Osteoporosis International (2019) 30:1145–1156
https://doi.org/10.1007/s00198-019-04906-x

CONCISE CLINICAL REVIEW

Glucocorticoid-induced osteoporosis: 2019 concise clinical review

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Received: 9 January 2019 / Accepted: 14 February 2019 / Published online: 25 February 2019

Abstract

Glucocorticoids remain widely used for many medical conditions, and fractures are the most serious common adverse event related to long-term glucocorticoid use. Glucocorticoid-induced osteoporosis (GIOP) develops in a time- and dose-dependent manner, but even at low doses, an increased risk of fragility fracture may be observed even within the first month of treatment. GIOP is mediated by multiple pathophysiologic mechanisms resulting in an inhibition of bone formation and an increase in bone resorption. The clinical assessment of GIOP has potential pitfalls since dual-energy X-ray absorptiometry (DXA) may underestimate the risk of fracture in patients treated with glucocorticoids. Many national organizations have developed guidelines for assessing fracture risk and treating patients with, or at risk for, GIOP. These groups advocate both antiresorptive agents and bone-forming agents based predominately on their efficacy in improving bone mineral density. Oral bisphosphonates are generally the first-line therapy for GIOP in most patients due to their proven efficacy, good safety, and low cost. For those patients at greater risk of fracture, teriparatide should be considered earlier, based on its ability to significantly reduce vertebral fractures when compared with alendronate. GIOP remains a major public health concern that is at least partially preventable with current and potential future therapeutic options.

Keywords Bone · Fracture · Glucocorticoid · Osteoporosis · Review

Introduction

Epidemiology and clinical burden of GIOP

Glucocorticoid-induced osteoporosis (GIOP) is the most common form of secondary osteoporosis. Glucocorticoids are used chronically by approximately 0.5–1% of the general population [1–3]. Glucocorticoids remain widely prescribed for many medical conditions by specialists and particularly by generalists [1–3]. Fractures are the most serious adverse event related to chronic glucocorticoid use [4]. Glucocorticoid use is associated with an increase of fragility fracture risk quickly following the first dose [5], leading to an "imminent risk of fracture," [6]. However, the risk of fracture also increases depending on dosage and length of use; the longer and the more intense the treatment, the higher the risk [7–10]. Compared with shorter-course users, heavy users (daily dose ≥ 15 mg prednisone equivalent and/or cumulative dose ≥ 1 g) have the greatest risk of fractures [7]. The annual incidence of vertebral and non-vertebral fracture from the control arms of glucocorticoid-induced osteoporosis clinical trials was 5.1% among the patients chronically using glucocorticoids and 2.5% in those who were newly initiating glucocorticoids [5].

Burden of GIOP in specific glucocorticoid-requiring diseases

Glucocorticoids are prescribed for the treatment of many chronic diseases affecting patients of different ages, sexes, and ethnicities. Glucocorticoids lead to bone loss and eventually fragility fractures; however, they might also serve a protective role by reducing inflammation associated with an underlying disease. For this reason, it is important to consider the major glucocorticoid-requiring conditions separately. Rheumatoid arthritis appears to constitute the disease that is most often associated with chronic glucocorticoid use. The fracture incidence rate in persons affected by rheumatoid arthritis was higher in patients taking doses of glucocorticoids

