Clinical Question 5

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Patients initiating long-term high dose glucocorticoid therapy (≥ 7.5 mg prednisone or equivalent daily for at least three months cumulative therapy in the previous year*) require osteoporosis prophylaxis of bone loss. FRAX may underestimate fracture risk in patients on high dose glucocorticoid and strong consideration should be given to early initiation of antiresorptive therapy to prevent the initial bone loss which occurs with glucocorticoid therapy.

* 2010 Clinical Practice Guidelines from Osteoporosis Canada.

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Clinical Vignette

Ken
70 years old

- Recent complaints of severe back pain
- Polymyalgia Rheumatica (PMR)

- Noted height loss (3 cm)
- Femoral Neck T-score: -2.8

- Prednisone 15 mg/day for 5 months
- PPI

What are your current strategies for assessing fracture risk in patients on glucocorticoid therapy?

Would you treat Ken for Glucocorticoid induced bone loss?

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Long-Term GIOP Causes Osteoporotic Fractures in 30% - 50% of Treated Adult Patients[1]

- **GIOP is the most common form of secondary osteoporosis[2]**
- **An estimated 3.6% of Canadian postmenopausal women currently take oral glucocorticoids[3]**
  - → 7-fold higher hip fracture risk[4*]
  - → 17-fold higher vertebral fracture risk[4*]
  - → Risk independent of underlying disease, age, and gender[5]
  - → Morbidity, mortality, and healthcare costs[4]
  - → Decreased quality of life[4]

*With prednisone equivalent doses of 10–12 mg/day for > 3 months in the past year.
1. Amiche MA et al. *Osteoporos Int*. 2016;27: 1709–1718; 2. Mazziotti G, et al. *Am J Med*. 2010;123, 877-884; 3. Diez-Perez A, et al. Bone.2011;49, 493-498; 4. Buehring B, et al. *J Allergy Clin Immunol*.2013;132, 1019-1030; 5. van Staa TP, et al. *Osteoporos Int*. 2002;13, 777-787.

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GIOP Associated with Reduced Bone Formation[1]

- **GIOP causes biphasic bone loss:[1]**
  - → Rapid bone loss of up to 12% during the first 12 months of GC treatment
  - → Followed by slower bone loss of 2-3% annually
- **Glucocorticoids induce:**
  - → Stimulators of osteoclast differentiation and increasing bone resorption[1]
  - → Inhibitors of bone formation and stimulate the differentiation of osteoblast precursors toward adipogenesis[2]

1. Khosla S. *Endocrinology*. 2001;142:5050-3.; 2. Amiche MA et al. *Osteoporos Int*. 2016;27:1709–1718.

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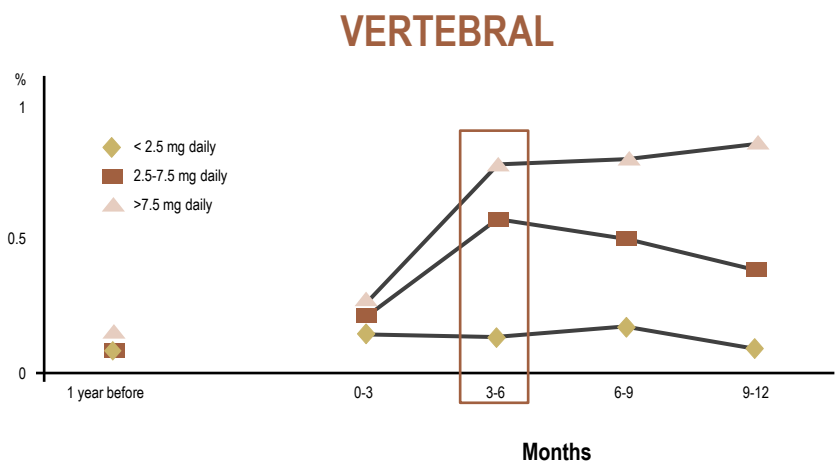
Glucocorticoid-Induced Osteoporosis
Risk of Vertebral Fracture Stratified By Dose



van Staa TP. *Osteoporos Int*. 2002:13;777-787.

