Glucocorticoid induced osteoporosis: overlooked and undertreated?

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Disclosure

- I have no financial disclosure relevant to this presentation

Objectives

Recognize	magnitude of the risk and clinical practice pattern of glucocorticoid induced osteoporosis (GIO)
Understand	the action of glucocorticoid on bone and mineral metabolism
Describe	current treatment options and update on 2017 American College of Rheumatology guideline for prevention and treatment of glucocorticoid induced osteoporosis

Overview

- Glucocorticoid induced osteoporosis (GIO) is the most common cause of secondary osteoporosis
- Up to 1% of adults are treated with glucocorticoids (GC) each year
- The first presentation of GIO may be a fracture
  - 10% of patients who receive long-term GC treatment are diagnosed with a fracture, and 30–40% have radiographic evidence of vertebral fractures

Previous and current GC use is a significant risk factor for fracture

- Meta-analysis included 42,500 men and women from 7 prospectively studied cohorts followed for 176,286 person-years
- The use of GC was associated with a significantly increased risk of any fracture at all ages compared with those with no history of GC use

TABLE 3. RISK RATIO OF ANY FRACTURE AND 95% CIS ASSOCIATED WITH EVER USE OF CORTICOSTEROIDS ACCORDING TO AGE AND ADJUSTED FOR BMD

	Any fracture		*Osteoporotic fracture*		*Hip fracture*	
Age (years)	*Risk ratio*[a]	*95% CI*	*Risk ratio*	*95% CI*	*Risk ratio*	*95% CI*
50	1.98	1.35–2.92	2.63	1.68–4.13	4.42	1.26–15.49
55	1.83	1.35–2.47	2.52	1.63–3.30	4.15	1.50–11.49
60	1.67	1.33–2.09	2.00	1.52–2.62	3.71	1.67–8.23
65	1.56	1.29–1.88	1.81	1.43–2.27	2.98	1.55–5.74
70	1.55	1.30–1.86	1.76	1.42–2.19	2.44	1.37–4.36
75	1.64	1.37–1.97	1.70	1.36–2.11	2.22	1.35–3.63
80	1.62	1.31–2.00	1.59	1.26–2.02	2.13	1.39–3.27
85	1.66	1.26–2.17	1.71	1.29–2.28	2.48	1.58–3.89
All ages	1.57	1.37–1.80	1.66	1.42–1.92	2.25	1.60–3.15
All ages[b]	1.53		1.61		2.13	

[a] Ever use vs. no use.
[b] Ever use vs. population risk.

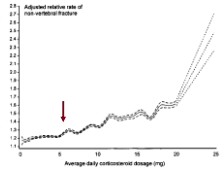
Kanis, JMBR 2004

Dose dependent effect of GC on fracture risk

- Examined fracture risk in the general practice research database of the UK, where 250,000 GC users were compared with age and sex-matched controls

TABLE 2. INCIDENCE OF FRACTURES STRATIFIED BY DAILY DOSE

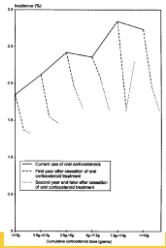
	Dose category					
	Low (n = 50 640)		Medium (n = 104 833)		High (n = 87 949)	
Fracture site	Rate (per 100 person-years)	Adjusted relative rate (95% CI)	Rate (per 100 person-years)	Adjusted relative rate (95% CI)	Rate (per 100 person-years)	Adjusted relative rate (95% CI)
Non-vertebral	1.6	1.0	2.2	1.18 (1.11–1.26)	2.6	1.44 (1.34–1.54)
Forearm	0.4	1.0	0.4	0.99 (0.88–1.13)	0.4	1.00 (0.85–1.17)
Hip	0.2	1.0	0.4	1.62 (1.32–1.98)	0.5	2.21 (1.75–2.64)
Vertebral	0.1	1.0	0.4	1.74 (1.29–1.86)	0.6	2.83 (2.35–3.46)



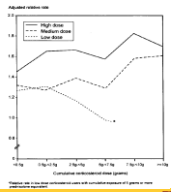
Low <2.5 mg of prednisone or its equivalent
Medium 2.5-7.5 mg of prednisone or its equivalent
High 7.5 mg daily dose of prednisolone or its equivalent

