Review

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Glucocorticoid-induced osteoporosis: an overview

Glucocorticoid-induced osteoporosis (GIOP) is one of the most serious adverse effects of glucocorticoids. Despite guidelines on the management of GIOP, effective medications and fracture outpatient clinics, this condition remains under-recognized and under-treated. This review covers recent insights into mechanisms involved in GIOP, monitoring for adverse effects of glucocorticoids on bone and prevention and treatment of GIOP. Recent guidelines on GIOP are discussed and a research agenda is proposed.

Keywords: bisphosphonates • bone mineral density • glucocorticoids • monitoring • osteoporosis • therapy

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Epidemiology

Despite development of many immunosuppressive nonbiological and biological drugs, glucocorticoids (GCs) still are widely used in the treatment of chronic allergic, inflammatory and autoimmune diseases and vasculitides, for their antiallergic, anti-inflammatory and immunosuppressive effects. A study showed that in the UK oral GCs were used by 0.9% of the adult population, with the highest use (2.5%) among elderly of 70–79 years of age; the most frequent indications overall for long-term GC treatment were respiratory diseases (40%) and arthropathies (19%) [1]. A recent study estimated that the prevalence of GC use, mostly of a long duration, in the USA is 1.2%, with infrequent use of a concomitant bisphosphonate [2].

Since their introduction in the 1950s by Hench and collaborators [3], adverse effects are recognized, but their management and prevention still are very actual issues nowadays, approximately 60 years later [4,5]. Of these adverse effects, glucocorticoid-induced osteoporosis (GIOP) is a frequent and potentially disabling condition. In a meta-analysis on oral GC therapy and loss of bone mineral density (BMD) or fracture risk, including 66 papers on bone density and 23 on fractures, the risk of fracture was found to increase rapidly already within 3–6 months after the start of oral GC therapy more than 5 mg prednisone-equivalent per day, independently of disease treated, age and gender [6]. In that study, strong correlations were observed between cumulative dose of GCs and loss of BMD and between daily dose of GCs and risk of fracture. In another study, the combined effect of higher daily dose (>10 mg per day), longer duration of therapy (≥90 days of use) and continuous GC intake was associated with a relative risk for hip fracture of 7.16 (95% CI: 2.13–24.0) and for vertebral fracture of 16.94 (95% CI: 8.17–35.11) [7]. These data indicate a rapid deleterious effect, especially on trabecular bone, in line with the clinical observation that the prevalence of vertebral fractures during GC treatment is higher than that of other common sites for osteoporotic fracture, such as femur, humerus, forearm and wrist, ribs and other nonvertebral sites [8]. Nonvertebral fractures, especially of the femur, cause acute pain and loss of function, and nearly always lead to hospitalization, with serious mortality and morbidity, for example, slow recovery and often incomplete rehabilitation, leading to decreased physical and social functioning

Future Medicine part of fsg

and reduced quality of life [9]. Vertebral fractures may occur without serious symptoms; in patients on chronic GC therapy, prevalence of asymptomatic vertebral fractures was found to be >37% [10]. However, vertebral fractures often recur, and the resulting disability increases with the number of fractures. GC-induced bone loss is partially reversible after cessation of this therapy [11]. The potential of recovery after cessation of GC therapy was demonstrated by osteodensitometry in patients with rheumatoid arthritis (RA) after cessation of GC treatment [12].

Despite guidelines on the management of GIOP, effective medications and fracture outpatient clinics, this condition remains under-recognized and undertreated. During the treatment with GCs, the overall use of bone-protective medication was low (4.0–5.5%) [1]. This review will cover mechanisms involved in GIOP, monitoring of patients on GC therapy, guidelines on GIOP and treatments for GIOP.

Pathogenesis

Osteoporosis is defined as a systemic skeletal condition characterized by low bone density and microarchitectural deterioration of bone tissue [13]. GIOP is the most common form of secondary osteoporosis. It is important to note that in patients with GIOP, there are other factors next to GC which contribute to bone loss, for instance advanced age, postmenopausal status, if present, and the disease for which GCs are prescribed [14–16]. It is estimated that GCs influence the transcription of about 1% of the entire genome, a very broad spectrum of effects induced by a single class of endogenous hormones and hormonal drugs. The effects of GCs are mediated via classic genomic mechanisms as effected by activation of the cytosolic GC receptor (GCR) and via nongenomic mechanisms, for example, involving binding to cytosolic or membrane-bound GCRs or involving interactions with cellular membranes [17]. The direct and indirect effects of GCs related to bone and fractures are manifold [18,19]; we will try to summarize them here (Figure 1). Not all of the effects and mechanisms are exactly known, however; especially the relative magnitudes of the effects and the interplay of positive and negative effects need to be further elucidated.

Effects of GCs on bone cells

GCs inhibit osteoblast differentiation (by suppressing the Wnt signaling pathway via stimulation of the production of Wnt pathway inhibitors, such as Dkk-1 and sclerostin; and by inhibition of the bone morphogenetic protein pathway), induce apoptosis of osteoblasts (by activating caspase 3), and stimulate bone marrow stromal cells to differentiate toward adipocytes instead of osteoblasts (via PPARγ2 and RUNX2). All these mechanisms result in decreased number of mature osteoblasts and decreased bone formation, which is the hallmark of GIOP. GCs also induce apoptosis of osteocytes (by activating caspase 3), which results in reduced bone strength. The lifespan of osteoclasts is prolonged (via inhibition of OPG and via increased RANKL expression; see Figure 2). Increased GC-induced apoptosis of osteoblasts and osteocytes could account for the decreased production of RANKL by these cells at GC therapy of longer duration, leading to a reduced number of osteoclasts [20]. This could explain the less rapid loss of bone after 6–12 months of therapy, compared with the first 6–12 months.