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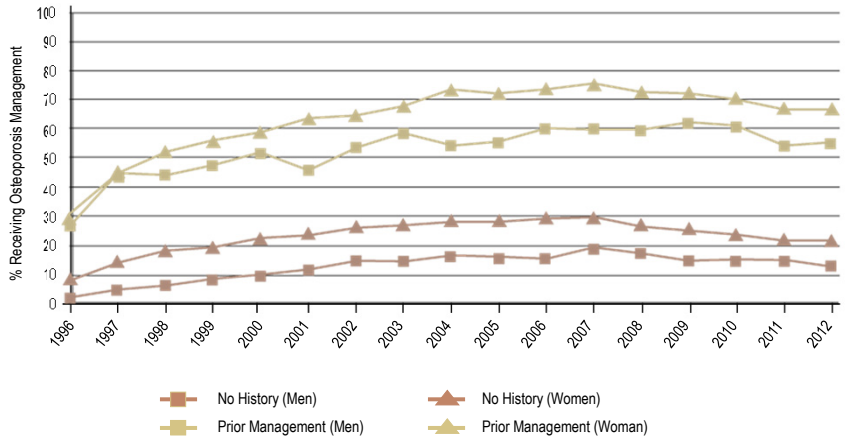
Glucocorticoid-Induced Osteoporosis

Management among Seniors, by year, sex, and indication, 1996–2012

72,099 men and 95,975 women starting chronic oral GC therapy (mean age=74.9 years, SD=6.5)



Albaum JM et al Osteoporos Int 2015; 26:2845–2852

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Approved Pharmacological Interventions for the Management of GIOP

INTERVENTION	DOSING REGIMEN	ROUTE OF ADMINISTRATION
Alendronate	5 or 10 mg once daily 70 mg once weekly[a]	Oral
Etidronate[b]	400 mg daily for 2 weeks every 3 months	Oral
Risedronate	5 mg once daily 35 mg once weekly[a]	Oral
Zoledronic acid	5 mg once yearly	Intravenous infusion
Denosumab	60 mg every 6 months	Subcutaneous injection
Teriparatide	20 µg once daily	Subcutaneous injection

[a] Only once-daily dosing regimens are approved for GIOP

Adapted form Compston J. Nat Rev Rheumatol 2010;6(2):82-8.

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Cohort Analyses: Effectiveness of Oral BPs in Reducing Fracture Risk Among Glucocorticoid Users

Matched cohort analyses comparing benefit of oral BPs in reducing fracture risk in GIOP in cohort of new oral GC users

	Hip fracture risk	Vertebral fracture risk	Forearm/ humerus fracture risk
Alendronate	HR = 0.46 95% CI 0.25-0.80	HR = 0.52 95% CI 0.39-0.68	No risk reduction
Etidronate	N/A	HR = 0.59 95% CI 0.48-0.73	No risk reduction
Risedronate	HR = 0.58 95% CI 0.36-0.90	HR = 0.47 95% CI 0.36-0.60	No risk reduction
Results were similar between men and women			

CI = confidence interval; GC = glucocorticoid; HR = hazard ratio; BP = bisphosphonates
Amiche MA, et al. *J Bone Miner Res* 2018 Mar;33(3):419-429.

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Bisphosphonates for GIOP

Outcomes	Relative effect RR (95% CI)	#Participants (studies)	Quality of evidence (GRADE)	Comments
Incident VFx	0.57 (0.35 to 0.91)	1343 (12 RCTs)	High	AR 2% fewer NNTB 31 (20 to 145)
Incident NVFx	0.79 (0.47 to 1.33)	1245 (9 RCTs)	Low Risk of bias, imprecision	AR 1% fewer NNTB n/a
Lumbar spine BMD	N/A	2042 (23 RCTs)	Moderate (indirectness)	+ 3.5% (2.9 to 4.1) NNTB 3 (2 to 3)
Femoral Neck BMD	N/A	1665 (18 RCTs)	Moderate (indirectness)	+ 2.06% (1.4 to 2.7) NNTB 5 (4 to 7)
Serious AEs	0.91 (0.74 to 1.12)	1703 (15 RCTs)	Low Risk of bias, imprecision	ARH 0% (2% fewer to 2% more)
Withdrawal due to AEs	1.06 (0.77 to 1.47)	1790 (15 RCTs)	Low Risk of bias, imprecision	ARH 1% (1% fewer to 3% more)

Allen CS, et al. Cochrane Database of Systematics Reviews 2016. Issue 10 CD 001347.