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greater or equal than 15 mg/day prednisone equivalents (16.0 per 1000 person-year) compared with those who were taking doses less than 15 mg/day (5 to 9 per 1000 person-years). In rheumatoid arthritis patients, after discontinuation of glucocorticoids, the fracture incidence returned to baseline levels only after 12 months [8]. Patients with polymyalgia and giant cell arteritis (diseases primarily observed in older Caucasians) had incidence fracture rates approximately 14.5 per 1000 person-years, and the risk of fracture was increased by approximately 65% compared with the control populations, an effect largely attributable to the use of glucocorticoids [11]. In systemic lupus erythematosus (SLE) (a disease predominately affecting young women and more prevalent in non-Hispanic blacks), there was a 20% increased clinical fracture risk compared to controls [12]. This result was mainly ascribable to chronic glucocorticoids, based on an earlier evaluation of approximately 6000 person-years of follow-up [13]. More than 3% of diabetic patients reported chronic use of glucocorticoids with a corresponding fracture prevalence greater than 30% [14]. In patients with chronic obstructive pulmonary disease (COPD) and asthma, there was an increased risk of osteoporosis [15]. This observed increased risk was associated with several factors such as cigarette smoking, systemic inflammation, and less activity but also with the use of oral glucocorticoids [16]. The independent role of inhaled glucocorticoids is difficult to discern since most COPD and asthma patients receive periodic bursts of oral or parenteral glucocorticoids [17]. A Cochrane systematic review on the effect inhaled glucocorticoids have on bone metabolism showed neither evidence of increased risk of fracture nor loss of BMD with conventional doses of inhaled glucocorticoids given for 2 or 3 years [18]. However, a longer duration of treatment (> 8 years) and greater mean daily dose (> 600 μg/day of beclomethasone or equivalent) resulted in an increased risk of fragility fractures [19, 20].

Observations

The pathogenesis and molecular basis of GIOP

Glucocorticoids exert a direct toxic effect on bone cell–regulating genes (e.g., osteoblasts) by binding to the promoter region of glucocorticoid response elements, ultimately leading to altered protein synthesis and regulation. 11β-Hydroxysteroid dehydrogenase converts hormonally active glucocorticoids to inactive hormone forms; polymorphism of this enzyme may help explain altered susceptibility to glucocorticoid toxicity [21]. Glucocorticoids produce a direct deleterious effect on bone formation through two primary pathways: first, via enhancement of peroxisome proliferator-activated receptor gamma receptor 2 (PPARγ2) expression [22] and second, through inhibition of the canonical Wnt/β-catenin signaling pathway [23]. Glucocorticoids enhance expression of Wnt antagonists, sclerostin (SOST), and dickkopf-related protein 1 (Dkk1), resulting in decreased production of osteoblasts and ultimately less bone formation; thus, Wnt signaling plays a central role in the pathogenesis of GIOP [24]. There is augmented osteoblast death which appears to also depend on an increased release of reactive oxygen species (ROS) [25]. Moreover, glucocorticoids directly reduce the production of growth hormone (GH) and insulin-like growth factor (IGF1), both osteoblast stimulators [26]. In addition to their inhibitory effect on bone formation, glucocorticoids also affect bone resorption. Glucocorticoids increase the production of receptor activator of nuclear factor kappa-B ligand (RANKL) and decrease the production of osteoprotegerin, resulting in enhanced bone resorption. RANKL expression is augmented directly not only by glucocorticoids but also by an increase in Dkk1 [27]. Glucocorticoids stimulate the secretion of interleukin-6 (IL-6), a cytokine that increases osteoclastogenesis and suppresses interferon-β an osteostimulating cytokine [28, 29]. The overall effect of glucocorticoids on bone resorption leads to bone loss, particularly early during the course of therapy. The effect of glucocorticoids on bone is not only driven by osteoclasts and osteoblasts but also by osteocytes [30]. Glucocorticoids impair the function of osteocytes and stimulate their apoptosis. The loss of osteocyte function leads to impaired bone architecture [31, 32] that could explain the bone mineral density (BMD)/fragility paradox; namely, that patients on glucocorticoid experience fracture at higher BMD compared with the general population [33]. Glucocorticoids induce hypogonadism through inhibition of estrogens and androgens, but without a clear bone effect. Glucocorticoids also have a deleterious effect on muscle strength resulting in increased risk of fall and subsequently, an increased risk of fracture [34]. Lastly, glucocorticoids might influence calcium homeostasis, but this effect remains controversial. There is some evidence that glucocorticoid inhibits calcium absorption in the intestinal tract, but other studies showed no decrement in calcium serum levels or a parathyroid hormone (PTH) increase [35]. These discordant reports may be related to the variability of vitamin D insufficiency prevalence in patients on glucocorticoids. Moreover, the renal handling of calcium and phosphate is also controversial due to the variable underlying conditions that can have independent effects on renal mineral excretion (e.g., sarcoidosis). In chronic glucocorticoid use, calcium net excretion increases due in part to mobilization of skeletal calcium. This perturbed mineral homeostasis may increase PTH secretion with the development of secondary hyperparathyroidism. Young healthy men who were administered 50 mg/day of prednisone for up to 6 months did not experience an increase in PTH nor a decrease in serum calcium [35]. Given the conflicting evidence to date, it is unlikely that changes in bone mineral homeostasis play a significant role in GIOP. In

summary, GIOP differs substantially from postmenopausal osteoporosis in terms of pathophysiological mechanisms and time course. Patients on glucocorticoids have reduced bone formation, enhanced bone resorption, impaired bone architecture and experience fractures earlier than postmenopausal osteoporosis.