Other effects of GC on bone

GCs inhibit intestinal calcium absorption and increase urinary calcium excretion (by inhibiting the renal tubular calcium reabsorption), leading to decreased bone mass [21]. Physiologically, decreased serum calcium might lead to increased levels of parathyroid hormone (PTH), or increased sensitivity of bone for PTH, leading to increased bone resorption. However, studies on a serum level of PTH in GC users are not consistent, and the role of secondary increase of PTH in GIOP has been questioned [22]. Furthermore, a study on PTH in chronic GC users showed that it is not the serum PTH level (which stays the same in patients and controls), but the mode of PTH pulsatility which is altered by GCs [23]. In this study, a reduced amount of PTH was secreted at the tonic mode, combined with increased fractional pulsatile PTH secretion. These latter changes might be a part of an intrinsic bone loss-compensating mechanism as they mimic the efficacious exogenous intermittent PTH treatment in GIOP [23]. GCs impair bone mineralization through a negative influence on the bone matrix proteins, such as collagen type I, and the bone-building IGF-1 and osteocalcin [24]. It is known that GCs affect gonadal function at multiple levels in the hypothalamic–pituitary–gonadal axis: on the hypothalamus level (decrease of synthesis and release of gonadotropin-releasing hormone); on the pituitary gland (inhibition of synthesis and release of luteinizing hormone and follicle-stimulating hormone); and on the testis and ovary (modulation of steroidogenesis and gametogenesis) [25]. In patients with endogenous GC excess, for example, Cushing's syndrome, hypogonadism with decreased sex hormone levels in men and women is common [25], leading to increased bone remodeling and bone resorption.

GCs lead to decreased loading of bone via muscle atrophy, through inhibition of the muscle production of insulin-like growth factor 1 (IGF-1), also called somatomedin C, a muscle anabolic growth factor, and by stimulating the muscle production of myostatin, a

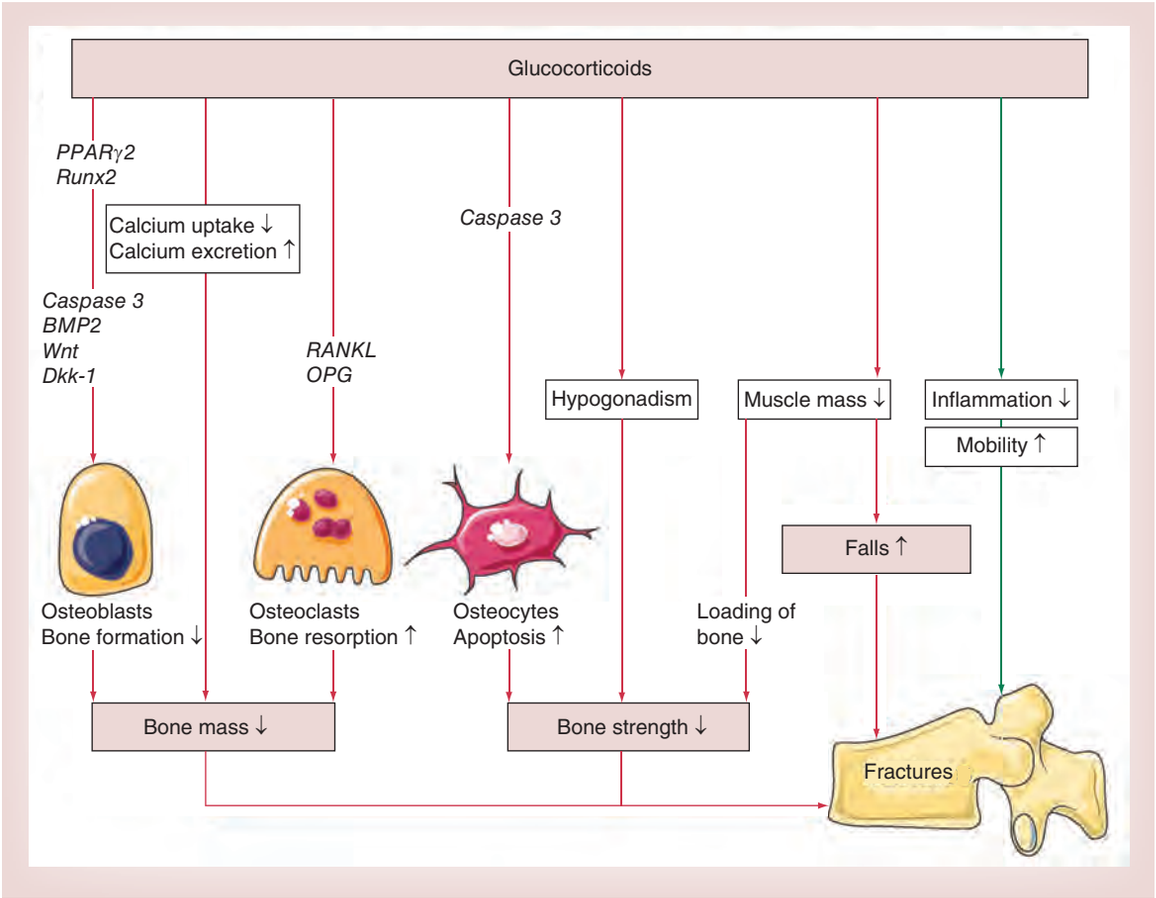

Figure 1. Effects of glucocorticoids on bone. The figure is not exhaustive: not all of the effects and mechanisms are exactly known. Red arrows: mechanisms negative for bone; green arrow: mechanism positive for bone. PPARγ2: Nuclear receptor peroxisome proliferator-activated receptor-gamma 2 signaling; Runx2: The Runx2 gene product, stimulating differentiation of mesenchymal cells into osteoblasts; Caspase 3: A critical enzyme for apoptosis and cell survival; BMP2: Bone morphogenetic protein-2 of the group of BMPs, which belong to the transforming growth factor-β superfamily, initiating bone formation; WNT: WNT signaling pathway regulating bone homeostasis; DKK-1: Dickkopf-1, WNT inhibitor; RANKL: Ligand of receptor activator of nuclear factor kappa B (RANK), differentiating and activating osteoclasts; OPG: Osteoprotogerin, the anti-osteoclastic decoy receptor for RANKL.

muscle catabolic growth factor [26]. Decreased muscle mass is associated with narrower bones, thinner cortices, decreased bending strength and impaired balance and thus an increased risk of falls and fractures in elderly men [27].

