Management of glucocorticoid-induced osteoporosis: prevalence, and emerging treatment options

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Abstract: An excess amount of glucocorticoids represents the primary and most frequent etiological factor influencing secondary osteoporosis. Patients receiving glucocorticoids, but also those with the endogenous form of hypercorticism, are at high risk for the loss of bone density, with the subsequent occurrence of pathological fractures. In this review, we summarize the currently available methods of prevention and the treatment of glucocorticoid-induced osteoporosis. We also include a proposal for both a prophylactic and therapeutic approach that takes into account the risk factors typical for long-term users of glucocorticoids.

Keywords: glucocorticoid-induced osteoporosis, bone mineral density, osteoporotic fractures, calcium and vitamin D, bisphosphonates, teriparatide

Introduction
Glucocorticoid-induced osteoporosis (GIOP) is the most frequent and severe form of secondary osteoporosis. The prevalence of oral glucocorticoid use is 0.9% of the total adult population rising to 2.5% at age over 70 years. The most frequent indications for oral glucocorticoid therapy are respiratory, musculoskeletal and cutaneous diseases.

Glucocorticoid therapy results in a rapid loss of bone mineral density (BMD) within the first weeks of treatment. The rate of loss is greatest in the first year of therapy and incidence of osteoporotic fractures may be as high as 20% in endogenous hypercorticism and 30% to 50% in patients with long-term glucocorticoid oral use. First osteoporotic fractures occur as early as the first 3 to 6 months of hypercorticism.

Histomorphometric analyses of biopsies from glucocorticoid-treated individuals have demonstrated a reduction in bone formation at the cellular and tissue level, resulting in reduced bone volume and trabecular thickness. Higher doses and long-term use of glucocorticoids, however, also may be associated with an increase in bone resorption, leading to greater bone loss and disruption of cancellous bone architecture.

According to several studies, it is estimated that a cumulative dose is 30 g of oral prednisolone per year or 5 mg (and more) of oral prednisolone per day for more than 3 months.

GIOP is most common in children, postmenopausal women, young men and patients with long-term immobilization.

The association between osteoporosis and glucocorticoid therapy was made shortly after the first use of these drugs in humans in the 1950s, particularly in patients treated for asthma. The first population-based study of limb fractures was by Hooyman et al, who reported that the relative risk of hip, distal forearm fractures...
and proximal humoral fracture was doubled in a group of patients with rheumatoid arthritis treated with glucocorticoids, compared with patients with rheumatoid arthritis alone. A subsequent British case-control study confirmed that use of glucocorticoids approximately doubles hip fracture risk.10

Long-term glucocorticoid use is one of the most important osteoporosis risk factors. It is also an indication for densitometry.

A fracture risk assessment tool (FRAX) has been developed by World Health Organization to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. The FRAX models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. The FRAX algorithms give the 10-year probability of fracture. Glucocorticoid use is considered as severe risk factor.

Mechanisms of bone loss in GIOP

Glucocorticoids may exert their actions on the skeleton and related tissues in many ways. Their overall effects depend on a number of factors including the dose, the duration, the steroid type, and the species tested. There are direct effects on bone that result in diminished bone formation and unchanged or enhanced bone resorption. The most important effect of glucocorticoids is suppression of bone formation, which probably involves several mechanisms. First, glucocorticoids effect the differentiation and activity of many cell types, including those of osteoblast lineage and other cells within bone. Second, glucocorticoids modulate the transcription of many of the genes responsible for the synthesis of matrix constituents by osteoblasts, such as type 1 collagen and osteocalcin. Third, glucocorticoids influence the synthesis and activity of many local acting factors that affect osteoblasts, including cytokines (eg, interleukin 1 and 6), and growth factors, especially the insulin-like growth factors (IGF-I and IGF-II) and several of the IGF-binding proteins (IGFBP-3, -4 and -5). The latter effects may contribute in particular to the stunting of growth and retarded skeletal development in children treated with glucocorticoids. Recently, the role of apoptosis has gained prominence.13 Glucocorticoids shorten the lifespan of osteoblasts and osteocytes, the latter also being involved in the pathogenesis in glucocorticoid-induced osteonecrosis;14 in addition, glucocorticoids may promote osteoclast survival.15 Interestingly, bisphosphonates can reverse the pro-apoptotic effects of glucocorticoids on osteoblasts and osteocytes, which may contribute to their efficacy in preventing glucocorticoid-induced bone loss.16 In addition to these direct effects on bone cells, other mechanisms may also contribute to bone loss. Thus reduced intestinal calcium absorption and increased renal calcium excretion have been reported after the administration of glucocorticoids;17 whether these changes are associated with secondary hyperparathyroidism is controversial, most studies showing no increase in serum parathyroid hormone levels in glucocorticoid-treated individuals. Low serum testosterone levels have been reported in glucocorticoid-treated men and are believed to be due both to direct effects on the testis and indirect effects on testosterone production mediated via suppression of gonadotropin hormone secretion. Hypogonadism leads also to muscle decrease and increased risk of falls.18,19

