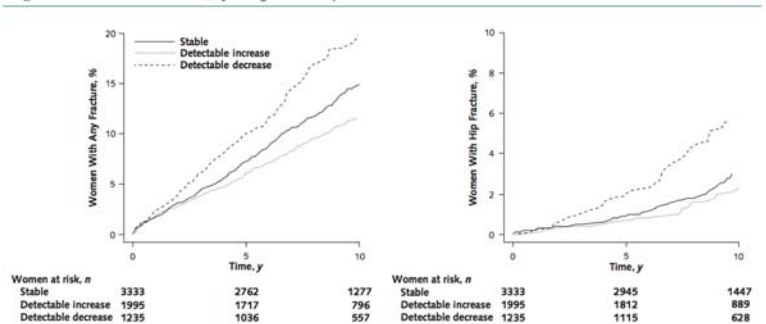
Cumulative incidence functions are directly adjusted for baseline fracture probability. BMD = bone mineral density. **Left.** For any fractures, the detectable decrease vs. stable BMD (P < 0.001) and detectable increase vs. stable BMD (P = 0.004) are depicted. **Right.** For hip fractures only, the detectable decrease vs. stable BMD (P < 0.001) and detectable increase vs. stable BMD (P = 0.167) are depicted.

Treatment Failure: Fractures after at least 12 months of therapy

Subsequent fractures in men and women following a first fracture
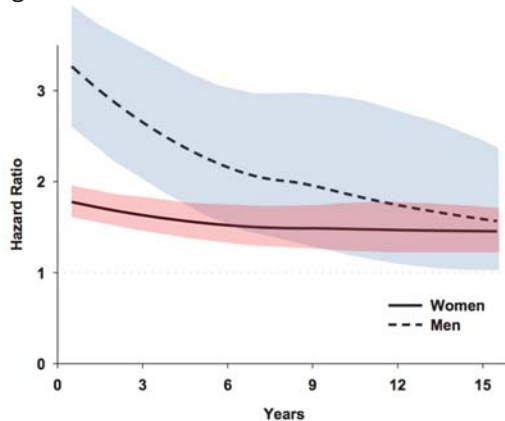
- Consider:
    - ? Adherence to treatment plan
    - ? New health issue (weight loss)

    - Switching therapies:
        - Bisph oral to iv
        - Bisph oral to Dmab
        - Antiresorptive to Anabolic
    - Referral to specialist

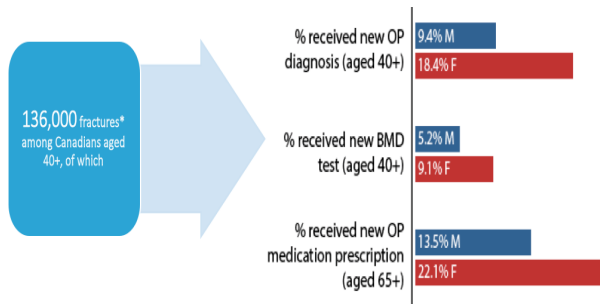# Key messages

- Fracture Risk Assessment:
- The management of osteoporosis should be guided by an assessment of the patient's 10-year absolute fracture risk using a validated fracture risk assessment tool
- The work up should include basic biochemistry and spine X-Rays

- Bisphosphonate: Duration of Therapy:
- 3 to 5 years and stop (holiday)
    - No recent fracture,
    - BMD has stabilized or improved
    - No uncontrolled conditions that increase falls and fracture risk
    - Can be resumed after a few years
- Denosumab:
- Should not be discontinued (No holiday)

Key Messages

136,000 fractures* among Canadians aged 40+, of which	% received new OP diagnosis (aged 40+) — 9.4% M / 18.4% F
	% received new BMD test (aged 40+) — 5.2% M / 9.1% F
	% received new OP medication prescription (aged 65+) — 13.5% M / 22.1% F

- Treatment Failure
- Monitor adherence, new issues
- BMD and Fractures
- Consider Tx switch
- Consider referral (anabolic therapy)

Thank you

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