Bone Health in Prostate Cancer

Luke T. Lavallée, Ryan McLarty, Christopher Tran,
Rodney H. Breau, Patrick Richard, Bobby Shayegan,
Brita Danielson, Marie-Paul Jammal, Fred Saad

Originally published online in Can Urol Assoc J 2021;15(12):375-82
doi:http://dx.doi.org/10.5489/cuaj.7660

Slides Prepared by: Ryan McLarty

Cancer treatment-induced bone loss

- Androgen deprivation therapy (ADT) disrupts bone homeostasis and promotes net bone resorption, thereby reducing bone mineral density (BMD)
- Fractures cause significant morbidity: 1 in 3 Canadian men who experience a hip fracture die within one year
- Men with prostate cancer on ADT are surviving longer. The prevention of bone loss and skeletal related events (SREs) is important for comprehensive patient centered care

Which men are at risk of bone loss?

- **Men initiating ADT of any duration**
  - Includes metastatic patients and those receiving treatment for curative intent (eg. in conjunction with radiation therapy)
- The minimum duration of ADT exposure that causes meaningful bone loss is unknown. Bone loss may be more pronounced during the first year of ADT
- Conceptually there are two patient populations addressed in this statement:
  1. Patients on ADT and at an ***elevated risk of osteoporotic fracture***
  2. Patients on ADT with ***Castrate Resistant Prostate Cancer (CRPC) and bone metastases***

Assessment of fracture risk

- **Men initiating ADT should be assessed for risk of osteoporotic fracture using a risk assessment tool**:
  - FRAX algorithm
  - CAROC tool

Fracture risk assessment tools:
FRAX: www.sheffield.ac.uk/FRAX/tool.aspx?country=19
CAROC: www.osteoporosis.ca

- A bone mineral density (BMD) DXA scan is recommended as part of osteoporotic risk assessment in addition to a clinical risk score, if available
  - Note: A FRAX risk score can be calculated with or without BMD scan measurements

Clinical risk factors for low bone mass

Previous fracture (fragility)	Spontaneous fractures or those induced by a minimal trauma that would not normally be expected to cause a fracture. Also includes asymptomatic vertebral fractures.
Glucocorticoid use	Oral glucocorticoids equivalent to ≥ 5 mg/day of prednisone (FRAX) or ≥ 7.5mg (CAROC) for >3 months.
Parental History of hip fracture	Mother or father with a history of prior hip fracture at age ≤ 80 years.
Age	Older age is associated with higher risk. FRAX accepts ages between 40 and 90 years, while CAROC includes ages 50-85.
Height and Weight (BMI)	Low BMI associated with higher risk of fracture.
Tobacco use (smoking)	Men who are currently smoking.
Alcohol consumption	Consumption of > 3 units of alcohol per day.
Rheumatoid arthritis	Rheumatoid arthritis diagnosis is a risk factor. Note osteoarthritis is not a risk factor.

BMI: body mass index; CAROC; The Canadian Association of Radiologists and Osteoporosis Canada fracture risk assessment; FRAX: The World Health Organization fracture risk assessment algorithm.

Management

- **All men on ADT should receive**:
  - Education regarding cancer treatment-induced bone loss
  - Education for smoking cessation, decreased alcohol consumption, weight bearing and balance exercises, fall prevention strategies
  - Target intake of 1200 mg calcium from all sources (supplement if needed)
  - Vitamin D supplementation of 800-1200 IU daily
  - Risk assessment with FRAX or CAROC +/- BMD scan

Pharmacotherapy options

- **Bone-targeted agents can prevent bone loss:**
- **Bisphosphonates**:
  - Pyrophosphate analogues that inhibits osteoclasts
  - Examples: *zoledronic acid, alendronate, risendronate*
- **Denosumab**:
  - Monoclonal antibody that binds the RANK ligand and prevents bone loss by reducing osteoclast function
- See 'Treatment algorithm' on slide 11 for available dosing options

Pharmacotherapy indications

- **Treatment with a bone-targeted agent (osteoporosis dosing) is indicated in all men on ADT with any of the following:**
  - Osteoporosis (T-score $\leq$ -2.5 on DXA scan)
  - (or) Prior fragility fracture
  - (or) 10-year major osteoporotic fracture risk > 20 % based on FRAX or CAROC