Table 1  Risk factors – indications for densitometry

| Risk factor                                                                 | Indication for densitometry |
|----------------------------------------------------------------------------|------------------------------|
| Estrogen deficiency                                                       |                             |
| Early menopause (<45 years)                                               | Surgery performed            |
| Prolonged secondary amenorrhea (>1 year)                                  | Surgery performed            |
| Primary hypogonadism                                                      | Surgery performed            |
| Glucocorticoid use (>5 mg prednisolone >3 months)                         | Surgery performed            |
| is expressly the indication of densitometry                               | Surgery performed            |
| Mother history of hip fracture                                            | Surgery performed            |
| Low body mass index (BMI < 19 kg/m²)                                      | Surgery performed            |
| Diseases that leads to secondary osteoporosis                             | Surgery performed            |
| Anorexia nervosa                                                          | Surgery performed            |
| Malabsorption                                                             | Surgery performed            |
| Primary hyperparathyroidism                                               | Surgery performed            |
| Diffuse diseases of connective tissue                                     | Surgery performed            |
| Rheumatoid arthritis                                                      | Surgery performed            |
| Chronic inflammatory bowel diseases                                       | Surgery performed            |
| Post-transplantation syndrome                                             | Surgery performed            |
| Chronic renal failure                                                     | Surgery performed            |
| Hyperthyroidism                                                           | Surgery performed            |
| Prolonged immobilization                                                  | Surgery performed            |
| Cushing’s syndrome                                                        | Surgery performed            |
| Chronic hepatopathies                                                     | Surgery performed            |
| Myeloproliferative diseases                                               | Surgery performed            |
| Hereditary and metabolic bone diseases                                    | Surgery performed            |
| Suspicion of osteoporosis from X-ray or finding vertebral deformity        | Surgery performed            |
| Hip, vertebral or forearm fracure with low trauma                         | Surgery performed            |
| Decrease in stature or thoracic kyphosis                                  | Surgery performed            |
| Monitoring antiresorptive therapy                                         | Surgery performed            |
| Chronic medications (antiagulants, antiepileptics, thyroid hormones, cytostatics) | Surgery performed |
| Women over 65 years                                                       | Surgery performed            |
| Men over 70 years                                                         | Surgery performed            |

Modified from Payer et al 2007.11

The diagnosis consists of the patient's history, clinical examination, densitometry and biochemical analysis (bone
The administration of vitamin D increases calcium absorption and reduces bone resorption. Calcitriol also has a direct action and reduce bone resorption. The recommended dose of vitamin D is 800 IU per day. An adequate intake of calcium and vitamin D is essential in all preventive and also therapeutic recommendations. A single 5-mg infusion of zoledronate and daily oral risedronate, 5 mg, were compared in a 1-year randomized, double-blind, double-dummy study of patients with less than 3 months’ exposure of glucocorticoids and those in treatment for longer than 3 months. After 12 months, lumbar spine BMD increased significantly more with zoledronate than risedronate in the two subpopulations. Zoledronate was also more effective than risedronate in terms of increasing BMD of femoral neck, trochanter and total hip. This superior effect was apparent at 6 months. Importantly, long-term treatment of GIOP with bisphosphonates is very safe.