Effects of GCs via suppression of inflammatory processes

GCs are the mainstay of therapeutic regimens in most inflammatory and autoimmune conditions. There are also positive effects of GCs on bone via inhibition of the inflammatory - bone loss inducing [14,28] - process, for which the GC therapy is prescribed. TNFα induces expression of Dkk-1 in synovial fibroblasts and of sclerostin in osteocytes, which both inhibit bone formation by osteoblasts [28]. Proinflammatory mediators stimulate M-CSF from osteoblasts and RANKL from osteoblasts and bone stromal cells [29]. These mechanisms result in bone resorption (Figure 2) [18]. Inhibition of these inflammatory processes by GCs leads to less negative influence of these inflammatory mechanisms on bone. In addition, improved mobility by GCs and resulting weight-bearing activities and possibly also increased exposure to sunlight exert positive effects on bone too. As an example, in the second 'computer-assisted management in early RA' trial (CAMERA-II), patients with early rheumatoid arthritis (RA) all got a methotrexate-based tight control strategy and were randomized to receive additionally 10 mg prednisone daily for 2 years or placebo [30]. After these 2 years, during which the additional prednisone group had lower disease activity and developed less joint erosions, there were no differences in BMD between both strategy groups (which had been prescribed calcium, vitamin

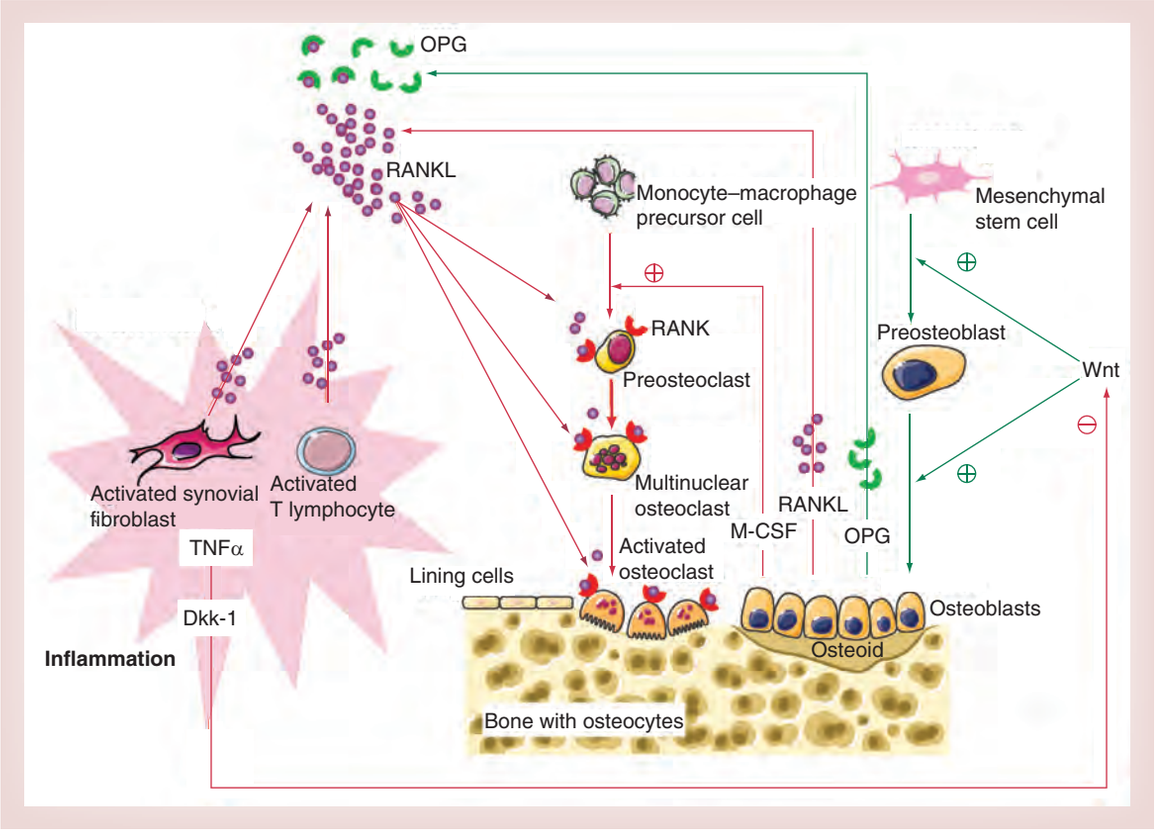

Figure 2. Mechanisms of inflammation and bone remodeling. Red arrows: mechanisms negative for bone; green arrows: mechanisms positive for bone. Inflammation stimulates osteoclastic bone resorption via RANKL: ligand of receptor activator of nuclear factor kappa B (RANK). Proinflammatory mediators stimulate osteoblasts to release macrophage colony-stimulating factor (M-CSF), stimulating osteoclastogenesis. Osteoblasts can also release osteoprotogerin (OPG), a decoy receptor for RANKL, inhibiting osteoclastogenesis by binding RANKL. Tumour necrosis factor alpha (TNFα) induces expression of dickkopf-1 (Dkk-1) in synovial fibroblasts, which inhibits osteoblastogenesis and bone formation via the Wnt signaling pathway.

D and bisphosphonates), and no bone loss occurred within either group [31]. At long duration of GC therapy and especially higher daily doses however [32], the negative effects of GCs very likely outweigh the positive effects of GCs on bone mediated by suppression of disease activity.

So, the GC-induced increased risk on osteoporotic fractures is based on multiple mechanisms, not all negative, affecting BMD, bone turnover, microarchitecture and other factors, like myopathy leading to a propensity to fall. Decreased bone formation seems to be the most important negative effect. A negative influence on bone microarchitecture is reflected by the finding that, at the same BMD, the risk of osteoporotic fractures is higher in patients on GCs compared with patients not using GCs [33].