Van Staa, Rheumatology 2000

Fracture risk is strongly related to daily GC dose rather than cumulative dose



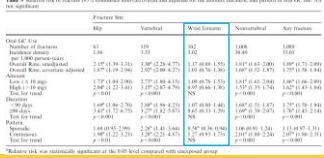
- Risk of non-vertebral fracture increased with higher cumulative dose
- Incidence of non-vertebral fracture decreased abruptly after GC cessation irrespectively with prior cumulative dose
- Risk of non vertebral fracture was strongly related to higher daily dose rather than cumulative dose



Van Staa, Rheumatology 2000

Combination of higher dose, longer duration & continuous pattern of GC use further increased fracture risk

- Retrospective cohort using claim database
- The most significant combination of >10 mg per day, >90 days use, and continuous pattern led to an RR of 7.16 (95% CI, 2.13-24.0) for the hip and 16.94 (95% CI, 8.17-35.11) for the vertebrae *vs.* those unexposed to oral



Wrist/forearm fractures were not significantly associated with oral GC exposure

Steinbuch Osteoporosis Int 2004

Suboptimal BMD measurement and GIO treatment in high risk populations

- Characterized GC use and osteoporosis screening and treatment patterns within a large U.S. health maintenance organization (HMO) 2000-2001
- Retrospective cohort study (n=3,031) used the HMO's EMR to identify patients who were dispensed the equivalent of >5 mg of prednisone per day for at least 90 days
- % who received a BMD measurement prior and within 6 mo after GC prescription
- % dispensed an osteoporosis medication within 6 months before or after GC prescription

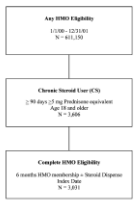
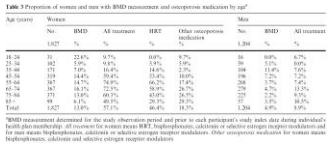


Fig. 1 Population selection for chronic steroid users

Feldstein Osteoporos Int 2005

Suboptimal BMD measurement and GIOP treatment in high risk populations

- Mean daily dose of GC was 20 mg of prednisone equivalents
- 8.9% had a diagnosis of osteoporosis documented at a visit or on the patient's problem list, and 9.3% had a fracture during their plan membership prior to GC index date
- Only 9.8% of the total population received a BMD measurement
- Only 38% of the population was dispensed osteoporosis medications within 6 months before or after GC prescription



Feldstein Osteoporos Int 2005

Modest improvement of GIO preventive care

- Population based cohort in Manitoba, Canada
- Examined high quality GIO preventive care in newly initiated long term (>90 d) GC treatment between 1998-2008
- High-quality GIOP preventive care
  - the composite of BMD testing or osteoporosis treatment within 6 months of starting GC
- 17,736 new long-term glucocorticoid initiations
- GIO prevention remains suboptimal
  - only 25% of those starting long-term GC received BMD test or were treated for osteoporosis within 6 months

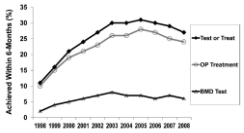


FIG. 1. Temporal trends in osteoporosis (OP) management among new initiations of long-term systemic glucocorticoids (1998–2008).

Majumdar JCEM 2012

High quality GIO preventive varied

- High-quality GIO preventive care varied significantly by
  - age (16% for those 50 yr *vs.* 27% for those 70 yr; aIRR 0.57; 95% CI 0.52–0.63)
  - sex (13% for men *vs.* 34% for women; aIRR 0.40; 95% CI 0.37–0.43)
  - prescriber (23% general practice *vs.* 44% Rheumatology aIRR 0.56; 95% CI 0.52–0.60)

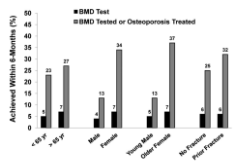


FIG. 2. Associations between quality of glucocorticoid preventive care and age, sex, and previous fracture history: exploratory analyses.

