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Prevention and Treatment of Bone Changes Associated with Exposure to Glucocorticoids

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Abstract

Rheumatologic diseases are associated with a pro-inflammatory state which is thought to lead to many of the bone changes seen in treatment-naïve patients. However, glucocorticoids remain a common treatment option for rheumatologic diseases and are known to have a negative impact on bone through direct effects on bone cells and indirect effects on calcium absorption. Despite the anti-inflammatory effect of glucocorticoids, fracture risk rises within the first three months of treatment. As such, osteoporosis prevention and treatment need to be considered in all patients started on chronic glucocorticoids (≥ 3 months of treatment). For very low risk patients, conservative management with non-pharmacologic strategies may be appropriate. For the moderate to high fracture risk patients treated with glucocorticoids, pharmacologic treatment with one of the four approved medications should be considered. The challenge of educating physicians and patients of the risks of glucocorticoid induced osteoporosis remain.

Keywords

Osteoporosis; Glucocorticoid; Treatment; Teriparatide; Bisphosphonates; Calcium; Vitamin D; Rheumatoid Arthritis; Lupus; Ankylosing Spondylitis

Introduction

Patients with rheumatologic diseases frequently receive glucocorticoids in attempt to control the disease and the associated symptoms. Glucocorticoids have both a direct and indirect effect on bone, leading to increased fragility and fracture risk. However, many underlying rheumatologic diseases are also associated with an increased fracture risk independent of the glucocorticoids. However, bone changes occur quickly after glucocorticoid initiation and it is estimated that up to half of patients treated with long-term glucocorticoids will fracture¹. Fracture risk increases with both the duration and the dose of glucocorticoid. The fracture risk also rises before changes are seen on imaging studies or by Dual-energy X-ray

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Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Absorptiometry (DXA). Therefore, glucocorticoid induced osteoporosis (GIOP) needs to be considered at the time of glucocorticoid initiation. Although non-pharmacologic treatments lend some benefit in fracture risk reduction, prescription GIOP treatments should be considered in all but the lowest risk patients. A main challenge is improving physician and patient awareness of the risks associated with GIOP.

Bone Changes in Rheumatic Diseases Independent of Glucocorticoids

It has been well described that bone changes occur in Rheumatoid Arthritis (RA) independent of glucocorticoid use and that these changes are associated with an increased risk of fracture. Recent findings have linked these bone changes that favor increased fragility to local and generalized inflammatory processes. Pro-inflammatory cytokines that are present in RA, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-17, upregulate the production of receptor activator of nuclear factor- κ B ligand (RANKL), which stimulates osteoclast production and activation²⁻⁴. Furthermore, osteoblast activation is likely altered due to the production of dickkopf-1 (DKK-1) and sclerostin, which alter Wnt-signaling⁵.

Beyond RA, it is now understood that disease-specific bone changes also occur in patients with Systemic Lupus Erythematosus (SLE). Similar to RA, SLE is associated with increased production of pro-inflammatory cytokines that affect the RANKL pathway⁶. Bone micro-architecture and strength may be modified in patients with SLE, even if untreated with glucocorticoids⁷. In addition to direct effects from SLE, indirect effects from the use of other medications may play a role in SLE-related bone disease. This is particularly true of hydroxychloroquine, which is thought to suppress the activity of 1- α -hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D to the active metabolite, 1,25-dihydroxy vitamin D.

Other rheumatologic diseases are also associated with an increased risk of fractures, but less is known about the underlying cause. In Ankylosing Spondylitis (AS), vertebral fracture risk is greatly increased with much lower fracture risk noted at other sites⁸. However, similar to RA and SLE, TNF- α is elevated in AS and may impact bone health through the RANKL pathway^{9,10}, a theory supported by improvements in bone mineral density among AS patients treated with TNF-inhibitors¹¹.

As a result of the majority of the disease-specific bone changes being linked to inflammation, one may conceive that glucocorticoids used at anti-inflammatory doses may infer bone protection. However, despite a reduction in inflammation, the detrimental effects on bone predominately outweigh the effect of reduced inflammation and fracture risk rises with the initiation of these glucocorticoids at supraphysiologic doses. However, similar to what has been observed in AS, TNF- α inhibitors appear to be modestly beneficial on bone turnover and bone mineral density when used in patients with RA and spondyloarthropathies¹².