Treatment by disease state

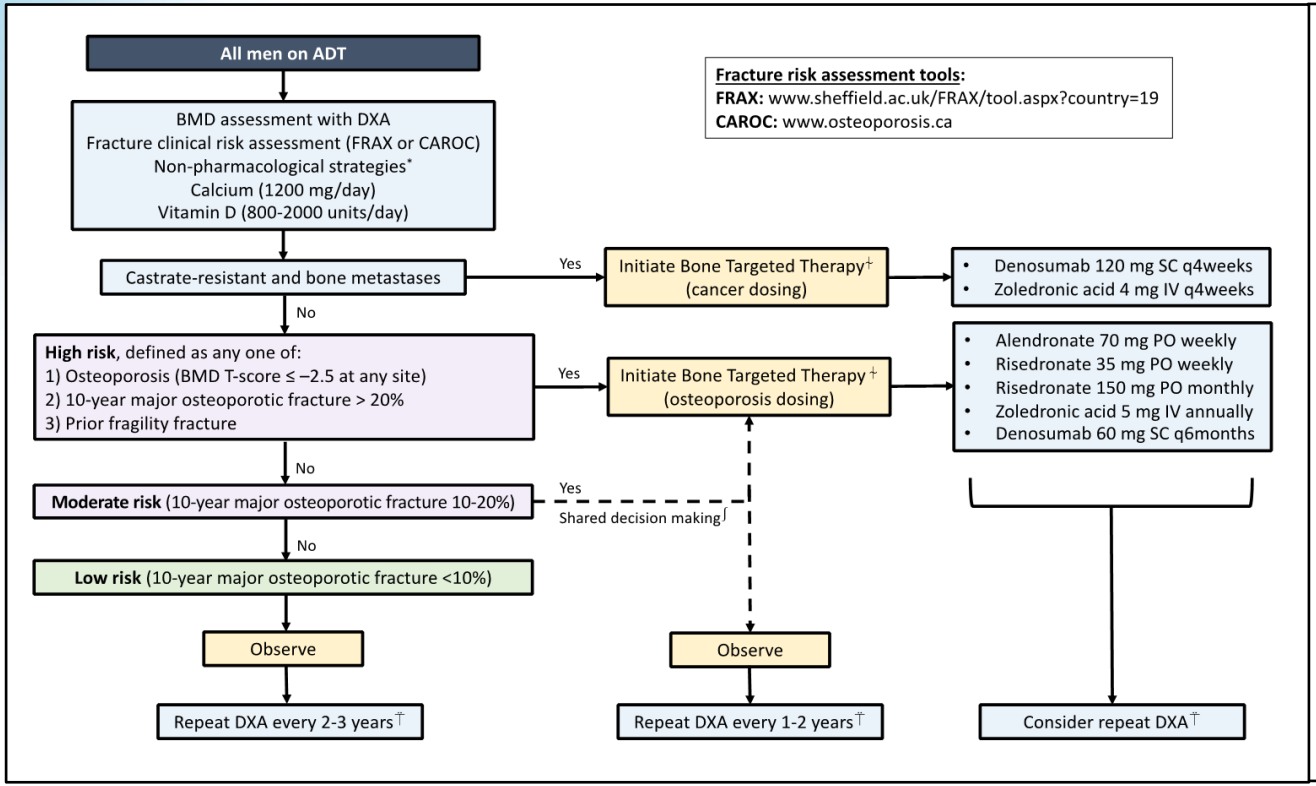
- **Men in any prostate cancer disease state receiving ADT should be assessed for risk of osteoporotic fracture** (slide 8)
- **All men with CRPC and bone metastases benefit from bone targeted agents to prevent skeletal related events**

M0 HSPC	Fracture risk assessment, treat with osteoporosis dosing if indicated
M1 HSPC	Fracture risk assessment, treat with osteoporosis dosing if indicated
M0 CRPC	Fracture risk assessment, treat with osteoporosis dosing if indicated
M1 CRPC	Bone metastasis: treat with cancer dosing to prevent skeletal related events No bone metastasis: fracture risk assessment, treat with osteoporosis dosing if indicated

Treatment considerations

- Men on ADT with a moderate risk of osteoporotic fracture (10-20% 10-year major osteoporotic fracture risk) may benefit from treatment and should be approached using a shared decision making model
- Baseline serum calcium and creatinine should be performed prior to initiating a bone targeted therapy
- Adverse events, including osteonecrosis of the jaw, are predominantly with cancer dosing (consider periodic calcium monitoring)
- Consultation with an osteoporosis expert may be considered for patients with unclear risk factors or whom desire more counselling

Summary treatment algorithm



Assessment and Management of Bone health in men on ADT

ADT – androgen deprivation therapy, BMD – bone mineral density, DXA – dual energy x-ray absorptiometry, FRAX – The World Health Organization fracture risk assessment algorithm, CAROC – The Canadian Association of Radiologists and Osteoporosis Canada fracture risk assessment

* Non-pharmacological strategies include smoking cessation, moderation of alcohol consumption, exercise and falls prevention.

∫ The Canadian Osteoporosis Society recommends bone targeted agents may be considered in men on ADT with Moderate risk of 10-year major osteoporotic fracture (10 to 20% risk). A shared decision-making approach is appropriate. May consider referral to an osteoporosis expert for patients wishing to discuss further.

⊤ Evidence to guide the optimal interval to repeat a DXA scan is limited. The panel recommends clinicians consider periodic follow-up every 2-3 years in low-risk patients and every 1-2 years for moderate-risk patients who are not on treatment. Men on bone targeted therapy may consider a repeat DXA scan to confirm effectiveness of therapy.

+ Recommend baseline serum calcium and creatinine.

Conclusions

- Men on ADT of any duration are at risk of cancer treatment-related bone loss
- All men on ADT should be assessed for bone health, receive counselling regarding lifestyle modification, and ensure appropriate calcium and vitamin D intake/supplementation
- Bone-targeted agents should be initiated for men at increased risk of osteoporotic fracture (osteoporotic dosing) or those with CRPC and bone metastases (cancer dosing)