Non-pharmacologic treatment options for GIOP: calcium and vitamin D

Sufficient calcium and vitamin D are critical for the prevention and treatment of GIOP, particularly in light of the calciuria that may occur early with glucocorticoid use. Meta-analyses showed a reduction of fracture rate in patients treated with alfacalcidol and calcitriol compared with a placebo [36, 37]. Despite these results, the use of calcium and vitamin D supplements alone for fracture preventions is controversial in osteoporosis overall and inferior to bisphosphonate treatment for GIOP [37].

Pharmacologic treatment options for GIOP

To date, six large randomized clinical trials on pharmacologic or biologic therapies for GIOP have been conducted. These clinical trials provide key information about GIOP therapy, but comparisons within and between studies are limited due to study design heterogeneity including variability in study subject age, menopausal status, underlying conditions, comorbidities, cotherapies, and baseline bone mass status and previous history of fractures. Another important difference between and within studies resides in a "prevention" vs "treatment" designation, referring to whether the study subject is a new or prevalent user of glucocorticoids, respectively. For example, a clinical trial of alendronate compared with placebo [38] had 53% post-menopausal women compared with a clinical trial evaluating teriparatide vs alendronate where 83% of women were post-menopausal [39]. Furthermore, the underlying condition that required glucocorticoids differed in the alendronate trial, 19% of the patients were affected by SLE and 30% by rheumatoid arthritis [38] compared with 8% and 40%, respectively, in a risedronate trial [40]. Baseline prevalence of vertebral fracture also differed 15% fracture rate in the treatment arm of the alendronate trial [38] compared with a 30% fracture rate in the risedronate trial [41].

Bisphosphonates

Similar to post-menopausal osteoporosis, bisphosphonates are the most widely used therapy in GIOP, and a number of studies have assessed their efficacy (Table 1). Oral alendronate (5/10 mg once a day or 70 mg once weekly) [38, 42, 43], risedronate (5 mg once a day or 35 mg once weekly) [40, 41, 44, 45], ibandronate (150 mg PO monthly or 2–3 mg IV every 3 months) [46–48], and zoledronic acid (5 mg IV once every year) [49] are all efficacious for treating GIOP. All four bisphosphonates increased lumbar spine and hip BMD more than placebo, or for zoledronic acid compared with risedronate and for ibandronate compared with alfacalcidol.

Alendronate In the pivotal clinical trial comparing daily oral alendronate to placebo [38] after 48 weeks, alendronate improved lumbar spine BMD by 2.9% compared with the baseline while with placebo BMD was reduced by 0.4%. In a 12-month randomized, placebo-controlled clinical trial, weekly alendronate appeared largely similar in effects on BMD to daily in GIOP [43]. Alendronate, risedronate, and ibandronate have all shown at least preliminary evidence for vertebral fracture prevention [38, 41, 44–46]. There was a trend towards vertebral fracture risk reduction in the first year of the pivotal alendronate study and 90% significant reduction of vertebral fracture risk in the open-label extension study at 2 years [42]. While non-vertebral fractures were far too few in number to draw conclusions from GIOP-randomized clinical trials, observational data from a Swedish national database demonstrated that alendronate significantly reduced the risk of hip fracture (HR 0.35, 95% CI, 0.22–0.54) [50].

Risedronate Risedronate increased the lumbar spine BMD by 3.4% compared with placebo but only by 0.6% compared with baseline [41]. Another study evaluating risedronate in GIOP patients with lower baseline BMD showed an improvement of 2.9% on lumbar spine BMD within 1 year compared with baseline [44]. These clinical trials were conducted in parallel, under similar protocols but were then combined for aggregate analysis [45]. In the combined analysis, the overall vertebral fracture risk reduction with risedronate was 70% versus placebo ($p = 0.01$).