Glucocorticoid Effect on Bone

Glucocorticoids remain the most common cause of iatrogenic osteoporosis and the second most common type of osteoporosis overall, behind postmenopausal osteoporosis. The detrimental effect of glucocorticoids on bone is largely due to a reduction in bone formation coupled with persistent bone destruction and increased osteocyte and osteoblast apoptosis¹³. Indirect effects of glucocorticoids on calcium absorption also play a role. The majority of these changes occur at a microarchitectural level and bone mineral density (BMD) measurement frequently will not be able to detect these initial changes in bone quality. These occult changes are likely responsible for early bone fragility seen within the first few months of glucocorticoid use, especially at sites rich in trabecular bone, such as the femoral neck and lumbar spine. It is currently thought that the bone changes in response to glucocorticoid exposure are biphasic, with an initial phase associated with rapid bone loss in the first year and then a slowing in subsequent years¹⁴.

Prevention and Treatment of Glucocorticoid Induced Osteoporosis

Non-pharmacologic Treatment

Although fracture risk is increased in all patients started on glucocorticoids, the classical osteoporosis risk factors, such as increased age, female sex, thin stature, tobacco and alcohol use, and lower BMD, further heighten fracture risk in the glucocorticoid-treated population. In addition, as noted above, certain medications can affect vitamin D metabolism. Stored vitamin D (25OH-vitamin D) may already be compromised due to sun avoidance in patients with skin sensitivity due to the underlying disease. As such, all patients receiving glucocorticoid treatment should receive counseling on smoking avoidance, alcohol limits, weight-bearing exercise, and appropriate calcium and vitamin D supplementation.

The Institute of Medicine (IOM) published recommendations for calcium and vitamin D supplementation in 2011¹⁵. In these updated recommendations, Recommended Dietary Allowances (RDA) for calcium intake is between 1000–2000 milligrams per day and for vitamin D between 600–4000 international units per day for adult men and women. Similarly, the U.S. Preventive Services Task Force (USPTF) published recommendations in 2013 and recommended calcium intake of 1000–1200 milligrams per day and vitamin D 600–800 international units per day for adult men and women¹⁶.

The more conservative USPTF recommendations highlight the recent concern of overuse of calcium supplementation. In a cross-sectional study of 11,035 patients in Spain, calcium supplementation was inappropriately recommended in 86% of patients¹⁷. The reasons for improper calcium recommendations were largely related to excessive consumption, in addition to inappropriate doses and the lack of combination with vitamin D. This study is a good reminder of the importance of assessing dietary calcium intake. Dietary calcium sources are better absorbed and if the daily intake is sufficient, this will obviate the need for further supplementation.

Pharmacologic Treatment

Bone changes associated with supraphysiologic glucocorticoid use is rapid and, thus, the potential for GIOP needs to be considered at the time of glucocorticoid initiation if a patient is expected to be continued on glucocorticoids for 3 months or longer. Fractures are possible, even in patients with normal BMD and without a change in BMD. There are several pharmacologic agents that have been well studied and approved for use in the prevention and treatment of GIOP (Table 1).

The American College of Rheumatology updated GIOP treatment guidelines in 2010¹⁸. These guidelines integrate absolute fracture risk assessment using the World Health Organization's FRAX calculator¹⁹. However, limitations of the FRAX calculator in estimating the effect of glucocorticoids on fracture risk have been raised²⁰. The International Osteoporosis Foundation and European Calcified Tissue Society are currently developing new GIOP guidelines in hopes of simplifying the treatment recommendations²¹. The European League Against Rheumatism (EULAR) recently released recommendations on the use of medium to high-dose glucocorticoid therapy (>7.5mg but 100mg of prednisone or equivalent daily doses) and management of possible side effects²². These guidelines recommend the use of calcium, vitamin D, and bisphosphonates for most patients treated with these higher doses of glucocorticoids. They also advocate the use of FRAX-based algorithms, as well as the FIGS (fracture risk in GC-induced osteoporosis score) algorithm to assess fracture risk²³. The latter algorithm integrates daily and cumulative glucocorticoid exposures into the fracture risk assessment but is not available as a calculator that can be used clinically and has not been validated in populations outside of the United Kingdom.