The effectiveness of bisphosphonate treatment depends on patients adhering to the therapeutic regimen. According to the VIVA study the vast majority of patients prefer a once-monthly regimen – the three most popular reasons

**Prevention and treatment of GIOP**

Although there are very few data on the effects of lifestyle interventions or modifications in GIOP, it seems reasonable to recommend certain measures that may reduce bone loss and fracture risk. These include reducing the dose of glucocorticoids to a minimum, the use of alternative routes of administration (e.g., inhaled or topical) or formulations (e.g., budesonide), and prescription of alternative immunosuppressive agents. Adequate levels of dietary calcium intake should be encouraged and good nutrition and normal body weight should be maintained where possible. In addition, individuals taking glucocorticoids should be advised not to smoke and to avoid alcohol abuse. Within the limits imposed by the underlying disease, physical exercise should be encouraged. Falls risk assessment and advice should be performed in those at increased risk of falling.21,22

Many studies report of inadequate prevention and also treatment of GIOP. According to the GPRD study in the United Kingdom,22 prophylaxis for GIOP was prescribed only to 14% of patients, but in the San Francisco General Hospital it was prescribed to only 8% of 215 patients.23

An adequate intake of calcium and vitamin D is essential in all preventive and also therapeutic recommendations.24 The recommended daily intake of calcium for an adult is 1200 to 1500 mg per day.25 In glucocorticoid-treated patients, combined intake of calcium and vitamin D is more effective. The recommended dose of vitamin D is 800 IU per day. The administration of vitamin D increases calcium absorption and reduce bone resorption. Calcitriol also has a direct effect on osteoblasts, opposing the effects of glucocorticoids on osteocalcin-gene expression, and calcitriol may reverse glucocorticoid-induced suppression of serum osteocalcin concentrations.18,25

Bisphosphonates are currently the major class of drugs used for GIOP, in addition to their primary role in the treatment of postmenopausal osteoporosis. They are synthetic analogues of pyrophosphates that are resistant to the action of endogenous pyrophosphates. They have a high affinity for the bone mineral of the skeletal surface and exert an inhibitory effect on several catalytic enzymes, of which the most important is farnesyl diphosphate synthetase, thus interfering with the mevalonate pathway of cholesterol formation. An insufficient prenylation results with a consequent dysfunction leading to apoptosis of osteoclasts. Osteoabsorption slows and, depending on the type of bisphosphonate, leads to disturbed remodeling, and prolongation of secondary mineralization. The following are bisphosphonates used in the treatment of osteoporosis: alendronate, ibandronate, risedronate, and zoledronate, with pamidronate, clodronate and etidronate used in some countries.26 First effect can be seen in 6 months, which means an increase in bone density.27 In most countries risedronate and alendronate are used for treatment of GIOP. Also intravenous ibandronate significantly reduced vertebral fracture risk in patients with GIOP in small study.28 Reid recently reported the safety and efficacy of intravenous zoledronic acid compared with oral risedronate in the prevention and treatment of GIOP.29,30 A single 5-mg infusion of zoledronate and daily oral risedronate, 5 mg, were compared in a 1-year randomized, double-blind, double-dummy study of patients with glucocorticoid-induced suppression of serum osteocalcin-gene expression, and calcitriol may reverse glucocorticoid-induced suppression of serum osteocalcin concentrations.31 Importantly, long-term treatment of GIOP with bisphosphonates is very safe.

### Table 2 FRAX™ Model — clinical risk factors (CRF)

| Risk Factor | CRF |
|-------------|-----|
| Age         |     |
| Sex         |     |
| Bone mineral density |     |
| Prior history of fracture |     |
| Parental history of fracture |     |
| Current smoking |     |
| Current alcohol >3 units/day |     |
| Rheumatoid arthritis |     |
| Glucocorticoid use |     |

**Notes:** Each CRF independently contributes to fracture probability. Presence of ≥1 CRF increases probability of fracture incrementally. FRAX™. http://www.shef.ac.uk/FRAX/index.htm