Majumdar JCEM 2012

Cared by rheumatologists are likely to receive intervention

- Using data from health care plan

Table 2. Patient Education, Screening, and Treatment for Osteoporosis of Study Subjects*

	Calcium†	Vitamin D‡	Exercise§	Bone Mineral Density‖	Drug Therapy¶	Any Intervention#
Women (n = 128)	66 (52)	64 (50)	26 (16)	55 (43)	45 (35)	97 (76)
Men (n = 96)	22 (23)	19 (20)	14 (15)	14 (15)	10 (10)	42 (44)
Total (N = 224)	88 (39)	83 (37)	34 (15)	69 (31)	55 (25)	139 (62)

Table 3. Patient Education, Screening, and Treatment for Osteoporosis of Study Subjects by Specialty of the Prescribing Physician*

Specialty	Calcium	Vitamin D	Exercise	Bone Mineral Density	Drug Therapy	Any Intervention
Rheumatology (n = 69)	44 (64)	44 (64)	16 (23)	39 (57)	27 (39)	62 (90)
Internal medicine (n = 60)	16 (27)	11 (18)	8 (13)	6 (10)	11 (18)	29 (48)
Pulmonary (n = 47)	17 (36)	16 (34)	5 (11)	13 (28)	11 (23)	26 (55)
All others (n = 48)	11 (23)	12 (25)	5 (10)	15 (31)	6 (13)	22 (46)

Yood JAMA 2001

Barriers in management of GIO

- Assess clinicians' knowledge of GIO clinical guidelines and perceptions of GIO management, primary care clinicians and subspecialists completed a questionnaire and participated in focus groups at academic VA medical center, VA Greater Los Angeles Healthcare System in West Los Angeles, California
- Characterized provider knowledge, beliefs, and practice behaviors regarding the prevention and management of GIOP in veterans
- Clinicians attended 1 of 4 focus groups lasting 45–60 minutes that were facilitated by a social worker trained in group dynamics. A clinical scenario was presented first to stimulate discussion.

Guzman-Clark, Arthritis & Rheumatism 2007

Barriers in management of GIO

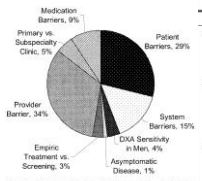


Figure 1. Most frequently identified barriers. DXA = dual-energy x-ray absorptiometry.

Table 3. Most frequently identified barriers to glucocorticoid-induced osteoporosis prevention and treatment*

Specific categories	Examples
Provider barriers	
Poor knowledge	"They're probably out there [guidelines] but I don't even know if anyone ever actually peruses them."
Other priorities	"You're basically just focusing on their chief complaint."
Limited time	"We don't have sufficient time really to even address all the problems at every visit."
Patient barriers	
Attitude regarding asymptomatic disease	"They like some treatment when things happen. They're not so great with prevention."
Nonadherence	"They can't feel their osteoporosis."
Effects of comorbid conditions	"I think in our population the compliance is low to begin with . . . for something like prevention, it's probably even lower."
	"Other barriers might be . . . somebody who is taking thyroid medications. Obviously that cannot be stopped . . ."
System barriers	
Obtaining DXA	"That has to be scheduled and coordinated. . . . You order it and pray it gets done."
Restricted drugs	". . . until pretty recently, I couldn't order Fosamax."
Computerized ordering system	"It is so time consuming . . . you really have to focus for 5 minutes on clicking the right things, that your brain can't be free."

Guzman-Clark, Arthritis & Rheumatism 2007

Potential interventions for GIO

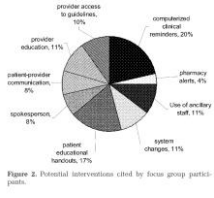


Figure 2. Potential interventions cited by focus group participants.

Table 4. Potential interventions to improve management of glucocorticoid-induced osteoporosis*

Categories	Examples
Computerized clinical reminders	". . . the computer rolls up how many days the patient has been on steroids over the past year and it will come up with a clinical reminder that the patient has exceeded a certain number. . ."
Patient educational handouts	"If you had a simple 1-page reminder for the patients . . . which would tell why they are at risk and how it could be prevented . . ."
System changes	". . . if it's [DXA] more readily available and easier, patients will be more willing to get that done if they're at risk."
Ancillary staff	"If we had one extra person who would be willing to take the patient down [to get DXA] . . . it would be a lot easier."
Provider education	"I think a medical grand rounds format would be good because it would get not just the residents but the attending staff also . . ."
Provider access to guidelines	"Say if it were even made into a palm pilot or something like that, a little table or a card . . . in a concise format with some of the guidelines and treatment and so forth . . . would probably be used."
Patient-provider communication	". . . probably individual counseling, just a few sentences really quick about that would . . . probably make the most difference."
Spokesperson	". . . there is a superstar attached to it, they'll say, oh yeah, that's what so-and-so has. I see that they sort of make that connection."
Pharmacy alerts	". . . the pharmacist who dispenses medication notices that this patient is on steroids for . . . x number of months and just automatically sends you a reminder."