First-line Treatment Options

Choosing which bone treatment to use and when to initiate that treatment is dependent on several factors. A bisphosphonate or teriparatide is indicated in older men (age 50 and older) and women (postmenopausal) with calculated fracture risk that is moderate to high, using FRAX or clinical judgment¹⁸. Those patients with lower overall fracture risk pose a greater conundrum. If a patient has a history of a fragility fracture, treatment should be initiated. Otherwise, in younger patients or older patients on lower doses of glucocorticoid (<7.5mg prednisone daily, or equivalent) with normal BMD, monitoring on calcium and vitamin D supplements alone may be appropriate.

Treatment options for GIOP that are approved by the Federal Drug Administration (FDA) are somewhat limited (Table 1). The current options are alendronate, risedronate, zoledronic acid and teriparatide. Teriparatide has proven to be very effective in reducing fracture risk among glucocorticoid users^{24–26} and has, in fact, proven superior to alendronate and risedronate in men and women with GIOP^{24,26}. The high cost of teriparatide relative to bisphosphonates (which now have generic options) has prevented it from being recommended for use, especially first-line use, except in those with very high fracture risk. However, a recent analysis found that teriparatide use is a cost-effective option for first-line use in both GIOP and postmenopausal osteoporosis²⁷.

Another limitation to the use of teriparatide is that it is currently only approved for use for a total of two years in a lifetime. The large randomized controlled trial of teriparatide vs. alendronate in GIOP patients used a 36-month treatment period for teriparatide²⁴. In addition, there have been studies in the treatment of postmenopausal osteoporosis showing the benefit of teriparatide retreatment and cyclical teriparatide in combination with oral bisphosphonates^{28,29}. Combined use of zoledronic acid and teriparatide also showed additive benefit over either treatment alone in women with postmenopausal osteoporosis at very high fracture risk³⁰. These options warrant further study as potential treatment options in GIOP.

Controversies regarding the use of bisphosphonates, particularly for prolonged periods of time, have led some patients and some physicians to be leery of using these medications. The long-term risks that have been associated with bisphosphonate treatment include atypical fractures (subtrochanteric fractures) and osteonecrosis of the jaw (ONJ). The absolute risk of these events is small and over the short run (treatment periods of up to 3 years) the benefits likely far outweigh risks for most patients.

A task force developed by the American Society for Bone and Mineral Research recently updated our understanding of atypical femur fractures based on new evidence reported since the prior report in 2010³¹. In this report, the definition of atypical femur fractures was slightly revised and the risk of atypical femur fractures was estimated to be between 3.2 – 50 cases/100,000 persons overall and up to 100cases/100,000 persons among those treated with long-term bisphosphonates (≥ 5years) ³¹. Thus, despite the well-described benefit of bisphosphonates (and other anti-resorptive treatments) on reducing the risk of vertebral and non-vertebral fractures, care must be taken with their use.

As a result of the concerns and lack of clear recommendations on duration of treatment with bisphosphonates, many clinicians are recommending “drug holidays” for postmenopausal osteoporosis treatment^{32,33}. There is less data on which to make this decision for chronic glucocorticoid users and this is an even greater challenge given the evidence showing an increased loss of bone mineral density when patients stop bisphosphonate treatment but continue on glucocorticoids. Of note, several of the case reports of atypical fractures have featured patients on glucocorticoids and it is conceivable that the deleterious effects of glucocorticoids on bone could synergistically increase the risk of these events in bisphosphonate users³⁴.

The current American College of Rheumatology guidelines for GIOP no longer recommend estrogen replacement in postmenopausal women for treatment or prevention of GIOP¹⁸. Estrogen replacement clearly reduces bone mineral density losses in women treated concurrently with glucocorticoids³⁵. Therefore, if a woman is otherwise unable to take an osteoporosis-specific prescription treatment or if a patient is already on estrogen treatment, estrogen therapy could be considered or maintained. A small Chinese study also demonstrated preservation of bone density in women on glucocorticoids who received raloxifene³⁶.