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The effectiveness of bisphosphonate treatment depends on patients adhering to the therapeutic regimen. According to the VIVA study the vast majority of patients prefer a once-monthly regimen – the three most popular reasons
are the need to take fewer pills, convenience and simplicity of treatment.32 Poor compliance to osteoporosis treatment is related to several different factors, including the asymptomatic nature of the disease (if fractures are not present) and the gastrointestinal complications of bisphosphonates.32 Therapeutic regimens with longer periods between applications are now available (ibandronate and risedronate once monthly by mouth, ibandronate 4 times yearly intravenous or intravenous zolendronate once a year) and seem to be an interesting way of increasing adherence.33

A very rare complication following administration of bisphosphonates is osteonecrosis of the jaw. It occurs most commonly in high doses parenterally, in the setting of poor dental hygiene with or without dental procedures. The risk with oral treatment is low. It presents with infection and necrosis of bone in the mandible or maxilla. It is important to check for good dental hygiene before administration of bisphosphonates, as treatment is difficult. Conservative management with limited debridement, antibiotics and mouth rinses assist healing.34 The vast majority of these cases with osteonecrosis of the jaw are seen in the oncology population receiving high doses of monthly intravenous zoledronic acid or pamidronate and chemotherapy.35

There are plausible scientific reasons to be vigilant about the potential for long-term negative effects of bisphosphonates on bone strength, bone turnover and bone quality. In the past 4 years, several cases of unusual femoral fragility fractures – subtrochanteric and diaphyseal fractures – among patients using oral bisphosphonates (usually alendronate) have been reported. In general, patients experiencing such fractures have had bone turnover markers in the low normal range and bone biopsies showed markedly reduced bone turnover.36 The most common safety issues revolve around the effects of bisphosphonates on upper gastrointestinal mucosa. There is no doubt that the amino bisphosphonates may induce esophagitis and that this problem can develop any time during the use of the bisphosphonate, not just at the initiation. This effect can be mitigated by carefully instructing the patient on the proper dosing of the oral bisphosphonate.35 There have been also reports of esophageal cancer in patients who had been taking oral bisphosphonates. Twenty-three cases including

Figure 1 Effects of glucocorticoids on bone. Derived from.38
Abbreviations: TST, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GI, gastrointestinal; Ca, calcium.

Decay: – muscle strength – LH, FSH, TST – GI Ca absorption
Increase: – urinary Ca excretion – risk of falls
Decrease: – proliferation – differentiation – matrix formation – osteocalcin
Increase: – apoptosis

Decrease of bone formation
Increase of bone resorption
Bone loss

Glucocorticoids
Osteoblasts
Osteoclasts
Osseous local factors

Decrease:
– cell recruitment
– differentiation
– activity
Decrease:
– apoptosis

Decrease:
– growth factors
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Bone loss

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8 fatalities have been reported in the United States, all of them associated with alendronate. In Europe and Japan, 31 cases of esophageal cancer have been reported, with alendronate as the suspected drug in 21 cases. Risedronate, ibandronate and etidronate were the suspected drugs in 6 and a concomitant drug in another. If patients take the oral bisphosphonate according to the dosing instructions, the incidence of these side effects is small. Patients with long-term glucocorticoid use are at high risk of developing various side effects, so the intravenous form may be more appropriate.

We have only partial evidence in terms of other therapeutic modalities – calcitonin, estrogens, testosterone (in men), raloxifen and strontium ranelate. According to various studies, there is no evidence for a reduction in vertebral fracture rates, so these drugs cannot be commended. Some authors suggest the administration of hydrochlorothiazide to reduce hypercalcuria in GIOP.

Studies of the effect of intranasal or subcutaneous calcitonin on glucocorticoid-induced bone loss have produced conflicting results. Five studies performed in patients undergoing organ transplantation failed to show a significant treatment benefit on BMD. In the study of Valero et al, in which there was no control group, patients treated with calcitonin or cyclic etidronate showed a significant increase in lumbar spine BMD after 1 year of treatment (mean 6.4% and 8.2%, respectively). In several studies performed in other patient groups, a significant treatment benefit has been demonstrated in lumbar spine BMD compared to controls. However, no effects on spine BMD was demonstrated in three studies, although in one study a significant gain in proximal femur BMD were demonstrated. In two of the studies in which a significant effects on spine BMD were demonstrated, bone loss was however not completely prevented by calcitonin.

