Clinical Question 7

- Do patients on androgen deprivation therapy require osteoporosis pharmacotherapy?

1

Learning Objectives

Upon completion of this module, participants will be better able to:

- Explain the impact of co-morbidities on the risk profile of patients with osteoporosis
- Describe why patients on androgen deprivation therapy are at risk for bone loss and will benefit from pharmacotherapy to prevent osteoporotic fractures
- Mitigate the impact of medication-related factors which may increase the risk of bone loss and fragility fractures

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Clinical Question 7

- Do patients on androgen deprivation therapy require osteoporosis pharmacotherapy?

Intermittent androgen deprivation therapy is being used more frequently in the management of prostate cancer in men and has known harmful effects on bone. Clinical trials indicate both the prevention of bone loss and prevention of osteoporotic fractures in men treated with denosumab.

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Clinical Vignette

Frank
66 years old

Frank's History

- 5-year history of prostate cancer
- Recently fractured his radius after tripping over the family dog
- Today's visit is to discuss his BMD results

Physical Exam & Tests

- Femoral neck BMD T-score now: -2.7

Medications

- Androgen Deprivation Therapy (ADT)

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Clinical Vignette

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66 years old

- 5-year history of prostate cancer
- Recently fractured his radius after tripping over the family dog
- Today's visit is to discuss his BMD results

- Femoral neck BMD T-score now: -2.7

- Androgen Deprivation Therapy (ADT)

What is Frank's risk of osteoporotic fracture?

1. Low
2. Moderate
3. High
4. Not sure

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Clinical Vignette

Frank
66 years old

- 5-year history of prostate cancer
- Recently fractured his radius after tripping over the family dog
- Today's visit is to discuss his BMD results

- Femoral neck BMD T-score now: -2.7

- Androgen Deprivation Therapy (ADT)

What osteoporosis treatment advice would you discuss with Frank?

1. Simply ensure that he has an adequate daily intake of calcium and vitamin D and tell him that he does not require anything more for his bones
2. Tell him to take some saw palmetto
3. Start him on a bisphosphonate or denosumab
4. Both A & B
5. Stop androgen deprivation therapy

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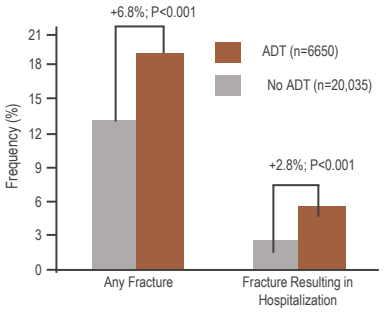
Androgen Deprivation Therapy (ADT)

- Despite therapy, up to 40% of men with prostate cancer develop metastases with a high propensity for bone, leading to skeletal related events[2]
- ADT is the standard of care in the management of advanced prostate cancer or as an adjunct therapy[1]
- ADT is associated with a well-known deleterious effect on bone health, resulting in a decrease in BMD and increased risk for fracture[2]
- Men undergoing ADT are 4x times more likely to develop significant bone deficiency[2]

Proportion of Men with Fractures 1-5 Years After Cancer Diagnosis[1]



1. Shahinian, V.B., et al. *N Engl J Med*. 2005;352(2):154-64; 2. Bienz, M., Saad, F. *BONEKEy Reports*. 2015 24;4:716.

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Androgen Deprivation Therapy (ADT)

- Prostate cancer is promoted by androgens and is often sensitive to androgen-deprivation treatments such as GnRH agonists.[1]
- Result of ADT is to reduce circulating testosterone and other androgens. This also reduces estradiol levels and BMD.[1]
- BMD declines up to 8.5% per year in men receiving ADT.[2,3]
- A retrospective study of 50,163 prostate cancer patients found significantly higher rates of fracture in patients treated with ADT vs. untreated (19.4% vs. 12.6%, p<0.001).[4]

BMD = bone mineral density; GnRH = gonadotropin releasing hormone

1. D'Oronzo S, et al. Cancer treatment-induced bone loss (CTIBL): Pathogenesis and clinical implications. Cancer Treat Rev. 2015;41:798-808.
2. Lipton A, Smith MR, Ellis GK, et al Treatment-induced bone loss and fractures in cancer patients undergoing hormone ablation therapy: efficacy and safety of denosumab. Clin Med Insights Oncol. 2012;6:287-303
3. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer. 2004;100:892-899.
4. Shahinian VB, et al Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005; 352:3154-164.

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Meta-Analysis: Androgen Deprivation Therapy: All Evaluated PMO Treatments Are Effective In Improving BMD

- Zoledronic acid was found to have a greater improvement in BMD compared to other active treatments at all three studied site[1*]
- All drugs (bisphosphonates, denosumab, and raloxifene) appeared to be effective in reducing the rate of bone loss[1]
- In ADT treated nonmetastatic prostate cancer, BPs were effective in increasing BMD, but no trial was sufficiently powered to detect reduction in fractures
  - → Denosumab improved BMD and reduced the incidence of new radiographic vertebral fractures in 1 high-quality trial[2]

*Except for risedronate, which had better BMD improvement compared to ZA at the femoral neck site in one small study. BP= bisphosphonates
1. Poon, Y., et al. *BJU Int*. 2018;121(1):17-28. 2. Alibhai, S.M.H., et al. *Ann Intern Med*. 2017:5;167(5):341-350.