Similarly, testosterone replacement in hypogonadal men improves bone mineral density⁸. Testosterone therapy should be considered as an adjunct to other osteoporosis treatments or as sole treatment if other treatments are contraindicated or not tolerated in a symptomatic hypogonadal man³⁷. However, testosterone is not recommended as first line for fracture risk reduction in men taking glucocorticoids.

Premenopausal women pose a specific concern due to their reproductive potential. Due to the prolonged risk of exposure to bisphosphonates based on their integration into the boney matrix, the potential for fetal exposure even years after bisphosphonate use exists. Although several case reports have reported the lack of known adverse events in bisphosphonate exposed women and fetuses, well controlled studies and long-term evaluation have not been completed³⁸. Teriparatide may be an option in premenopausal women at high risk of fracture, as long as their growth plates are fully closed. There are two studies that have evaluated the use of teriparatide in premenopausal women^{39,40}, including one in GIOP patients³⁹. Both of these studies showed effectiveness and safety during the study periods^{39,40}. Further evaluation is required to verify safety and long-term effectiveness. If teriparatide initially is chosen for these premenopausal women on glucocorticoids, the question still persists of what to do afterward this course of therapy. However, one could theorize that the presence of estrogen (if ovarian function is intact) may be sufficient.

Patients with chronic kidney disease, such as SLE patients on glucocorticoids, pose a difficult situation due to the concomitant risk of adynamic bone disease. Product labeling does not recommend the use of a bisphosphonate in persons with a calculated CrCl of less than 30–35 mL/minute. Due to the risk of osteomalacia in persons with stage 5 CKD (e.g. dialysis dependent), bone biopsy before the initiation of any anti-osteoporosis therapy may be useful to rule out adynamic bone. Based on evidence from a pooled analysis of postmenopausal women with osteoporosis and varying degrees of renal insufficiency, no significant differences in side effects or renal outcomes were seen between women with mild to severe renal impairment when treated with daily risedronate⁴¹. Zoledronic acid has been associated with only a few cases of renal impairment when used in patients with multiple myeloma or bone metastases⁴². Based on this evidence, care needs to be taken with patients with renal insufficiency but it appears safe to treat patients with mild renal impairment with FDA-prescribed doses of bisphosphonates. The role of teriparatide in patients with CKD is not well defined, but anecdotal evidence from case studies provides evidence of its potential safety and very preliminary efficacy in adynamic bone disease^{43,44}.

Improving Care of Patients at Risk of Glucocorticoid Induced Osteoporosis

Despite the effectiveness of the above medications for prevention and treatment of GIOP, only a small proportion of patients treated with chronic glucocorticoids receive treatment^{45–48}. Despite newer guidelines and broader use of electronic health records, GIOP remains under-recognized and under-treated⁴⁹. Efforts to improve the care of GIOP have been of limited benefit, to date. Two interventions aimed at educating physicians through direct interaction or on-line continuing medical education had no effect on either screening or treatment of participants at risk of GIOP^{50,51}. Alternately, methods directly educating patients who are taking chronic glucocorticoids of the risks of GIOP have also led to

disappointing improvements in GIOP prevention and treatment⁵². Combined efforts of educating patients and physicians were assessed in a non-randomized, uncontrolled study and resulted in minimal uptake in GIOP treatment among patients at risk⁵³. Identifying effective means to improving the care of patients treated with chronic glucocorticoids remains a challenge.

Conclusion

The harmful effects of glucocorticoids on bone are known and there is an increasing understanding of the underlying pathophysiology. Beyond glucocorticoid effects, patients with rheumatologic disorders also frequently have bone changes related to the disease itself, with probable cause related to the increased inflammation and release of inflammatory cytokines. Thus, patients will commonly have an increased risk of fracture even prior to glucocorticoid initiation. However, once glucocorticoids are initiated, bone changes occur rapidly and are evident in the first three months of treatment. Of particular concern is the increased fracture risk at regions that are predominantly trabecular, such as the spine and femoral neck. Treatment should be considered early, especially for those at highest risk. Approved prescription treatment options are currently restricted to bisphosphonates and teriparatide. Although bisphosphonates have been considered first-line treatment for most patients with GIOP, there is increasing evidence of the benefit of teriparatide as a suitable first-line option. A better understanding of which patients should receive GIOP preventive treatment, how long to continue GIOP treatment, and when to consider combined use (with a bisphosphonate) or re-initiation of teriparatide is needed. Beyond treatment effectiveness, procedures to improve the diagnosis and treatment of patients with, or at risk of, GIOP are essential.