Ibandronate Ibandronate prevented bone loss associated with glucocorticoid use [46–48], and in a high-risk cohort of cardiac transplanted patients treated with 15 mg/day of prednisone equivalent, ibandronate reduced fracture risk by 75% after 12 months compared with placebo [48].

Zoledronic acid Zoledronic acid improved BMD to a greater extent than risedronate but failed to achieve direct evidence of fracture prevention, possibly due to a low fracture rate in the population under analysis in an active comparator study that did not require a BMD inclusion criteria [49].

A 2016 meta-analysis on bisphosphonates for GIOP included 27 randomized controlled trials containing 3075 patients [51]. In this analysis, 7.7% of people experienced a new vertebral fracture in the control arm compared with 4.4% in the bisphosphonate arm; overall fracture risk reduction was 43% with bisphosphonates (95% CI, 9.0 to 65.0%).

Table 1 Clinical tips—comparing treatment options in glucocorticoid-induced osteoporosis

Drug	Dosing	Bone formation	Bone resorption	Evidence of vertebral fracture prevention	Evidence of BMD improvement	Approved for GIOP in the US	Clinical tips
Alendronate	5 or 10 mg daily or 70 mg once weekly PO	↓	↓↓	✓ (versus PBO extension study)	✓ (versus PBO)	✓	Available as generic, GI AEs±
Risedronate	5 mg daily or 35 mg once weekly PO	↓	↓↓	✓ (versus PBO post-hoc analysis)	✓ (versus PBO)	✓	Available as generic, GI AEs±
Ibandronate	150 mg monthly PO or 2 mg every 3 months IV	↓	↓↓	✓ (versus alfacalcidol extension study)	✓ (versus alfacalcidol)	✓	Available as generic, GI AEs±
Zoledronic acid	5 mg once yearly IV	↓	↓↓	✖	✓ (versus RIS)	✓	Available as generic, greater compliance due to one yearly IV infusion. Acute phase reactions
Denosumab	60 mg once every 6 months SC	↓	↓↓↓	✖	✓ (versus RIS)	✓	Branded, greater compliance with twice yearly use. Increased fracture risk with discontinuation±*
Teriparatide	20 μg once a day SC	↑↑	↑	✓ (versus ALN)	✓ (versus ALN)	✓	Branded, reduced compliance due to daily subcutaneous injection. Flushing and hypercalcemia
Raloxifene	60 mg daily PO	↓	↓	✖	✓ (versus PBO)	✓	Available as generic, rare VTE and CV events

GIOP glucocorticoid-induced osteoporosis, *PO* oral administration, *PBO* placebo, *GI AEs* gastrointestinal adverse events, *IV* intravenous, *RIS* risedronate, *SC* subcutaneous, *BMD* bone mineral density, *ALN* alendronate, *BPs* bisphosphonates, *VTE* venous thromboembolism, *CV* cardiovascular. ± Atypical femoral fracture and osteonecrosis of the jaw have been reported rarely with the use of alendronate, risedronate, ibandronate, zoledronic acid, and denosumab. *Most of the multiple vertebral fractures have been reported after long-term treatment with denosumab

Bisphosphonates are relatively safe, well-tolerated drugs. The risk of osteonecrosis of the jaw and atypical femur fractures remains exceedingly low; however, there are anecdotal reports of these rare events and a theoretical concern that in a low turnover state such as GIOP these problems might be accentuated [52–54]. Indeed, glucocorticoid use has been associated with an increased risk of osteonecrosis of the jaw [55]. Compelling data on these safety signals are lacking from GIOP clinical trials due to the comparatively small number of patients included in these studies.