Patients receiving prolonged glucocorticoid therapy may develop hypogonadism due to inhibition of secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary gland, as well as direct effects on hormone production by the ovary and testes. All patients receiving long-term glucocorticoid treatment should be assessed for hypogonadism, and when present, this should be corrected if possible. In a trial of postmenopausal women with rheumatoid arthritis who were taking prednisone and were randomized to receive either hormonal replacement therapy (HRT) or placebo, those who received HRT had a significant (3%–4%) increase in their lumbar spine BMD compared with controls, while there was no significant change in femoral neck BMD in either group. In a randomized controlled trial of injectable parathyroid hormone, postmenopausal women receiving long-term low-dose glucocorticoid therapy and HRT in the control group showed no change in BMD at the lumbar spine, hip, or distal radius over the course of 1 year.

These data suggest that HRT is adequate therapy to prevent bone loss in postmenopausal women receiving prolonged low-to-moderate-dose glucocorticoid therapy. Currently, however, there are no published reports on the efficacy of HRT in preventing bone loss at the initiation of glucocorticoid treatment, or the degree of the protective effect of HRT when moderate-to-high doses of glucocorticoids are used for long-term treatment.

Observational studies in premenopausal female athletes with menstrual irregularities suggest that women who receive oral contraceptives have higher adjusted bone mineral content and BMD than do women who do not take oral contraceptives. Therefore, premenopausal women who experience menstrual irregularities (oligo- or amenorrhea) while taking glucocorticoids should be offered oral contraceptives or cyclic estrogen and progesterone if contraindications are not present. At this time, no data are available on the efficacy of selective estrogen receptor modulators (SERMs) in the prevention or treatment of glucocorticoid-induced bone loss. The SERM raloxifene is available for the prevention and treatment of postmenopausal osteoporosis. A SERM could theoretically be used to prevent glucocorticoid-induced bone loss in selected postmenopausal glucocorticoid-treated women who either have contraindications to or do not wish to take HRT or other antiresorptive medications.

There is less information available about men with hypogonadism secondary to glucocorticoid treatment. A randomized crossover trial demonstrated the effectiveness of testosterone replacement therapy in 15 men with glucocorticoid-treated asthma. All of the men had low serum testosterone levels prior to therapy. Lumbar spine BMD, but not hip BMD, was significantly increased (nearly 4%) after 12 months of monthly intramuscular testosterone injections; in addition, there was an increase in lean body mass and a reduction in fat mass. Thus, men with low serum levels of testosterone who are receiving glucocorticoids should receive replacement therapy. Based on recommendations published by the American Association of Clinical Endocrinologists and the American College of Endocrinology, men with serum testosterone levels below the physiologic range (<300 ng/mL) should receive replacement therapy. Multiple different testosterone preparations are available, including short- and long-acting intramuscular injections and transdermal patches and gels.
The goal of testosterone replacement therapy is to provide physiologic-range serum testosterone levels. It is important to emphasize that if testosterone replacement therapy is to be used in a hypogonadal man, the patient should be adequately assessed for the possibility of prostate cancer, with a digital rectal examination and measurement of prostate-specific antigen at baseline and annually thereafter. Prostate cancer is an absolute contraindication to testosterone replacement therapy.

Teriparatide is a recombinant aminoterminal fragment (1–34) of the human parathyroid hormone, which has a predominantly stimulating effect on bone formation. Human parathyroid hormone is a single chain of polypeptide with 84 amino acids and a molecular weight of 9425 Da and the N-terminal region (1–34) is biologically active and sufficient for regulation of mineral ion homeostasis. Teriparatide affects the metabolism of calcium and phosphates in several ways – stimulation of the release of calcium and phosphate from the bone, stimulation of the reabsorption of calcium from the glomerular filtrate and loss of phosphate to urine, and stimulation of the renal synthesis of 1, 25-(OH)₂-vitamin D₃ – and therefore the absorption of calcium and phosphate from the gastrointestinal tract. Patients with large deficits in BMD are at high risk for fracture and might preferentially benefit from such anabolic therapy. The effectiveness of the treatment with teriparatide consists of fracture reduction in females with severe osteoporosis and patient with GIOP.