Assessment of risk of GIOP

The challenge is to prevent GIOP rather than to diagnose and treat osteoporosis when the first fracture has occurred already. This involves assessment of clinical risk factors and BMD, where appropriate; several different approaches have been recommended worldwide.

Clinical risk factors

Next to GC use (>7.5 mg prednisone equivalent daily for 3 months or more) and the inflammatory disease for which the GC is prescribed, in patients treated with GCs there are often other risk factors for osteoporosis, such as postmenopausal status, smoking, advanced age, physical inactivity, malnutrition, parental history of osteoporotic hip fracture and low body weight [34]. Additional risk factors for future fracture include a fracture after the age of 50 years, prevalent vertebral fracture and previous fragility fracture. To assess risks, questionnaires can be used or online algorithms, such as FRAX® [35,36].

FRAX

This is an online tool developed by the WHO Collaborating Centre for Metabolic Bone Diseases in Sheffield,

UK. This algorithm calculates fracture probability from easily obtained clinical risk factors in men and women: age, sex, BMI and dichotomized variables comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, use of long-term oral GCs, RA, other causes of secondary osteoporosis and high alcohol consumption (see Box 1). Femoral neck BMD can optionally also be imputed to enhance the precision of fracture risk prediction [35]. The output of FRAX is the 10-year probability of a major osteoporotic fracture in general and the 10-year probability of hip fracture.

Precision of fracture estimates is compromised by dichotomizing several risk factors, without further quantification, for example, it probably is important how active and long standing RA is to estimate the magnitude of its negative influences on bone. Similarly, risks probably are different for smoking a few cigarettes a day compared with many; the same may hold true with respect to alcohol intake. Quantification of risk of GCs dependent on duration of GC therapy and dosing schedules is not possible in FRAX either [37], although conversion factors are available for the adjustment of the risk of a major fracture in low dose (<2.5 mg prednisone equivalent per day) and high-dose (>7.5 mg prednisone equivalent per day) chronic GC users [38]. Additional risk factors such as the risk of falls are not represented in FRAX and warrant clinical judgment of the individual patient [39].

The current American National Osteoporosis Foundation Guide recommends treating patients with 10-year risk scores according to FRAX of 3% or more for hip fracture or 20% or more for major osteoporotic fracture, to reduce their fracture risk [40].

Assessment of vertebral fractures

Prevalent vertebral fracture is a risk factor for future osteoporotic fractures. Plain radiographs of the thoracolumbar spine are still the gold standard for diagnosis of vertebral fracture. Vertebral fractures can be graded semiquantitatively, by estimating the loss of height of the vertebrae, using the Genant classification, as mild (grade 1: 20–25% height loss), moderate (grade 2: 25–40% height loss) or severe (grade 3: >40% height loss) [41]. Vertebral fracture assessment (VFA) is a technique available in modern BMD measuring machines via dual x-ray absorptiometry (DXA), permitting diagnosing of vertebral fractures. Although concordance between conventional x-ray assessments and assessments obtained from VFA seems acceptable, if in doubt of VFA results, plain radiographs may be performed.

BMD assessment

Dual x-ray absorptiometry

The technique generally of choice for the measurement of BMD is DXA, which has been demonstrated to be reliable in diagnosing osteoporosis and monitoring bone mass variations over time, also in GIOP [42].

The BMD of lumbar spine and of the nondominant total hip is measured by a densitometer in g/cm^2 and the deviations from peak bone mass and age-matched normal value are expressed in standard deviations, T-score and Z-score, respectively. From the measurements at the two sites, the worst score can be used for diagnosis, according to WHO criteria (T-score ≥ -1: normal BMD; -2.5 < T-score < -1: osteopenia, T-score ≤ -2.5: osteoporosis).

BMD is only a surrogate marker of bone strength. In patients with GIOP, at the same BMD, the risk of osteoporotic fractures is higher compared with patients not using GCs [33]. This is the reason that BMD thresholds in different guidelines for the prevention of GIOP are debated and often differ. A study on vertebral fractures in male GC users showed increased prevalence of vertebral fractures, not accounted for by BMD [43].

Other techniques

Quantitative computed tomography (QCT) is useful to separately study cortical and trabecular bone and

Box 1. Parameters and risk factors used in FRAX®.

- Country
- Age
- Gender
- Clinical risk factors:
  - Low BMI (weight and height)
  - Previous fragility fracture, yes or no
  - Parental history of hip fracture, yes or no
  - Glucocorticoid treatment, yes or no
  - Current smoking, yes or no
  - Alcohol intake (3 or more units per day), yes or no
  - Rheumatoid arthritis, yes or no
  - Other secondary causes of osteoporosis, yes or no
- Optionally: femoral neck bone mineral density

to measure true 'volumetric' BMD. It has been suggested to be a better predictor of vertebral fractures than DXA. However, QCT has the drawback of possible underestimation of bone mass and T-scores for the same skeletal site compared with DXA [42]. Bone density assessed by peripheral QCT (assesses BMD in a peripheral part of the body, such as the forearms or legs) or volumetric QTC and bone quality assessed by high-resolution QTC or high-resolution MRI of bone have been evaluated in prediction of the risk of fracture in human GIOP [44]. A microstructural model combining aspects of cortical and trabecular bone reflects fracture severity accurately and assessment of bone quality might be more accurate to predict fractures than BMD measurement, but these techniques are not generally available, and have some other disadvantages like costs, and radiation exposure in case of CT.

Quantitative ultrasound (QU) is considered to reflect both BMD and structural properties of bone such as connectivity and elasticity. QU is able to diagnose low BMD in GIOP and to predict future fractures [45], but its role in monitoring BMD changes and in predicting fracture risk in daily practice remains unclear.