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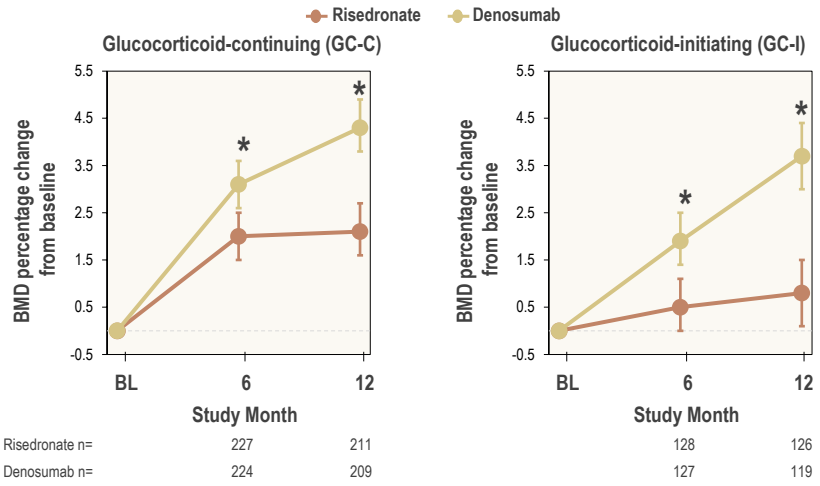
Phase 3: Effect of Denosumab and Risedronate on Glucocorticoid-treated Patients†: Lumbar Spine BMD



n = Number of subjects with observed values at baseline and the time point of interest; *p ≤ 0.002. † glucocorticoids (≥7·5 mg prednisone daily, or equivalent) for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating) before screening. Adapted from Saag K, et al. American College of Rheumatology. ACR, Washington, DC. November 2016.

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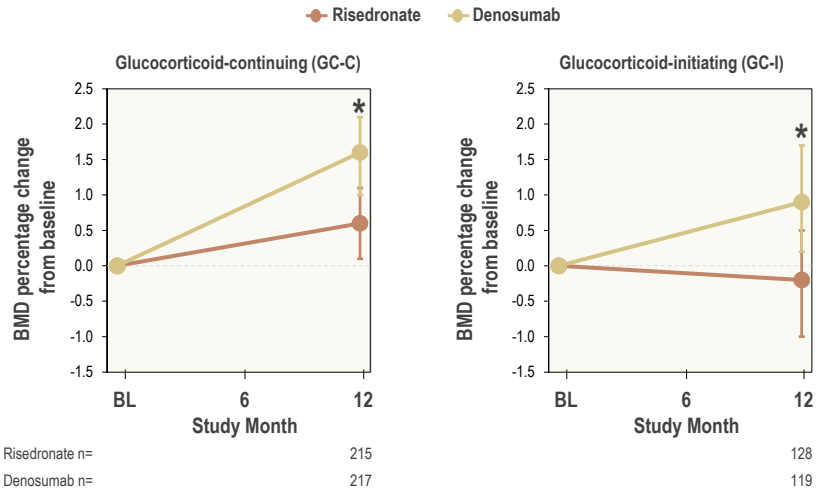
Phase 3: Effect of Denosumab and Risedronate on Glucocorticoid-treated Patients†: Total Hip BMD



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Switching of Oral BPs to Denosumab in Chronic Glucocorticoid Users

- **Switching from oral BP to denosumab* resulted in greater gain of the spinal BMD and suppression of bone turnover markers after 12 months of therapy**
  - → Denosumab group at month 12: BMD of the spine increased by +3.4±0.9% (p=0.002) and +1.4±0.6% (p=0.03) at hip
  - → BP group at month12: BMD of spine +1.5±0.4% (p=0.001) and +0.80±0.5% (p=0.12) at hip

*Randomized, controlled trial in 42 women, n=21 participants per group; mean age 54±12.9 years.
Mok CC, et al. Bone 2015;75:222-8.

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Clinical Vignette

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- Noted height loss (3 cm)
- Femoral Neck T-score: -2.8

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How do you mitigate GIOP risk in your patients?

Which treatment would you select for Ken?

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Discussion: Clinical Takeaways

1. GIOP is the most common form of secondary osteoporosis.
2. GIOP causes biphasic bone loss:
   - → Rapid bone loss of up to 12% during the first 12 months of GC treatment
   - → Followed by slower bone loss of 2-3% annually
3. Vertebral fractures often happen within the first year
4. All adult patients initiated with long-term glucocorticoids (prednisone > 7.5 mg/d for > 3 months should be rapidly (< 3 months):
   - → Assessed for bone health (DXA ± Lateral Spine X-Rays, lab. tests)
   - → Initiated on antiresorptive treatment with Ca/vitamin D
   - → Monitored annually (DXA ± Lateral Spine X-Rays, lab. tests)
5. Patients should be re-assessed periodically to evaluate the need to continue pharmacological treatment.

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