Denosumab

A randomized double-blind, double-dummy, active-controlled study on the use of denosumab versus risedronate in GIOP [56] showed greater BMD at lumbar spine compared to risedronate in both glucocorticoid-continuing (4.4% vs 2.3%) and glucocorticoid-initiating (3.8% vs 0.8%) subpopulations. Serious infections were similar in the two groups, although the study was underpowered for this safety outcome. Of the 17 patients in the denosumab group who were also taking concomitant biologic medications for inflammatory diseases, none experienced serious infection compared with two (7%) in the risedronate group. There was no difference between treatment arms in fracture outcomes. One concern of particular special relevance to GIOP is the possible increase in vertebral fracture after stopping denosumab [57, 58], particularly since these patients are younger and may discontinue glucocorticoid at some point. Thus, how to prescribe and manage denosumab (when to stop and what to follow it with) in those who stop glucocorticoids requires pre-planning, and further studies are needed to evaluate the efficacy of possible discontinuation strategies.

Teriparatide

Teriparatide is an attractive therapeutic option for patients affected by GIOP due to its anabolic mechanism of action and the pathophysiologic considerations in GIOP discussed above. Rats treated with both PTH and glucocorticoids had only a partial inhibition of the bone formation than seen with glucocorticoids alone, and the strength of the bone was the same after combined treatment [59]. However, the response to teriparatide was somewhat attenuated by glucocorticoids doses greater than 15 mg/day of prednisone equivalent. This partial inhibition of the response at higher doses of glucocorticoids was not seen for alendronate [60]. Human clinical trials have not only demonstrated teriparatide as efficacious for GIOP [39, 61–65], but that it was superior to alendronate in prevention of a small number of vertebral fracture at 24 and 36 months (0.6% vs 6.1% and 1.7% vs 7.7% respectively) [39, 64]. Teriparatide is used for 24 months of treatment in patients with GIOP. Providers should consider teriparatide in selected,

high-risk patients (i.e., older adults starting higher dose steroids, multiple prior fractures, and very low initial bone mass), potentially even as an initial GIOP drug. However, due to teriparatide's significantly higher cost than generic therapies and the inconvenience of a once-daily subcutaneous administration, its use in GIOP is limited.

Hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and testosterone

The efficacy of sex steroid as therapeutic agents in GIOP had been seen in small clinical trials without drug registration indications [66–69]. However, a large randomized controlled trial from the Women's Health Initiative provided evidence of increased risk of coronary heart disease, stroke, pulmonary embolism, and breast cancer in older women treated with estrogens who were not on glucocorticoids [70]. Nevertheless, short-term HRT and SERMs may be considered, respectively, in symptomatic women with postmenopausal symptoms and young women with contraindications to more extensively tested GIOP therapies, who do not have contraindications to estrogen or estrogen-like moiety. This may be problematic in patients with connective tissue diseases taking glucocorticoids who, not uncommonly, are at higher risk of thromboembolic diatheses. Data from three clinical trials evaluating testosterone in GIOP patients demonstrated efficacy in increasing BMD, particularly of note was a moderate increase in lumbar spine BMD [71–74]. Similar to HRT and SERMs, testosterone should be considered in selected patients (i.e., men suffering from symptomatic hypogonadism) taking chronic glucocorticoids and may be contraindicated due to possibly short- and long-term safety concerns when other better-tested and more bone-specific therapies.

Cost-effectiveness of treatment and long-term compliance

GIOP treatment should take into account efficacy, safety, adherence, and at a societal level, cost-effectiveness. With the lengthening of life expectancy and the surprising growing worldwide usage of glucocorticoids, GIOP is both an economic and clinical problem. Despite the overwhelming clinical evidence available, only approximately 1 out of 5 US patients on glucocorticoids is taking an osteoporosis medication [75, 76]. Bisphosphonates are now all available as generic drugs and represent the least expensive medication option for GIOP. A Markov microsimulation model determined the cost-effectiveness of using bisphosphonates for patients with GIOP [77]. Assumptions included that the intervention had no incremental cost, and under these circumstances, the resultant incremental cost-effectiveness ratios (ICERs) were $188,000 per hip fracture averted and $273,000 per quality adjusted life years (QALY). The same analysis revealed that when a generic antiosteoporotic drug is used in a high-risk cohort of patient with optimal treatment adherence; the ICERs improved significantly to $84,000 per QALY and $57,900 per fracture averted [77]. In another analysis of the use of bisphosphonates in patients taking 5 mg of prednisone equivalent daily, the cost per one QALY gained with bisphosphonates varied from approximately $53,300 in women aged < 60 years, $22,100 in women aged 60–79 years, and $6500 in women aged ≥ 80 years. With 15 mg of prednisone equivalent, the same set of women varied from $22,100, $16,900, and $19,500 respectively [78]. Another analysis showed that the ICER of 5-year alendronate therapy ranged from $10,958 in the best-case scenario (45-year-old women with prevalent fracture treated with 10 mg/day of prednisone equivalent) to $66,791 in the worst-case scenario (65-year-old woman without previous fractures treated with 2.5 mg/day of prednisone equivalent) [79]. Teriparatide may be one of the most effective treatments for GIOP having shown superior fracture prevention to alendronate [39]; however, it is currently the most expensive drug available to treat GIOP. A computer simulation model among higher risk patients (women aged more than 69 years with T-score ≤ 2.5) showed that teriparatide is justifiable as first-line treatment at a cost per QALY (quality-adjusted life year) threshold of $50,000.