Pharmacological options to prevent & treat GIOP

This section focuses on calcium and vitamin D, bisphosphonates, and PTH and PTH analogues, since these are currently the only groups of medications that are clinically used for prevention and therapy of GIOP. Other medications are described in short. Only of bisphosphonates and the PTH analogue teriparatide, prevention of vertebral fractures in GC users has been demonstrated; vertebral fracture has not been a primary end point of any study. There is no medication that has clearly been proven to prevent nonvertebral fractures [46].

Calcium & (active) vitamin D

Because of beneficial effects, low toxicity and low cost, all patients being started on GCs should receive prophylactic therapy with calcium and vitamin D, unless there is evidence of an adequate dietary calcium intake and vitamin D status [47], which is seldom the case. Clinically and statistically significant prevention of bone loss at the lumbar spine and forearm was demonstrated in an early meta-analysis in GC treated patients [48], but another systematic review did not find any effects of calcium and/or (active) vitamin D on either vertebral or nonvertebral fractures [49]. Yet another meta-analysis showed that active vitamin D treatment during GC therapy was more capable of preserving BMD and decreasing the risk of vertebral fractures, compared with no treatment, placebo or plain vitamin D3 and/or calcium [50]. However, active vitamin D cannot completely prevent bone loss during GC-treatment, that is, there is still a decrease in BMD; in this respect it has been shown inferior to alendronate [51]. Evidence for an association between calcium intake and risk of cardiovascular death remains controversial [52–55]. It seems sensible to supplement calcium 500 mg/day in those using dairy products, but insufficiently, and 1 g in those using virtually no dairy products. For vitamin D, supplementation should aim at increasing serum 25-hydroxy vitamin D levels to the 50–75 nmol/l range, which is generally achievable with a vitamin D dose of 800 IU/day [56].

Bisphosphonates

Bisphosphonates attach to hydroxyapatite binding sites of bone. During bone resorption by osteoclasts the bisphosphonate is released, impairing the ability of osteoclasts to form a ruffled border, to adhere to the bony surface and to produce the protons necessary for continued bone resorption [57]. Bisphosphonates also decrease development of osteoclast progenitor cells and promote apoptosis of osteoclasts. On the other hand, bisphosphonates also reduce bone formation because bone resorption and bone formation are coupled. So bone turnover is decreased [58].

In an older meta-analysis including mainly studies on the currently no longer used first-generation bisphosphonate etidronate, bisphosphonates as a group compared with placebo were found effective at preventing and treating GC-induced bone loss at the lumbar spine and femoral neck [59]. In a trial, alendronate showed significantly higher BMD in prevention and treatment of GIOP as compared with placebo [60], and risedronate has been shown to improve BMD in two trials [61,62].

Although the effectiveness of bisphosphonates in preventing and treating GIOP is generally accepted – based on the surrogate outcome of increased BMD – proof of their antifracture effect is scarce. Of the bisphosphonates, only risedronate has been proven to be effective in preventing GC-induced vertebral fractures in a meta-analysis [49], and only one randomized clinical trial – comparing the effect of alendronate with that of alfacalcidol in patients with rheumatic diseases starting on GCs – has been done since; this study showed as a secondary outcome a trend of less vertebral fractures [51]. In an extension trial on the 2-year effects of alendronate on BMD and vertebral fracture in patients receiving GCs, there were fewer patients with new vertebral fractures in the alendronate group compared with the placebo group [63]. An observational study indicated that both alendronate and risedronate

decreased the risk of symptomatic vertebral and nonvertebral fractures over time [64]. These bisphosphonates generally are considered cost effective in patients with high fracture risks, such as elderly patients (with a life expectancy over 5 years), and younger patients with a history of fragility fracture, low BMI, active RA or on high GC doses [65]. Alendronate and risedronate most frequently are taken once a week, orally.

Zoledronate, which is given once a year intravenously, could be a solution to the poor compliance and adherence to treatment of daily or weekly oral bisphosphonates [66]. In a trial, there was noninferiority and possibly more effectiveness of once-yearly zoledronate versus daily risedronate, in the prevention and treatment of GC-induced bone loss [67]. *Post hoc* analyses of the study showed more preservation of BMD by zoledronate compared with risedronate among men [68], and more effectiveness of zoledronate in increasing lumbar spine BMD across diverse subgroups of patients [69].

Ibandronate, which is given once monthly orally, increased BMD in contrast to placebo with an acceptable safety profile in postmenopausal women treated with low-dose GCs for inflammatory rheumatic diseases [70], and in cardiac transplant patients [71]; in the latter group there were also less vertebral fractures.

Neridronate intramuscular injections once monthly in rheumatic patients on GC therapy similarly increased lumbar and femoral BMD over 12 months [72].

Adverse effects

Although adverse events of bisphosphonates have not specifically in detail been studied for the GC-using population, it is assumed they will occur in this population similarly as in other populations.

Osteonecrosis of the hip, knee & of the jaw

In a large case–control study on the epidemiology of osteonecrosis, 76% of osteonecrosis cases was osteonecrosis of the hip (ONH); systemic GC use during the previous 2 years was one of the risk factors for developing osteonecrosis. Only 4.4% of patients with osteonecrosis had been exposed to bisphosphonates within the previous 2 years; bisphosphonate use was not a significant risk factor. [73]. Clinical experience is that at higher dosages of GCs, especially in specific populations, such as systemic lupus erythematosus (SLE) patients, ONH and osteonecrosis of the knee joints is not very rare. Although many of these patients will be using a bisphosphonate to prevent GIOP, in general, osteonecrosis in these patients is attributed to the GC, not to the bisphosphonate therapy.

Osteonecrosis of the jaw (ONJ) has many related etiologic factors, including dental surgery and GC therapy [74,75]. Intravenous bisphosphonates have been identified as a risk factor for ONJ in oncology patients, especially when undergoing dental surgery, whereas oral bisphosphonate use in patients with benign diseases increases the risk of ONJ only marginally [76]. Osteoporosis patients with appropriate dental care and good oral hygiene receiving oral or intravenous bisphosphonates do not require an extra dental examination prior to initiating therapy.