Guzman-Clark, Arthritis & Rheumatism 2007

Why are we doing so poorly?

- Quality of care for GIO is still suboptimal although it has modestly improved over the recent years
- Older women, higher dose steroid, previous history of fracture, physician specialty (rheumatologist) prescriber are likely to receive GIO preventive care
- Major gap between guideline recommendations and actual clinical practice
  - *Lack of awareness of the problem*
  - *Lack of awareness of the treatment guidelines*
  - *The guidelines are confusing*
  - *The guidelines are hard to implement*
  - *Lack of adequate data on cost-effectiveness of prevention and treatment of GIO, especially in premenopausal women and younger men*
  - *Patients may not accept treatment*
- Efforts should be built to reduce the barriers to such treatment and increase the proportion of patients given preventive care

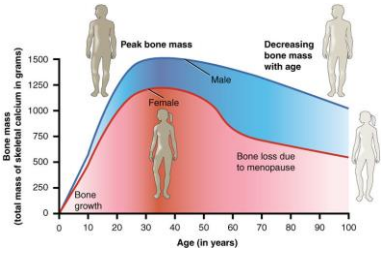
Yood, J Rheum 2006

Understanding GIO pathophysiology

Risk factors of GIO

Risk Factor	Evidence of a Contribution
Advanced age	Patients 60 to 80 years of age receiving glucocorticoid therapy, as compared with patients 18 to 31 years of age, had a relative risk of vertebral fracture of 26 and a shorter interval between initiation of treatment and the occurrence of fracture[8]
Low body-mass index (<24)†	Low body-mass index is a risk factor for glucocorticoid-induced osteoporosis and probably fractures as well[11]
Underlying disease	Rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, chronic pulmonary disease, and transplantation are independent risk factors[4]
Prevalent fractures, smoking, excessive alcohol consumption, frequent falls, family history of hip fracture	All are independent risk factors for osteoporosis but have not been extensively studied in patients receiving glucocorticoids
Glucocorticoid receptor genotype	Individual glucocorticoid sensitivity may be regulated by polymorphisms in the glucocorticoid receptor gene[10]
Increased 11β-HSD1 expression	11β-HSD1 expression increases with the age of the patient and with glucocorticoid administration[9,11]
High glucocorticoid dose (high current or cumulative dose; long duration of therapy)	Risk of fracture escalates with increased doses and duration of therapy; alternate-day or inhaled therapies also confer risks of glucocorticoid-induced osteoporosis[9,12]
Low bone mineral density	Glucocorticoid-induced fractures occur independently of a decline in bone mass, but patients with very low bone mineral density may be at higher risk[1,4]

Weinstein, NEJM 2011



Age related bone loss occurs at rate of 0.5%-1.0% per year
During menopause, bone loss accelerates 1-2% per year

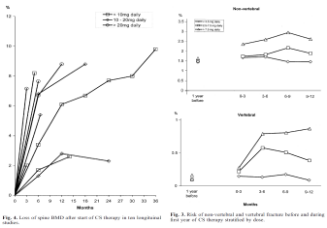
Glucocorticoid induced osteoporosis

- Predominantly affects regions of the skeleton that have abundant cancellous bone, such as the lumbar spine and proximal femur
- Biphasic bone loss
  - Occur rapidly 6-12% within the first year
  - Slower approximately 3% yearly thereafter
- The risk of fracture escalates by as much as 75% within the first 3 months after the initiation of therapy, typically before there is a substantial decline in bone mineral density, suggesting that there are adverse effects of glucocorticoids on bone that are not captured by bone densitometry

Weinstein, NEJM 2011

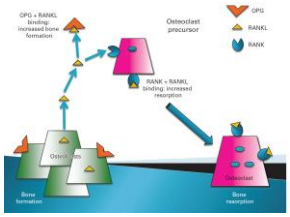
Bone loss and fracture occur early

- Meta-analysis of 56 cross-sectional studies and 10 longitudinal studies, can be 5-15% during the first year of treatment
- The main determinant of BMD at any time is the cumulative dose although some study found more strong relationship with daily dose