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References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

• Of importance

1. Adler, RA.; Curtis, JR.; Saag, K.; Weinstein, RS. Glucocorticoid-induced osteoporosis. 3rd ed. Elsevier-Academic Press; 2008.
2. Cascao R, Moura RA, Perpetuo I, et al. Identification of a cytokine network sustaining neutrophil and Th17 activation in untreated early rheumatoid arthritis. *Arthritis Res Ther*. 2010; 12(5):R196. [PubMed: 20961415]
3. Kim KW, Kim HR, Park JY, et al. Interleukin-22 promotes osteoclastogenesis in rheumatoid arthritis through induction of RANKL in human synovial fibroblasts. *Arthritis Rheum*. 2012 Apr; 64(4):1015–1023. [PubMed: 22034096]
4. Xu S, Wang Y, Lu J, Xu J. Osteoprotegerin and RANKL in the pathogenesis of rheumatoid arthritis-induced osteoporosis. *Rheumatol Int*. 2012 Nov; 32(11):3397–3403. [PubMed: 22057136]

5. Walsh NC, Reinwald S, Manning CA, et al. Osteoblast function is compromised at sites of focal bone erosion in inflammatory arthritis. *J Bone Miner Res*. 2009 Sep; 24(9):1572–1585. [PubMed: 19338457]
6. Carmona-Fernandes D, Santos MJ, Perpetuo IP, Fonseca JE, Canhao H. Soluble receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio is increased in systemic lupus erythematosus patients. *Arthritis Res Ther*. 2011; 13(5):R175. [PubMed: 22027240]
7. Tang X, Griffith J, Qin L, et al. SLE disease per se contributes to deterioration in bone mineral density, microstructure and bone strength. *Lupus*. 2013 Jul 24.
8. Rodriguez-Tolra J, Torremade J, di Gregorio S, Del Rio L, Franco E. Effects of testosterone treatment on bone mineral density in men with testosterone deficiency syndrome. *Andrology*. 2013 Jul; 1(4):570–575. [PubMed: 23686863]
9. Im CH, Kang EH, Ki JY, et al. Receptor activator of nuclear factor kappa B ligand-mediated osteoclastogenesis is elevated in ankylosing spondylitis. *Clin Exp Rheumatol*. 2009 Jul-Aug; 27(4): 620–625. [PubMed: 19772794]
10. Taylan A, Sari I, Akinci B, et al. Biomarkers and cytokines of bone turnover: extensive evaluation in a cohort of patients with ankylosing spondylitis. *BMC musculoskeletal disorders*. 2012; 13:191. [PubMed: 23025387]
11. Kang KY, Ju JH, Park SH, Kim HY. The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis. *Rheumatology (Oxford)*. 2013 Apr; 52(4):718–726. [PubMed: 23275389]
12. Barnabe C, Hanley DA. Effect of tumor necrosis factor alpha inhibition on bone density and turnover markers in patients with rheumatoid arthritis and spondyloarthropathy. *Semin Arthritis Rheum*. 2009 Oct; 39(2):116–122. [PubMed: 18585759]
13. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *The New England journal of medicine*. 2011 Jul 7; 365(1):62–70. [PubMed: 21732837]
14. LoCascio V, Bonucci E, Imbimbo B, et al. Bone loss in response to long-term glucocorticoid therapy. *Bone Miner*. 1990 Jan; 8(1):39–51. [PubMed: 2306553]
15. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011 Jan; 96(1):53–58. [PubMed: 21118827]
16. Moyer VA. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013 May 7; 158(9):691–696. [PubMed: 23440163]
17. Sanfelix-Gimeno G, Sanfelix-Genoves J, Rodriguez-Bernal CL, Peiro S, Hurtado I. Prevalence, determinants and inappropriateness of calcium supplementation among men and women in a Spanish Mediterranean area. Cross-sectional data from the ESOSVAL cohort. *J Bone Miner Res*. 2013 May 9.
18. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*. 2010 Nov; 62(11):1515–1526. [PubMed: 20662044]
19. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008 Apr; 19(4):385–397. [PubMed: 18292978]
20. Deal CL. Recent recommendations on steroid-induced osteoporosis: more targeted, but more complicated. *Cleve Clin J Med*. 2013 Feb; 80(2):117–125. [PubMed: 23376917]
21. Lekamwasam S, Adachi JD, Agnusdei D, et al. An appendix to the 2012 IOF-ECTS guidelines for the management of glucocorticoid-induced osteoporosis. *Arch Osteoporos*. 2012 Dec; 7(1–2):25–30. [PubMed: 23225278]
22. Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis*. 2013 Jul 19.
23. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. *QJM*. 2005 Mar; 98(3):191–198. [PubMed: 15728400]

24. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum*. 2009 Nov; 60(11):3346–3355. [PubMed: 19877063]
25. Karras D, Stoykov I, Lems WF, et al. Effectiveness of teriparatide in postmenopausal women with osteoporosis and glucocorticoid use: 3-year results from the EFOS study. *J Rheumatol*. 2012 Mar; 39(3):600–609. [PubMed: 22247365]
26. Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res*. 2013 Jun; 28(6):1355–1368. [PubMed: 23322362]
27. Murphy DR, Smolen LJ, Klein TM, Klein RW. The cost effectiveness of teriparatide as a first-line treatment for glucocorticoid-induced and postmenopausal osteoporosis patients in Sweden. *BMC musculoskeletal disorders*. 2012; 13:213. [PubMed: 23110626]
28. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. *J Bone Miner Res*. 2009 Jun; 24(6):1110–1115. [PubMed: 19113926]
29. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. *The New England journal of medicine*. 2005 Aug 11; 353(6):566–575. [PubMed: 16093465]
30. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1–34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011 Mar; 26(3): 503–511. [PubMed: 20814967]
31. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American society for bone and mineral research. *J Bone Miner Res*. 2013 May 28.
32. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis--where do we go from here? *The New England journal of medicine*. 2012 May 31; 366(22):2048–2051. [PubMed: 22571168]
33. Black DM, Bauer DC, Schwartz AV, Cummings SR, Rosen CJ. Continuing bisphosphonate treatment for osteoporosis--for whom and for how long? *The New England journal of medicine*. 2012 May 31; 366(22):2051–2053. [PubMed: 22571169]
34. Teitelbaum SL, Seton MP, Saag KG. Should bisphosphonates be used for long-term treatment of glucocorticoid-induced osteoporosis? *Arthritis Rheum*. 2011 Feb; 63(2):325–328. [PubMed: 21279986]
35. Lukert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. *J Bone Miner Res*. 1992 Sep; 7(9):1063–1069. [PubMed: 1329440]
36. Mok CC, Ying KY, To CH, et al. Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial. *Ann Rheum Dis*. 2011 May; 70(5): 778–784. [PubMed: 21187295]
37. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010 Jun; 95(6):2536–2559. [PubMed: 20525905]
38. McNicholl DM, Heaney LG. The safety of bisphosphonate use in pre-menopausal women on corticosteroids. *Curr Drug Saf*. 2010 Apr; 5(2):182–187. [PubMed: 19534636]
39. Langdahl BL, Marin F, Shane E, et al. Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. *Osteoporos Int*. 2009 Dec; 20(12):2095–2104. [PubMed: 19350340]
40. Cohen A, Stein EM, Recker RR, et al. Teriparatide for idiopathic osteoporosis in premenopausal women: a pilot study. *J Clin Endocrinol Metab*. 2013 May; 98(5):1971–1981. [PubMed: 23543660]
41. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res*. 2005 Dec; 20(12):2105–2115. [PubMed: 16294264]