GIOP monitoring

Dual-energy X-ray absorptiometry, FRAX, and trabecular bone score

Algorithms had been developed to better quantify the fracture risk in GIOP patients most incorporating use of FRAX to help risk stratify [80, 81]; however, the FRAX algorithm instrument includes only a dichotomous variable for glucocorticoids, an assumption that does not consider treatment duration and dosage concurrently. FRAX can be adjusted to account for daily dosage but not for the cumulative dosage or length of use [82]. The FRAX and a number of other algorithms lack the ability to provide estimates for young patients, many of whom use glucocorticoids. The current American College of Rheumatology (ACR) guidelines on prevention and treatment of GIOP advise a baseline DXA evaluation to better discriminate the high-risk patients from lower-risk patients and where appropriate to consider serial DXA after treatment [83]. The trabecular bone score may preferentially capture differences between drugs in therapeutic response in women treated with glucocorticoids relative to routine DXA [61].

High-resolution peripheral computed tomography (HRpQCT) with finite element analysis

Comparing postmenopausal women treated with glucocorticoids and controls, women treated with glucocorticoids had lower cortical and trabecular volumetric BMD, with fewer

Table 2 Comparison of international guidelines on glucocorticoid-induced osteoporosis (GIOP)

Guideline	2017 ACR	2012 IOF-ECTS	2017 NOGG	2016 SIOMMMS/SIR	2014 SFR/GRIO	2014 JSBMR
General measures	✓	✓	✓	✓	✓	✓
Young patients (< 40 years)	✓ (with special population considerations)	✓	✓	✖	✓	✓
Initial fracture risk assessment	Baseline FRAX/ BMD (within 6 months of GC initiation)	Clinical risk factor (i.e., FRAX without BMD); if risk intermediate: BMD	UK FRAX model (GC-adjusted: medium dose 2.5–7.5 mg/d; high dose ≥ 7.5 mg/d)	DeFRA (FRAX derived fx risk assessment GC-adjusted)	BMD (if ≥ 7.5 mg/d) VFA (if ≥ 3 months at ≥ 7.5 mg/d)	Spine X-ray and BMD (with % YAM) at baseline
Follow-up fracture risk assessment	Clinical fx risk assessment± Every 12 months in GC continuing patients BMD/FRAX • Every 1–3 years, if never treated with OP medication (earlier if very high dose GC use or history of fx) • Every 2–3 years during OP treatment, if very high GC doses, concern for poor adherence, or absorption of OP medication • Every 2–3 years after treatment	BMD at appropriate intervals Height measurement annually Spine X-ray or VFA if vertebral fx suspected	N/A	N/A	X-ray, if height loss ≥ 4 cm (compared to height at 20 years) or ≥ 2 cm (compared to previous follow-up) or back pain	X-ray and BMD (with % YAM) every 6–-12 months
Risk stratification	FRAX (GC-adjusted)	FRAX (GC-adjusted)	UK FRAX model (GC-adjusted)	DeFRA FRAX derived fx risk assessment (GC-adjusted)	FRAX (adjusted assuming same-age women having a history of fx)	JSBMR individual patient's score (0–19) Based on prior fx, age, GC dose, and lumbar spine BMD
Treatment indications	Men and women (not of childbearing potential) < 40 years. and ≥ 40 years at moderate to high fx risk	Previous OP fx(s) OR age ≥ 70 years OR prednisolone ≥ 7.5 mg/d OR FRAX (GC-adjusted) above intervention threshold*	Previous OP fx(s) OR age ≥ 70 years OR prednisolone ≥ 7.5 mg/d OR FRAX (GC-adjusted) above intervention threshold*	Independent of BMD, all PM women or men aged ≥ 50 years receiving or planning to receive ≥ 5 mg/d for 3 months	PM women or men aged ≥ 50 years • Prednisone ≥ 7.5 mg/d or fx(s) or age ≥ 70 years or BMD T-score ≤ − 2.5 • Prednisone < 7.5 mg/d and no fx(s) and age < 70 years and BMD > − 2.5 with adjusted FRAX above intervention threshold	Score ≥ 3 JSBMR individual patient's score