Van Staa Osteoporos Int 2002

Bone remodeling

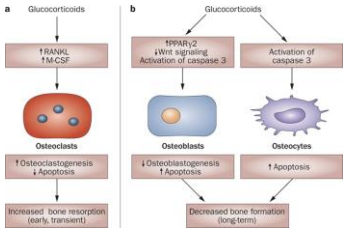


Lustberg, JCO 2012

Glucocorticoid uncoupling bone remodeling

- Early effects -- increase bone resorption
  - Increase renal calcium wasting
  - Reduce intestinal calcium absorption
  - Promote osteoclastogenesis by increase RANKL and decrease OPG (osteoprotegerin)
- Late effects -- profoundly reduce bone formation
  - Decrease osteoblast proliferation and differentiation by inhibit gene for osteocalcin, type 1 collagen and IGF-1
  - Increase osteoblast apoptosis

Direct effects of glucocorticoids on bone



Compston, *Nat Rev Rheumatol* 2010

Glucocorticoid potency and effect

Name	Equivalent dose (mg)	Anti-inflammatory potency	Duration of action (hrs)*
Cortisol (hydrocortisone)	20	1	8-12
Cortisone	25	0.8	8-12
Prednisone	5	4	12-36
Prednisolone	5	4	12-36
Methylprednisolone	4	5	12-36
Triamcinolone	4	5	12-36
Betamethasone	0.75	25	36-72
Dexamethasone	0.75	25	36-72
Fludrocortisone†	—	10	12-36

Data from Axelrod[3] and Nierman.[32]
*Short acting, 8-12 hours; intermediate acting, 12-36 hours; and long acting, 36-72 hours.
†Not used for glucocorticoid effects.

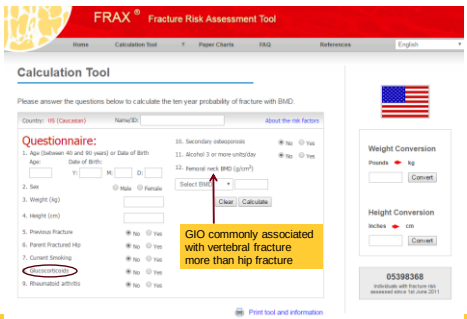
Other Glucocorticoid effects

- Decrease
  - IGF1 synthesis
  - Gonadal steroid production
  - Muscle mass and strength
  - Physical activity

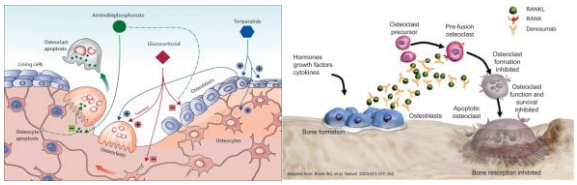
Evaluation

- BMI
- Height measurement
- Lab: 25-hydroxyvitamin D, PTH, calcium and creatinine
- Bone turnover: not usually helpful as glucocorticoid suppressed bone turnover
- DXA and/or VFA (vertebral fracture assessment)
- FRAX
  - Estimate the 10-year risk of hip and other major fractures (clinical spine, humerus or wrist fracture) based on clinical risk factors, with or without BMD
  - **Limited as it does not take current, accumulation dose of glucocorticoid and duration of treatment so FRAX is likely to underestimate the risk of osteoporosis.**

Weinstein, NEJM 2011



Options of treatment



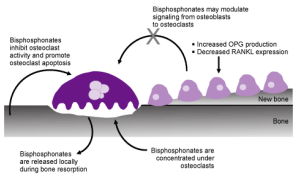
Treatment of GIO

Table 2. Treatment of Glucocorticoid-Induced Osteoporosis.[a]