Daily dose of 20 µg of teriparatide stimulates the production of growth factors IGF-1 and TGF-β in osteoblasts without reduction of osteoprotegerin.

Neer and colleagues documented in a group of postmenopausal females with prevalent vertebral fracture a decrease in risk of vertebral and non-vertebral fractures in an 18-month prospective study. The treatment was associated with significant improvement in quality of life.

Saag have reported the results of the first 18 months of a 36-month prospective trial and later also results of all 36 months. In this randomized, double-blind clinical trial, the primary outcome was the change from baseline to 36 months in BMD at the lumbar spine associated with the administration of daily teriparatide (at a dose of 20 µg), compared with that of daily alendronate (at a dose of 10 mg), in patients with established GIOP. Prespecified secondary outcomes included changes in BMD at the total hip and markers of bone turnover, the time to changes in BMD at the lumbar spine and total hip, the incidence of vertebral and non-vertebral fractures, and adverse events. Ambulatory patients were eligible for enrollment if they met the following criteria: an age of 21 years or more, a history of sustained glucocorticoid therapy, and a T-score for BMD density at the lumbar spine or total hip of either −2.0 or less or −1.0 or less in addition to at least one fragility fracture during treatment with glucocorticoids. Sustained glucocorticoid therapy was defined as a mean daily dose of 5 mg or more of prednisone or its equivalent for 3 or more consecutive months immediately preceding the screening visit. Patients were randomly assigned to receive either injectable teriparatide (Forteo®; Eli Lilly) at a daily dose of 20 µg plus an oral placebo or oral alendronate (Fosamax®; Merck) at a daily dose of 10 mg plus an injectable placebo. They also received supplementation with calcium carbonate (at a dose of 1000 mg of elemental calcium) and vitamin D (at a dose of 800 IU). According to the results of the first 18 months, the anabolic agent teriparatide appeared to show significant skeletal benefits in patients with GIOP, compared with the bisphosphonate alendronate. In a recent trial comparing a bisphosphonate with teriparatide in postmenopausal women with osteoporosis, teriparatide therapy was associated with increased areal and volumetric BMD and estimates of bone strength at the lumbar spine, compared with alendronate. Although the time course of changes in markers of bone turnover in this trial resembled that observed in postmenopausal women, the magnitude of gains in BMD in the teriparatide group was less than that seen previously. This differential response may reflect the characteristic ability of glucocorticoids to inhibit osteoblast and osteocyte function profoundly by several mechanisms, including the stimulation of apoptosis. In this study, patients in the teriparatide group had fewer new vertebral fractures than did patients in the alendronate group, although the overall number of fractures was small. Bisphosphonates have been associated with a reduced incidence of vertebral fractures in this patient population in randomized trials of alendronate, in pooled studies of risedronate, and in a non-randomized, open-label study of ibandronate. Although there were more non-vertebral fractures in the teriparatide group than in the alendronate group in this study, the difference was not significant. In previous studies of teriparatide, there was a reduction in non-vertebral fractures in postmenopausal women with osteoporosis. The standard of care for patients at risk for glucocorticoid-associated bone loss and osteoporosis includes a choice of antiresorptive agents. However, for patients with established osteoporosis who are at high risk for fracture, more aggressive and expensive therapy may be
warranted. Patients in this trial had lower BMD and more prevalent fractures than those in previous trials involving patients with GIOP, which suggests an even greater need for an efficacious intervention.\textsuperscript{31,69,70–74} The occurrence of sporadic hypercalcemia was more frequent in the teriparatide group than in the alendronate group.\textsuperscript{75}