Medication recommendations	First line: (in order of preference: oral bisphosphonate, IV bisphosphonates, teriparatide, denosumab, raloxifene (for PM women none of the medications listed above is appropriate) Second line: if fx ≥ 18 months of treatment or ≥ 10%/year loss of BMD:	First line: alendronate, etidronate, risedronate, zoledronic acid, and teriparatide for the majority of patients	First line: oral bisphosphonates Second line: IV bisphosphonates or teriparatide	Without OP fx: First line: alendronate, risedronate, zoledronic acid Second line: denosumab With OP fx: First line: teriparatide Second line: denosumab, zoledronic acid	First line: zoledronic acid or risedronate; teriparatide can be prescribed as first line in patients with at least two prevalent vertebral fxs at diagnosis	First line: alendronate, risedronate Second line: teriparatide, ibandronate, alfacalcidol, calcitriol

Table 2 (continued)

Guideline	2017 ACR	2012 IOF-ECTS	2017 NOGG	2016 SIOMMMS/SIR	2014 SFR/GRIO	2014 JSBMR
	teriparatide or denosumab or consider IV bisphosphonates if poor absorption/poor adherence			Third line: alendronate, risedronate, ibandronate, strontium ranelate‡		
Drug discontinuation	Consider if GCs are discontinued and low risk of fx	Consider if GCs are discontinued	Consider if GCs are discontinued	N/A	Duration of first treatment sequence 3 to 5 years; same criteria for stopping/continuing as PM women	N/A

All glucocorticoid doses are prednisolone equivalent. *ACR* American College of Rheumatology, *IOF/ECTS* International Osteoporosis Foundation/European Calcified Tissue Society, *NOGG* National Osteoporosis Guideline Group, *SIOMMMS/SIR* Società Italiana dell'Osteoporosi del Metabolismo Minerale e delle Malattie dello Scheletro/Società Italiana di Reumatologia, *SFR/GRIO* Société Française de Rhumatologie/Groupe de Recherche et d'Information sur les Ostéoporoses, *JSBMR* Japanese Society for Bone and Mineral Research, *FRAX* fracture risk assessment tool, *BMD* bone mineral density, *GCs* glucocorticoids, *Fx* fracture, *YAM* young adult men, *OP* osteoporosis, *VFA* vertebral fracture assessment, *DeFRA* derived FRAX, *PM* post-menopausal. ± Guidelines for adults of more than 40 years. *Threshold will vary according to country, guidelines for adults of > 50 years. ‡Strontium ranelate for patients whom none of the medications listed above is appropriate

trabecular plates, abnormality in the alignment of trabeculae, and less connectivity between trabeculae, all resulting in altered microarchitecture relative to controls [84]. Average volumetric BMD (vBMD) and cortical vBMD were significantly reduced in systemic lupus erythematosus patients treated with glucocorticoids. In these patients, the cortical microarchitecture was mainly affected with a 6.3% reduction in cortical thickness and higher cortical porosity [85]. HRpQCT using finite element analysis may also be useful in comparing therapeutic efficacy. For example, teriparatide appeared significantly more effective than risedronate in improving finite element analysis measures that assessed anterior bending, axial compression, and axial torsion [65].