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RCT: Androgen Deprivation Therapy: Effect of Denosumab on BMD and New Vertebral Fractures

- 234 diagnosed OP patients on ADT for prostate cancer
- Denosumab 60 mg subcutaneously every 6 months or alendronate (70 mg/week) for 2 years
- Both drugs provided significant improvements in back pain and general health conditions
  - → Mean changes in BMD at final follow-up differed significantly between two groups
  - → New vertebral fractures over 24 months: Denosumab 18 [15.38 %] vs. alendronate 24 [20.51 %] P=0.10 (not significant)
  - → BMD changes at the lumbar spine at 24 months were 5.6% with denosumab vs. -1.1% with alendronate (P<0.001)

OP = osteoporosis
Doria C, et al. *Minerva Urol Nefrol*. 2017;69(3):271-277.

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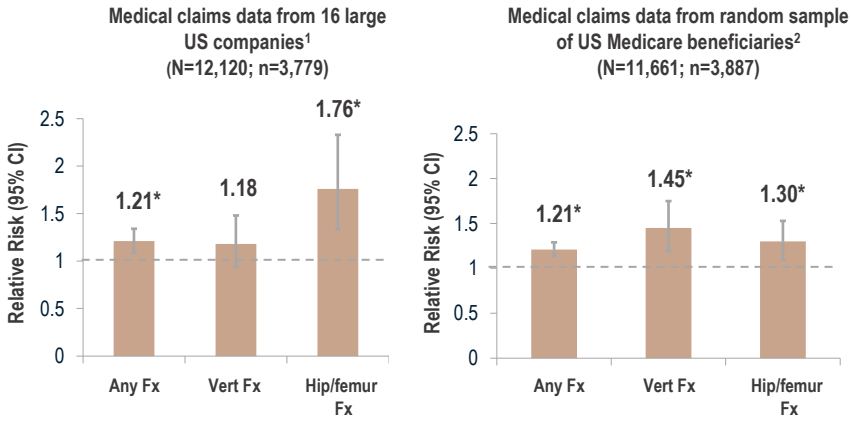
Retrospective Studies Have Also Found Increased Fracture Risk with GnRH Agonists in Non-Metastatic Prostate Cancer



*p < 0.05. Fx = fracture; Vert = vertebral

1. Smith MR, et al. (2006) *J Urol.* 175, 136-139. 2. Smith MR, et al. (2005) *J Clin Oncol.* 23, 7897-7903.

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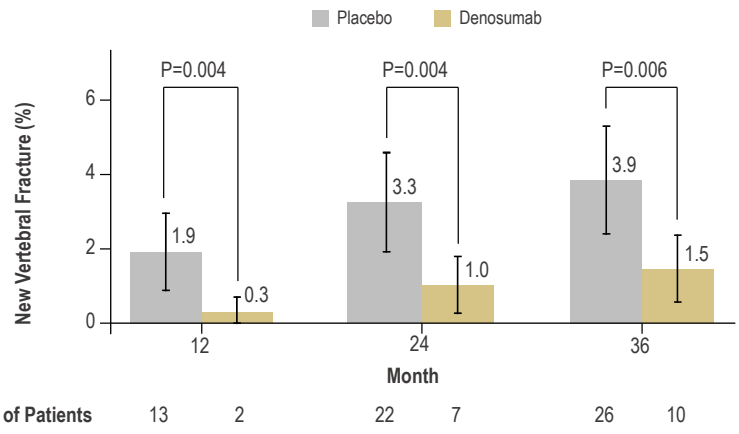
Cumulative Incidence of New Vertebral Fracture at 12, 24, and 36 Months, Denosumab HALT Prostate Cancer Study Group



Smith MR et al. (2009) *N Engl J Med.*, 361, 745-755.

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Guidelines Recommend Considering Treatment to Prevent Bone Loss in Patients on ADT

US Endocrine Society Clinical Practice Guideline: Osteoporosis in Men (2012)

- We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture based on low bone mineral density and/or clinical risk factors [Strong recommendation, moderate quality evidence].
- All evaluated PMO therapies are improving bone mineral density in men receiving Androgen Deprivation Therapy (ADT) but denosumab is the only treatment option that also reduced the occurrence of new vertebral fracture in that population.

Watts NB, et al. (2012) *J Clin Endocrinol Metab.*, 97(6), 1802-1822.

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Discussion: Clinical Takeaways

1. AIs are anti-estrogen agents used in the treatment of estrogen receptor positive breast cancer in postmenopausal women[1]
2. AIs decrease aromatase activity and inhibit the conversion of adrenal androgens to estrogen, which reduces circulating and tissue levels of estrogen[2]
3. Lack of estrogen leads to increased RANK ligand activity and an overall increase of mature osteoclasts, which results in increased bone resorption[2]
4. AI users are at an increased risk for fracture and bone loss[3,4]
5. Patients treated with ADT have an increased risk of fracture and need to be treated[5]

1. Rinaldi RZ. (2013) *Curr Osteoporos Rep.*,11, 61–64. 2. Michaud LB, Goodin S. (2006) *Am J Health Syst Pharm.*, 63, 419-430.
3. Gaillard and Stearns. (2011) *Breast Cancer Research*, 13, 205-216. 4. Brufsky et al. (2008) *The Oncologist*, 13, 187-195.
5. Shahinian VB, et al (2005) *N Engl J Med.*, 352, 3154-164.

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