Stopping smoking, limiting alcohol intake, appropriate physical activity and maintaining good oral hygiene might be emphasized as lifestyle measures to prevent ONJ for all patients receiving bisphosphonate therapy [77].

Long bone mid-shaft fractures

Long-term bisphosphonate therapy may increase the risk of atypical long bone mid-shaft fractures; other risk factors are GCs, and proton pump inhibitors and other antiresorptive agents [78,79]. Prolonged suppression of bone turnover could lead to accumulation of microdamage of bone and development of hypermineralized bone [20] both inducing decreased bone strength. More caution might be needed if bone is already compromised by prolonged use of GCs [80]. However, although the risk of this problem in any patient receiving bisphosphonates remains unknown and although the true incidence of the problem may be masked by lack of awareness and underreporting, the risk is considered to be small [79], particularly when comparing the number of atypical fractures with that of osteoporotic fractures prevented by bisphosphonates.

Teratogenicity

In animal studies with bisphosphonates, serious complications have been shown for the fetus; bisphosphonates are therefore relatively contraindicated in pregnancy (US FDA category C: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women, despite potential risks") [81]. As bisphosphonates are accumulated in mineralized bone for several years, can be released from bone and can cross the placenta, they might also pose a teratogenic risk after the therapy has been stopped, their usage is also relatively contraindicated in premenopausal women prior to future conception [81].

PTH & PTH analogues

The rationale for using these drugs in the treatment of GIOP is that daily injections of PTH analogues decrease osteoblast and osteocyte apoptosis and increase bone formation and bone strength; as such

they counteract the key pathogenic mechanisms of GCs on bone, attenuating the GC effects on osteoblast survival and Wnt signaling [82]. Both recombinant full-length PTH (amino acids 1–84) and the recombinant shortened molecule PTH (N-terminal amino acids 1–34), named teriparatide, are available for clinical use; however, only teriparatide has been studied in GIOP. GIOP patients treated with teriparatide for 36 months had greater increases in BMD and fewer new vertebral fractures than GIOP patients treated with alendronate [83]. *Post hoc* analyses showed similar findings among subgroups of men and pre- and post-menopausal women with GIOP; in premenstrual women no vertebral fractures occurred [84]. In another 18-month trial in male patients with GIOP, teriparatide induced larger improvements than risedronate in spinal BMD and microstructure as assessed by high-resolution QCT [85].

There is evidence of absence of synergy between PTH and alendronate [86], but a combined regimen of teriparatide and denosumab increased BMD more than either agent alone in women with postmenopausal osteoporosis; the combination therapy therefore might be used to treat patients at a high risk of fracture [87], but its value in GIOP has yet to be investigated. Sequential antiresorptive therapy, for example, with bisphosphonates, after PTH (analogue) treatment might consolidate the beneficial effects of PTH on the skeleton [88]. An observational study in which postmenopausal women on GC therapy with severe osteoporosis were treated with teriparatide for up to 18 months, followed during 18 months by other osteoporosis medications seems to confirm this hypothesis [89].

Due to its high costs, PTH analogues are in many countries predominantly used for bisphosphonate-refractory osteoporosis or in case of adverse effects of bisphosphonates. Data from a Swedish cohort indicate that the selection of teriparatide instead of an oral bisphosphonate as a first-line treatment for a high-risk GIOP cohorts is justified at a cost per quality-adjusted life year threshold of €50,000 [90], which is above the threshold for approval from instances such as the British National Institute for Health and Clinical Excellence (NICE). The adverse effects of teriparatide are generally considered to be mild. It increased serum calcium in a study among 360 women, with the maximum effect (median increase of 0.1 mmol/l) observed at approximately 4.25 h after injection; serum calcium returned to predose levels by 16–24 h after each dose [91].

Other medications

A systematic review did not find any effects of calcitonin, estrogen or fluoride on vertebral or nonvertebral fractures in GIOP [49]. A small study among postmenopausal women receiving long-term GCs reported that the selective estrogen receptor modulator raloxifene significantly increased BMD of the spine and hip after 12 months of treatment, but no statistically significant difference in vertebral fractures could be demonstrated between the placebo and raloxifene group in this underpowered study [92].

Denosumab

The human monoclonal antibody denosumab is an antibone-resorptive drug acting via inhibition of RANKL, decreasing the maturation of osteoclasts (see Figure 1). No randomized controlled trial has yet been performed to compare its effect with that of other treatments, bisphosphonates in particular, among GC users. A *post hoc* analysis of a Phase II trial in RA patients showed an increase in mean lumbar spine and hip BMD in patients treated 12 months with denosumab, irrespective of concomitant bisphosphonate or GC use, but the trial was not designed to study GIOP [93]. An adverse effect is hypocalcemia [94].

Strontium ranelate

Strontium ranelate is incorporated in bone at the position of calcium. A recent histomorphometric study showed that patients treated with strontium ranelate had a significant decrease in the parameters of bone formation after both 6 and 12 months, but no change in bone resorption [95].

Clinical trials, however, provide strong evidence for its effectiveness at preventing fractures in women with postmenopausal osteoporosis, with studies showing a 41% reduction in vertebral fracture risk and a 16% reduction in nonvertebral fracture risk after 3 years of treatment [96,97]. There are no prospective data on the effects of strontium ranelate in GIOP, but a retrospective analysis of its use among a subgroup of chronically GC-treated patients suggested an even greater BMD increase compared with that among risedronate users [98]. Strontium ranelate causes a clinically significant overestimation of BMD because of the high attenuation of x-rays by strontium atoms in bone, compromising the correct interpretation of future BMD measurements [99].