Microindentation

A small pilot study of microindentation in GIOP patients showed that the bone material strength index, a qualitative measurement of bone strength, significantly decreased in patients using glucocorticoids in combination with calcium and vitamin D after 7 weeks of therapy, remained stable in patients using a glucocorticoid in combination with risedronate, and increased in patients taking a glucocorticoid in combination with denosumab or teriparatide [86].

International guidelines on GIOP treatment

Numerous groups have developed societal and national guidelines for GIOP. Some differences and similarities exist between the more recent national and international guideline on the treatment of GIOP patients (Table 2). Most of the guidelines advocate that patients should receive at least 400 UI/day of cholecalciferol or equivalent and at least 1200 mg/day of elemental calcium intake [35–37]. The BMD threshold for pharmacological intervention in GIOP patients is generally a T-score between − 1.5 and − 1.0. Most guidelines recommend evaluating fracture risk with FRAX [87–89]. The ACR 2017 guidelines recommend pharmacologic intervention in patients with a 10-year risk of major osteoporotic fracture > 10% or with a history of previous osteoporotic fracture or with T-score less than − 2.5 or those treated with very high dose of glucocorticoids [83]. ACR guidelines recommend oral bisphosphonates as the first line of treatment in all GIOP patients not of childbearing potential [83]. Furthermore, 2017 ACR guidelines suggested zoledronic acid, teriparatide, denosumab, and raloxifene as the second, third, fourth, and fifth lines of treatment, respectively, for patients who do not tolerate oral bisphosphonates. This conditional recommendation about treatment order preference was determined based on efficacy, toxicity, and the cost of treatments. It is notable that this treatment order preference was formulated prior to the denosumab clinical trial in GIOP [56]. Other society guidelines do not

incorporate the FRAX and set the threshold for intervention at ≥ 7.5 mg of prednisone equivalent [90, 91]. The UK National Osteoporosis Guideline Group (NOGG) on GIOP suggests antiosteoporotic therapies for women and men age ≥ 70 years, with a previous fragility fracture, or who are taking high doses of glucocorticoids (≥ 7.5 mg/day prednisone equivalent). They recommend that in all other individuals, the risk should be assessed with the 2011 updated FRAX. These strategies might underestimate the risk in patients chronically treated with a lower dosage of glucocorticoids. Another example of prevention and treatment strategy comes from 2016 Italian guidelines and reimbursability criteria for treatment of GIOP [92]. In this guideline, postmenopausal women and men > 50 years without history of fragility fracture, with an expected treatment of > 3 months, and with ≥ 5 mg/day of prednisone equivalent should be treated with oral or IV bisphosphonates as the first line and with denosumab as the second line of treatment. Within this same guideline, patients with a vertebral or hip fracture treated with ≥ 5 mg/day of prednisone equivalent should be treated with teriparatide as the first line of treatment.

Conclusions

GIOP is a well-recognized public health problem that causes disability and mortality. The key points to be aware in the treatment of GIOP are as follows: (1) GIOP is a problem not only in the elderly; (2) imminent fracture risk in GIOP rises quickly after the initiation of glucocorticoids but is also related to time and dosage of glucocorticoids (i.e., the higher the dosage and the longer the treatment, the greater the risk); (3) the pathogenesis of GIOP is complex, including reduced bone formation and increased bone resorption; (4) the assessment of fracture risk in GIOP patients can be difficult, but guidelines suggest tools to better estimate the risk and to guide the treatment selection; and (5) clinicians have GIOP medications in their armamentarium, all with demonstrated efficacy for improving bone mineral density and several with suggested efficacy in reducing fracture, in particular reducing vertebral fracture risk.

Learning objectives

1. To understand pathogenesis, epidemiology, and clinical and societal burden of GIOP.
2. To understand the risk of glucocorticoid depending on duration and dose of treatment.
3. To acknowledge all the possible therapeutic options and international society guidelines differences.

Compliance with ethical standards

Conflict of interest Giovanni Adami declares that he has no conflict of interest. Kenneth G Saag declares research grant from Amgen and Merck and consultant fee from Amgen, Lilly, Merck, and Radius.

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