Intervention	Advantages	Disadvantages
Bisphosphonates		
Alendronate, 10 mg/day or 70 mg/wk, taken orally Risedronate, 5 mg/day or 35 mg/wk, taken orally	Osteoclast inhibition reduces bone loss and reduces vertebral fractures in patients with glucocorticoid-induced osteoporosis; alendronate also prevents glucocorticoid-induced osteocyte apoptosis; if glucocorticoid therapy is discontinued, these drugs can be stopped	Antiresorptive agents do not directly address the decreased bone formation that is characteristic of glucocorticoid-induced bone disease and have not been shown to reduce hip fractures; gastrointestinal side effects may occur; musculoskeletal discomfort, osteonecrosis of the jaw, uveitis, and atypical femoral fractures have occurred in rare cases; bisphosphonates should be avoided in patients with creatinine clearance of ≤30 ml/min; patients have poor adherence to oral therapy; as compared with intravenous therapy, a longer time is required to obtain skeletal protection
Zoledronic acid, 5 mg/yr, given intravenously	Osteoclast inhibition reduces bone loss; as compared with oral treatment, there is increased adherence to intravenous treatment and more rapid onset of skeletal effects; gastrointestinal side effects are unlikely	Acute-phase reaction (influenza-like syndrome) may occur within 2 to 3 days and last 3 days or less, particularly after first dose,[81] but can be effectively managed with acetaminophen or ibuprofen
Teriparatide, 20 μg/day, given subcutaneously, for 2 years, followed by bisphosphonate treatment for as long as glucocorticoids are required	Teriparatide directly addresses the increase in osteoblast and osteocyte apoptosis and the decrease in osteoblast number, bone formation, and bone strength that are characteristic of glucocorticoid-induced osteoporosis and reduces vertebral fractures	Costs are greater than with oral or intravenous bisphosphonates; daily injections are required; response is reduced when teriparatide is given with high-dose glucocorticoids; it has not been studied in patients with elevated parathyroid hormone levels; adverse effects include mild hypercalcemia, headache, nausea, leg cramps, and dizziness; caution must be taken in patients with preexisting nephrolithiasis; serum calcium should be checked at least once 16 hours or more after injection and oral calcium intake adjusted as needed[82]

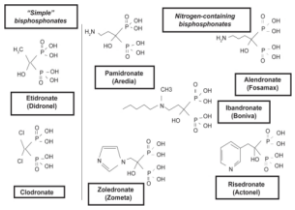
Weinstein, NEJM 2011

Bisphosphonates



Bisphosphonates

- The molecular structure of the bisphosphonates (P-C-P) is analogous to pyrophosphates (P-O-P), with two short side chains (R1 and R2) attached to the C core
- Bind avidly to bone with no substantial affinity with other tissues
- 40-60% of the dose distributed to bone, the remainder excrete unchanged in the urine
- No substantial metabolism



Bisphosphonates

- Cochrane reviewed bisphosphonate for prevention and treatment of glucocorticoid induced fracture and bone loss (27 RCTs with 3075 participants in the review)
  - 46/597 people experienced new vertebral fractures in the control group *vs.* 31/746 in the bisphosphonate group;
    Relative improvement of 43% (9% to 65% better) with bisphosphonates;
    NNTB was 31 meaning that 31 people would need to be treated with bisphosphonates to prevent new vertebral fractures in one person
- Bisphosphonates are beneficial in preventing new spinal fractures but not in nonvertebral fracture and preventing and treating steroid-induced bone loss at the lumbar spine and femoral neck
- Bisphosphonate groups reported stabilization or increase in BMD, while the control groups showed decreased BMD over the study period
  - At the lumbar spine, absolute increase in BMD of 3.5% with bisphosphonates
  - At the femoral neck, absolute increase in BMD was 2.06% in bisphosphonates

Allen Cochrane review 2016

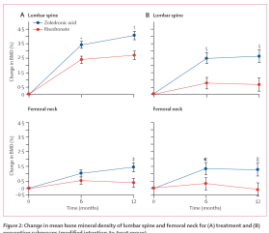


Figure 2: Change in mean bone mineral density of lumbar spine and femoral neck for (A) treatment and (B) prevention subgroups (modified intention-to-treat group)

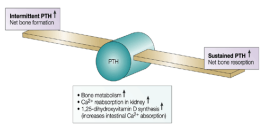
Data are least-squares mean. Error bars=95% CI. BMD=bone mineral density. p values compare change in bone mineral density relative to baseline between drug groups, calculated from a three-way analysis of variance with adjustment for drug group, study region, and sex. *p<0·0001. †p<0·0001. ‡p<0·0050. §p<0·0001. ¶p<0·0150. ‖p<0·0045.