In a 36-month study BMD at the lumbar spine and femoral neck increased significantly more in the teriparatide compared with alendronate group. Fewer patients had new radiographic vertebral fractures in the teriparatide than the alendronate group. The number of patients with new non-vertebral fractures was not significantly different between groups versus alendronate. There was no significant difference between groups in the number of patients with $\geq 1$ adverse event (91% teriparatide versus 86% alendronate).\textsuperscript{65,76} It should be mentioned that the therapy with teriparatide at various doses causes osteosarcoma and abnormalities in bone tissue in the rat model.\textsuperscript{73,74,77–79} On the other hand, in the study of Neer et al and other major clinical trials with teriparatide no osteosarcomas were found.\textsuperscript{73}

On the basis of the known pathophysiology of GIOP, teriparatide might be considered as a therapeutic strategy for patients at high risk for fracture.\textsuperscript{65,66}

According to the literature, there are no recommendations for prevention and treatment of GIOP in children or premenopausal women. This treatment is always individual.\textsuperscript{63} General principles of management include preferring other than oral glucocorticoids, minimizing the oral dose when possible and attention to nutrition, exercise and calcium and vitamin D status.\textsuperscript{80}

Many factors influence a patient’s decision to begin GIOP therapies and to adhere them over time, such as the results and quality of evidence-based medicine studies, the clinician’s know-how, and the patient’s values, preferences and compliance. According the most national and international studies effective therapies of GIOP such as the use of sufficient calcium, vitamin D and early prescription for bisphosphonates can lower the risk of fragility fractures. Despite accumulating evidence, GIOP therapies are underutilized.\textsuperscript{81}

There are no multicenter, prospective, randomized, double-blinded clinical studies with enough patients, unlike postmenopausal osteoporosis, which could define effective treatment modalities to reduce vertebral and non-vertebral fractures. In clinical practice we have only trials with surrogate markers (like BMD, bone turnover markers) that can be correlated with fracture-risk reduction.

**Monitoring of therapy**

The role of monitoring the effects of bone-sparing agents in GIOP, using either BMD or biochemical markers of bone turnover, has not been established. Depending on the rate of bone loss prior to treatment, significant treatment responses in individuals may be detectable within 1 to 2 years using dual energy X-ray absorptiometric measurements of bone density. However, in individuals taking high doses of glucocorticoids, large changes in BMD may be detectable earlier and measurement at 6 months may be appropriate. The spine is the preferred site for monitoring because of the low precision error of bone density measurements at this site. Bone loss from the spine during the first year of glucocorticoid therapy may vary between 3% and 10%; since the precision error of measurements is approximately 1%, a loss of more than 3% (the least significant change) is likely to be significant. Rates of bone loss are less during established glucocorticoid therapy and in this situation the target is to increase BMD above the least significant change, ie, an increase of more than 3%. Bone resorption markers, such as N-telopeptide or C-telopeptide of type I collagen, show similar changes with treatment in individuals taking glucocorticoids to those in women with postmenopausal osteoporosis. However, bone resorption markers may also be affected by changes in inflammatory activity and hence a decrease following initiation of glucocorticoid therapy may reflect suppression of disease activity rather than reduced bone resorption.\textsuperscript{22}

There are many recommendations for the prevention and treatment of GIOP. Here we describe the most important.

**Recommendations for the prevention and treatment of GIOP (American College of Rheumatology 2001)\textsuperscript{82}**

The Committee recommends obtaining a baseline measurement of BMD at the lumbar spine and/or hip when initiating long-term (ie, $>6$ months) glucocorticoid therapy. Longitudinal measurements may be repeated as often as every 6 months for monitoring glucocorticoid-treated patients to detect bone loss. In patients who are receiving therapy to prevent bone loss, annual follow-up measurements are probably sufficient. These recommendations divide patients into two groups in terms of glucocorticoid use.