Management of GIOP

During the past decade, several guidelines for the prevention and treatment of GIOP were published [100–102]. Recently, a framework for the development of guidelines for the management of GIOP was published by an international working group [103], helping to provide standardized care for patients at risk of GIOP. In a review of the American College of Rheumatology

(ACR) guidelines [104], the lack of information about safety of long-time treatment with bisphosphonates and teriparatide in patients on long-term GC use is discussed; based on expert opinion, and a preference for short-acting drugs like teriparatide instead of bisphosphonates, is expressed in fertile premenopausal women [104]. In general, guidelines on management of GIOP all have a similar structure (Figure 3). Management can also be classed into five stages:

- Stage 0 (before start of GC therapy): awareness, agreement and infrastructure;
- Stage 1: tailoring of the GC dose and regimen;
- Stage 2: lifestyle advice, screening for osteoporosis and assessment of fracture risk, supplementation and preventive medication;
- Stage 3: addressing compliance and adherence of supplementation and preventive medication;
- Stage 4: GIOP data evaluation, reflection and search for improvement.

Stage 0: awareness, agreement & infrastructure

Awareness of the risk of GIOP and of local protocols and guidelines on GIOP, agreement between the health professionals on management and a solid infrastructure are the basis of real tight GIOP management. A small study among UK rheumatologists found a high level of awareness of GIOP and most patients identified to be at high risk of bone loss were offered treatment [105]. In Denmark an increasing trend of alendronate treatment in patients with systemic GC exposure was found, indicating increased awareness of GIOP [106]. However, in another study on postmenopausal women with osteoporosis, many patients were untreated [107]; similarly, bone health-related care was found suboptimal in specific patients groups [108], such as a community-based cohort of SLE patients [109], and RA patients using GCs [110]. On average, approximately 27–40% of those who should receive a prescription for bone protective drugs receive one [111,112].

Agreement between the health professionals is important, but physicians within the same practice setting managed osteoporosis patients not more similarly compared with physicians working apart in different practices [113]. Patient and rheumatologist perspectives should be included in recommendations, to improve the implementation and patient adherence [114].

Stage 1: tailoring of the GC dose & regimen

Tailoring the GC regimen to the individual patient, that is, evaluation of indication and dose at the start of GC treatment and of the need of continuation and dose during GC treatment (Figure 3), is the first, logical step to limit adverse effects of GCs, including GIOP [4].

Stage 2: lifestyle advice, screening for osteoporosis & assessment of fracture risk, supplementation & preventive medication

Patient information and lifestyle advice, including on diet, stopping smoking, fall prevention and prescription of calcium and vitamin D supplements, where appropriate, are following steps. Depending on fracture risk, medication (especially bisphosphonates) may be indicated, with teriparatide as a second-line option for patients on GC [47]. In general, therapies effective for postmenopausal osteoporosis have the potential to be effective for GIOP [115], but their efficacy has yet to be proven. The jury is still out on how optimally manage the risk of GIOP in premenopausal fertile women, young males and children on GCs.

Stage 3: addressing compliance & adherence of supplementation & preventive medication

This is perhaps most challenging of all the stages and should not be underestimated, as adherence is a major problem in all chronic medication prescriptions, also for GIOP [66]. Improvement could be expected from education of patients and health care providers [116], although the desired effect could be modest [117]. Written information might enhance awareness of osteoporosis in patients and improve compliance and adherence [118].

Stage 4: GIOP data evaluation, reflection & search for improvement

Not all fractures will be prevented even with adequate strategies, and the data on treated patients should be collected as much as possible for evaluation, reflection and search for improvements. In addition, cost–effectiveness and implementation programs should be evaluated [119]. Safer treatment with low-dose GCs in daily practice might be enhanced with implementation of a limited set of recommendations [120].

Research agenda

For the GIOP research agenda the following three groups of items are of relevance:

- Optimizing treatment with GCs;
- Developing new treatment modalities for GIOP;
- Solving GIOP specific uncertainties.

Optimizing treatment with GCs

If treatment with GCs could be improved, leading to better efficacy, the dose could be lower and with it, the

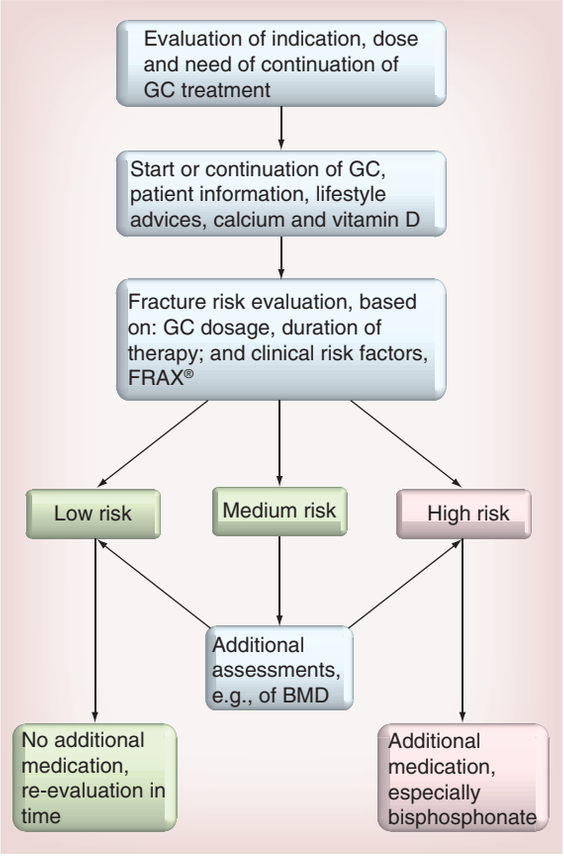

Figure 3. Management of glucocorticoid-induced osteoporosis.
BMD: Bone mineral density; GC: Glucocorticoid.

risk of adverse effects such as GIOP could be lower. Basically, there are two ways to optimize treatment with GCs: improving the treatment with (adaptations of) conventional GCs; and the development of new drugs with GC activity, for example, GCR ligands.