Bisphosphonates

- Alendronate increased BMD at the lumbar spine and femoral neck (~3.9% and 0.6%) and reduced the relative risk of glucocorticoid-induced vertebral fractures by ~40%
  - patients in these trials typically had been taking 10 to 20 mg of prednisone daily or the equivalent for at least 1 year before enrollment
  - most trials were only 12 to 24 months in duration and were not powered to study hip fractures
- HORIZON – compared zoledronic acid *vs.* residronate for prevention and treatment for 12 months

Reid Lancet 2009

Teriparatide



- Anabolic hormone
- Recombinant human parathyroid hormone (1-34) – analog to PTH
- Stimulates bone formation, increases bone mass, and reduces the risk of vertebral and nonvertebral fractures

Teriparatide *vs.* Alendronate

- 18-month randomized, double-blind, controlled trial, compared teriparatide with alendronate in 428 women and men with osteoporosis (ages, 22 to 89 years) who had received GC for at least 3 months (prednisone equivalent, 5 mg daily or more)
- BMD increased more in patients receiving teriparatide than in those receiving alendronate
- Fewer new vertebral fractures in teriparatide
- Non significant incidence in nonvertebral fracture

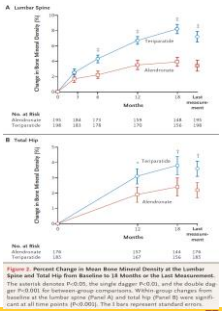


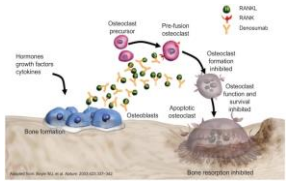
Figure 2. Percent Change in Mean Bone Mineral Density at the Lumbar Spine and Total Hip from Baseline to 18 Months or the Last Measurement.

*The asterisk denotes P<0.05, the single dagger P<0.01, and the double dagger P<0.001, for between-group comparisons. Within-group changes from baseline at the lumbar spine (Panel A) and total hip (Panel B) were significant at all time points (P<0.001). The I bars represent standard errors.

Saag NEJM 2007

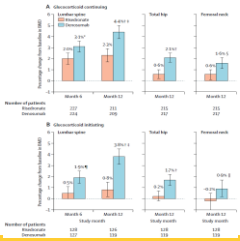
Denosumab

- Human monoclonal antibody against RANKL. After binding to RANKL, it prevents RANKL from binding to receptor, which is necessary for the formation and function of osteoclasts, and therefore inhibits osteoclast activity



Denosumab *vs.* Residronate

- 24-month, double-blind, active-controlled, double-dummy, non-inferiority study
- Receiving glucocorticoids (≥7.5 mg prednisone daily, or equivalent) for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating)
- Denosumab was non-inferior and superior to risedronate in increasing BMD at the lumbar spine at 12 months in patients already taking or newly initiating glucocorticoid therapy. Superiority of denosumab over risedronate was also shown at the total hip.
- Serious infection were similar in both groups



Saag NEJM 2007

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Lenore Buckley,[1] Gordon Guyatt,[2] Howard A. Fink,[3] Michael Cannon,[4] Jennifer Grossman,[5] Karen E. Hansen,[6] Mary Beth Humphrey,[7] Nancy E. Lane,[8] Marina Magrey,[9] Marc Miller,[10] Lake Morrison,[11] Madhumathi Rao,[12] Angela Byun Robinson,[13] Sumona Saha,[6] Susan Wolver,[14] Raveendhara R. Bannuru,[12] Elizaveta Vaysbrot,[12] Mikala Osani,[12] Marat Turgunbaev,[15] Amy S. Miller,[15] and Timothy McAlindon[12]

Buckley, Arthritis and Rheumatology 2017

Initial fracture risk assessment

- Initial clinical fracture risk assessment should be performed asap, but at least within 6 months of the initiation of long-term GC treatment
- This assessment should include
  - History with the details of GC use (dose, duration, pattern)
  - Evaluation for falls, fractures, frailty, and
  - Other risk factors for fracture (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [>3 units/day] or smoking)
  - Other clinical comorbidities
  - Measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis)