A – patient beginning therapy with glucocorticoid (prednisone equivalent of 5 mg/day) with plans for treatment duration of 3 months:
- Modify lifestyle risk factors for osteoporosis (smoking cessation or avoidance, reduction of alcohol consumption if excessive, instruct in weight-bearing physical exercise)
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated form)
- Prescribe bisphosphonate (use with caution in premenopausal women)
  B – patient receiving long-term glucocorticoid therapy (prednisone equivalent of 5 mg/day)
- Modify lifestyle risk factors for osteoporosis (smoking cessation or avoidance, reduction of alcohol consumption if excessive, instruct in weight-bearing physical exercise)
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated form)
- Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated
- Measure BMD at lumbar spine and/or hip
  a) if BMD is not normal (T-score below $-1.0$ SD)
     - Prescribe bisphosphonate (use with caution in premenopausal women)
     - Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy
  b) if BMD is normal
     - Follow up and repeat BMD measurement either annually or biannually.

The American Society for Bone and Mineral Research 2004\textsuperscript{83}

In patients receiving prednisone more than 3 months 5 mg/day and with risk factors of osteoporosis (premenopausal women, men over 50 years, low BMI, prior osteoporotic fracture, high doses of glucocorticoids, diseases that leads to secondary osteoporosis, low calcium intake, immobilization, family history of osteoporosis) – measure BMD:

A – T-score below $-2.5$ SD
- start treatment with oral or intravenous bishosphonates
- calcium, vitamin D

B – T-score $-1.5$ to $-2.5$ SD
- consider treatment with oral or intravenous bishosphonates
- calcium, vitamin D

C – T-score more than $-1.5$ SD
- calcium, vitamin D

- measure BMD after 12 months of glucocorticoid therapy.

The Dutch Society for Rheumatology 2004\textsuperscript{84}

The stream diagram (Figure 2) shows the diagnostic and therapeutic steps in making decisions for the prevention of GIOP. Factors that influence this decision include the dose of glucocorticoids and the presence of other risk factors such as age, sex, previous fracture, and BMD. The main message is that treatment with bisphosphonates should be started immediately in patients at high risk (high dose of glucocorticoids, prevalent fracture, postmenopausal women, and elderly men).

In the Slovak Republic we have currently accepted recommendations for patients with long-term glucocorticoid use. These recommendations reflect information about the efficiency of teriparatide.

Recommendations for prevention of GIOP in the Slovak republic\textsuperscript{63}

1. Patients receiving long-term glucocorticoid therapy (>3 months $>7.5$ mg prednisone/day or cumulative dose 27 g/year) – without risk factors:

   Preventive actions – reducing the dose of glucocorticoids to a minimum, exclusion of all risk factors, instruct in weight-bearing physical exercise, BMI $>19$, calcium supplementation 1000 to 1500 mg per day, vitamin D supplementation 800 IU per day.

   Measure BMD at lumbar spine and hip:
   - T-score $>-2.0$ SD measure BMD after 12 months of glucocorticoid therapy
   - T-score $\leq -2.0$ SD treatment with bisphosphonates
   - T-score $\leq -2.9$ SD treatment with teriparatide
   - osteoporotic fracture–treatment with teriparatide

2. Patients receiving long-term glucocorticoid therapy (>3 months $>7.5$ mg prednisone/day or cumulative dose 27 g/year) – with risk factors

   Preventive actions – reducing the dose of glucocorticoids to a minimum, exclusion all risk factors, instruct in weight-bearing physical exercise, BMI $>19$, calcium supplementation 1000 to 1500 mg per day, vitamin D supplementation 800 IU per day.

   Measure BMD at lumbar spine and hip:
   - T-score $>-1.5$ SD measure BMD after 12 months of glucocorticoid therapy
   - T-score $\leq -1.5$ SD treatment with bisphosphonates
   - T-score $\leq -2.9$ SD treatment with teriparatide
   - osteoporotic fracture – treatment with teriparatide.
Conclusion

Glucocorticoids are widely used to treat a number of medical disorders. The administration of oral glucocorticoids is associated with a significant increase in fracture risk at the hip and spine. Measurement of BMD using dual energy x-ray absorptiometry is currently recommended for assessment of fracture risk in individuals treated with glucocorticoids. In general, the pharmacological agents that have undergone assessment for the prevention and treatment of GIOP are similar to those used for postmenopausal osteoporosis. But, according to character of GIOP, the indications for treatment have to be earlier in comparison with postmenopausal osteoporosis.

Disclosures

The authors declare no conflicts of interest.

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