Improving the treatment with (adaptations of) conventional GCs

Deflazacort, an oxazoline analog of prednisolone, was associated with decreased loss of total skeleton and lumbar spine BMD, comparing to prednisone, in kidney transplant patients [121], but there is the issue of the real equivalence ratio compared with prednisolone [122]. More pharmacologic studies are needed to elucidate whether it has greater immunosuppressive activity and, therefore, increases the risk of opportunistic infections compared with other synthetic GCs [123].

Modes of administration are important, for example, weekly oral GC-pulse therapy was found to induce no significant bone loss or adrenal suppression [124]. A modified release prednisone tablet has been developed, which, taken by the patient at 10:00 PM, releases the drug and targets the hypothalamic–pituitary–adrenal axis from 02:00 AM onwards, to prevent the early morning rise of interleukin-6 (IL-6) and TNFα: chronotherapy. In two studies [125,126], the efficacy of this formulation in RA has been shown; studies are needed to see whether this modification is effective also in other diseases, can lead to lower dosages of GCs and to lower incidence of adverse events.

To increase the anti-inflammatory activity of GCs the antithrombotic drug dipyridamole has been added in a combination drug, allowing the use of a lower dose of prednisolone; though effective in animal models, efficacy was not confirmed in preliminary human studies [127]. Liposomal formulations have been developed to enable targeted delivery of GC to the side of inflammation; some positive experience in patients with RA have been reported and a Phase II study is planned [128].

Development of new drugs with GC activity, for example, GCR ligands

The idea behind the development of selective GCR agonists (SEGRAs) is that these new compounds inhibiting the anti-inflammatory transrepression mechanisms of GCs without affecting transactivation mechanisms leading to metabolic adverse effects would have an improved benefit:risk ratio. Several SEGRAs have been and are being developed, but none of them have reached the clinic. A study in a mouse strain with a transactivation deficiency showed classic side effects, such as osteoporosis, challenging the concept of SEGRAs [129]. Therefore, the development of successful SEGRAs now seems even more a challenge than ever before [130].

Developing new treatment modalities for GIOP

As indicated above, denosumab and strontium ranelate need further testing for prevention and treatment of GIOP. There are some medications that are further away from clinical practice. Dehydroepiandrosteron (DHEA) therapy might indirectly influence GIOP; in a study on GIOP in women, significant increase of BMD in the lumbar spine and femoral neck was observed after 6 and 12 months [131]. The significantly increased serum androstenedione and testosterone concentrations – as expected – impede implementation DHEA in daily clinical practice. A review described a positive effect on the bone of patients treated with GCs of menatetrenone (vitamin K) [132]; further research is needed. Glycyrrhizic acid has been shown to reduce serum concentration of the bone resorption marker pyridinoline and to inhibit 11-β-hydroxysteroid dehydrogenase 1 activity in bone, which converts inactive GCs into active GCs [133]. This compound has to be tested further.

Also new nonpharmacological approaches might be worthwhile to develop. In rats, low-intensity and high-frequency mechanical vibration was able to partially inhibit the deleterious consequences of GCs on bone structure [134]. Pulsed electromagnetic fields during dexamethasone administration upregulated early mRNA expression of insulin-like growth factor 1 (IGF-1), which has a positive effect on bone [135].

Solving GIOP specific uncertainties

As indicated above, optimal management of premenopausal fertile women, young males and children needs to be further elucidated. Long-term suppression of bone turnover by bisphosphonates (and denosumab) could lead to decreased strength of bone and atypical fractures; strategy GIOP studies are needed to evaluate the place and sequence of bone-stimulating therapies (such as PTH and teriparatide) and these bone resorption-inhibiting drugs. Also more data are needed on risk factors predicting fractures among patients on GCs; thresholds of BMD and clinical risk factors for intervention in the management of GIOP need to be established. A clear difference between the association of BMD and fracture risk in postmenopausal osteoporosis versus that in GIOP makes it difficult to translate many of the general osteoporosis data to the specific condition of GIOP.

Conclusion & future perspective

GIOP is potentially one of the most devastating side effects of chronic GC use, but it can be prevented and treated. In inflammatory diseases, both GCs and the disease treated contribute to deterioration of bone. Although awareness of GIOP among the physicians and patients increases, it still is insufficient. Proper assessment and management according to national guidelines should be broadly implemented. Once on bone-protective treatment, patients' adherence becomes a crucial key to success; more effort is needed to educate both patients and professionals. Research is needed to develop new GC treatment modalities, new agents for bone protection, elucidating novel mechanisms of GCs action on bone, and, most of all, for developing evidence-based treatment strategies with different drug categories, tailored to specific patient groups and the individual patient.

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Executive summary

Magnitude of a problem

- Glucocorticoid-induced osteoporosis (GIOP) is a frequent and potentially disabling condition.
- The risk of fracture increases rapidly after the start of oral glucocorticoid (GC) therapy.
- GIOP remains under-recognized and under-treated.

Pathogenesis

- GC excess inhibits osteoblast differentiation, induces apoptosis of osteoblasts and osteocytes, and prolongs the lifespan of osteoclasts.

Assessment of risk of GIOP

- Clinical risk factors for future fracture can be easily assessed.
- Osteoporosis can be diagnosed by bone mineral density measurement and vertebral fracture assessment.

Pharmacological options to prevent & treat GIOP

- Calcium and vitamin D supplementation is needed in inadequate intake, respectively deficiency.
- Bisphosphonates are the first choice treatment of GIOP and impair osteoclast development and function.
- Daily injections of parathyroid hormone analogues counteract the key pathogenic mechanisms of GCs on bone.
- There are no data yet on strontium ranelate or denosumab in GIOP.

Management of GIOP

- Start with tailoring of the GCs dose and regimen (as low and as short as possible).
- Pharmacological and nonpharmacological interventions for treatment and prevention of GIOP are available.
- Monitoring compliance and adherence is vital in therapy success.

Research agenda & future perspective

- Treatment with GSs needs to be optimized for lowering risk of GIOP.
- New treatment modalities for GIOP have to be developed.
- More knowledge on treatment options for specific osteoporosis patient groups is needed.

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