42. Cha YJ, Lee YJ. Risk factors for renal impairment in patients with solid tumors or multiple myeloma treated with zoledronic acid. *Int J Clin Pharmacol Ther*. 2013 Apr; 51(4):274–282. [PubMed: 23357846]
43. Cejka D, Haas M. Should teriparatide ever be used for adynamic bone disease? *Semin Dial*. 2011 Jul-Aug;24(4):431–433. [PubMed: 21851406]
44. Cejka D, Kodras K, Bader T, Haas M. Treatment of Hemodialysis-Associated Adynamic Bone Disease with Teriparatide (PTH(1–34)): A Pilot Study. *Kidney Blood Press Res*. 2010 Jun 24; 33(3):221–226. [PubMed: 20588059]
45. Chantler IW, Davie MW, Evans SF, Rees JS. Oral corticosteroid prescribing in women over 50, use of fracture prevention therapy, and bone densitometry service. *Ann Rheum Dis*. 2003 Apr; 62(4):350–352. [PubMed: 12634236]
46. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *BMJ (Clinical research ed)*. 1996 Aug 10; 313(7053):344–346.
47. Curtis JR, Westfall AO, Allison JJ, et al. Longitudinal patterns in the prevention of osteoporosis in glucocorticoid-treated patients. *Arthritis Rheum*. 2005 Aug; 52(8):2485–2494. [PubMed: 16052570]
48. Mudano A, Allison J, Hill J, Rothermel T, Saag K. Variations in glucocorticoid induced osteoporosis prevention in a managed care cohort. *J Rheumatol*. 2001 Jun; 28(6):1298–1305. [PubMed: 11409123]
49. Majumdar SR, Lix LM, Yogendran M, Morin SN, Metge CJ, Leslie WD. Populationbased trends in osteoporosis management after new initiations of long-term systemic glucocorticoids (1998–2008). *J Clin Endocrinol Metab*. 2012 Apr; 97(4):1236–1242. [PubMed: 22298803]
50. Solomon DH, Katz JN, La Tourette AM, Coblyn JS. Multifaceted intervention to improve rheumatologists' management of glucocorticoid-induced osteoporosis: a randomized controlled trial. *Arthritis Rheum*. 2004 Jun 15; 51(3):383–387. [PubMed: 15188323]
51. Curtis JR, Westfall AO, Allison J, et al. Challenges in improving the quality of osteoporosis care for long-term glucocorticoid users: a prospective randomized trial. *Arch Intern Med*. 2007 Mar 26; 167(6):591–596. [PubMed: 17389291]
52. Warriner AH, Outman RC, Markward NJ, et al. A Web-Based Intervention Aimed to Improve Bone Health among Individuals on Chronic Glucocorticoids. *Arthritis Rheum*. 2012; 64(Suppl 10):1978. [PubMed: 22161819]
53. Chitre MM, Hayes W. 3-year results of a member and physician intervention to reduce risk associated with glucocorticoid-induced osteoporosis in a health plan. *J Manag Care Pharm*. 2008 Apr; 14(3):281–290. [PubMed: 18439050]

Table 1

Currently Available Prescription GIOP Prevention and Treatment Options

	Recommended Use in GIOP	Comments
Anti-resorptive Agents		
Bisphosphonates		
Alendronate (Fosamax®)	FDA approved for treatment	Generic alternative is available. Less data on fracture risk reduction in GIOP than other bisphosphonate options. Vertebral fracture reduction seen in extension to original clinical trial.
Risedronate (Actonel®, Atelvia®)	FDA approved for prevention and treatment	Reduced vertebral fracture risk by more than 50% in post hoc analyses of placebo controlled GIOP trials.
Zoledronate (Reclast®)	FDA approved for prevention and treatment	Intravenous option. Consider in patients with intolerance to oral bisphosphonates due to gastrointestinal side effects or those unable to comply with the dosing schedule of other treatment options. No fracture benefit seen in an active comparator study vs. risedronate, but BMD efficacy was demonstrated.
Anabolic Agents		
Teriparatide (Forteo®)	FDA approved for GIOP/high fracture risk	Superior to alendronate in randomized controlled trials in GIOP in reducing vertebral fractures (although study was not originally powered to detect this outcome).

IV, intravenous

SQ, subcutaneous