Buckley, Arthritis and Rheumatology 2017

Risk Stratification

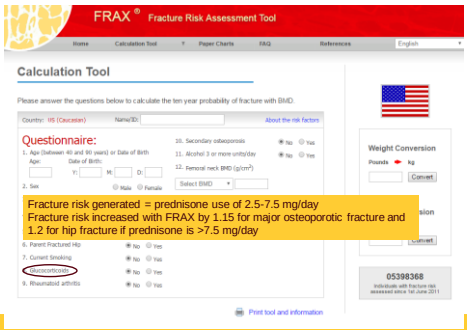
ACR 2017

Table 1. Fracture risk categories in GC-treated patients

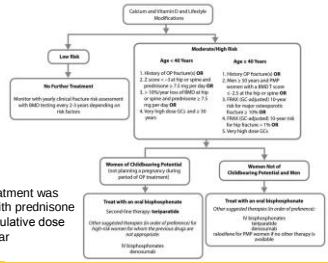
	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤ −2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https/www.shef.ac.uk/FRAXtool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

Buckley, Arthritis and Rheumatology 2017



Treatment Recommendation



Very high-dose GC treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year

Adults on very high dose GC

Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year)

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional antifracture benefits from other OP medications.

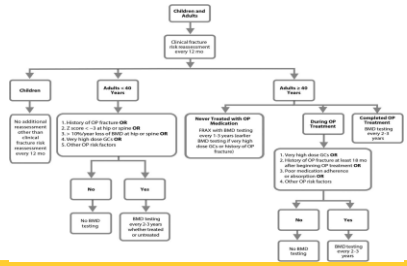
If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and <40 years) in Table 2.

Conditional recommendations because of low-quality evidence on absolute fracture risk and harms in this population

General recommendation

- Optimizing calcium intake (1,000-1,200 mg/day)
- Vitamin D intake (600–800 IU/day; serum level >20 ng/ml)
- Lifestyle modifications
  - a balanced diet
  - maintaining weight in the recommended range
  - smoking cessation
  - regular weightbearing or resistance training exercise
  - limiting alcohol intake to 1–2 alcoholic beverages/day

Reassessment every 12 months



Follow-up treatment recommendation

Table 4. Recommendations for follow-up treatment for prevention of GIOP*

Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year)

Treat with another class of OP medication (teriparatide or denosumab) or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence: with calcium and vitamin D over calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate.

Conditional recommendation because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation.

Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture

Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate (if concern with regard to adherence or absorption) or switch to an OP treatment in another class) over calcium and vitamin D alone.

Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture

Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication.

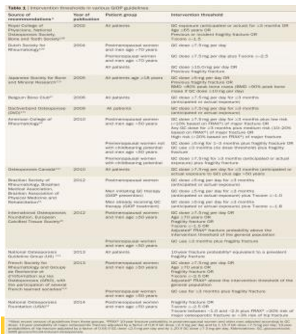
Conditional recommendation made by expert consensus; evidence informing it too indirect for the population and very low-quality

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture

Complete the treatment with the OP medication over discontinuing the OP medication.

Strong recommendation for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D

Conditional recommendation for moderate-risk patients because of lower fracture risk compared to potential harms



Intervention thresholds in various GIO guidelines

Rizzoli, R, *Nat. Rev. Rheumatol* 2014

Current guidelines

- Difference in treatment threshold between GIO guidelines
- Fracture data are very limited in GIO-specific clinical trials and population studies
- New 2017 ACR guideline is still complicated
- FRAX tool is not perfect to estimate fracture risk in GIO
  - FRAX using hip BMD not spine BMD
  - validity of FRAX fracture risk estimates after pharmacologic treatment

Conclusions

- GIO is a second most common cause of secondary osteoporosis and still be a serious health problem
- Populations with, or at risk of, GIO are defined on the basis of dose and duration of GC therapy, bone mineral density and other risk factors or co-morbidities
- Despite available, effective preventive measures, many patients receiving or initiating GC therapy are not appropriately evaluated and treated for bone health and fracture risk.
  - **Patient barriers** may include lack of knowledge about their risk, frailty due to the underlying illness for which the glucocorticoid was prescribed, hesitance to take additional medication or medication cost.
  - **Clinician barriers** may include lack of experience with osteoporosis medications/treatments, lack of time and lack of access to integrated patient information and decision-making support for patients with multiple conditions
  - **Improving the management of GIOP will likely require a fundamental redesigning of care processes for this disorder in order to overcome provider, patient-related, and system barriers.**

Conclusions

- Patients with GIO should be evaluated and treated as early as possible; however, diversity remains in intervention thresholds and management guidelines.
- Available anti-osteoporotic therapies such as anti-resorptives including bisphosphonates and the bone anabolic agent teriparatide are effective for the management of GIO, although the data on fracture risk is limited.

Thank you