REVIEW

Glucocorticoid-induced osteoporosis in rheumatic diseases

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The aim of this article is to review rheumatological diseases that are associated with glucocorticoid-induced osteoporosis or fractures and to perform a critical analysis of the current guidelines and treatment regimens. The electronic database MEDLINE was searched using the date range of July 1986 to June 2009 and the following search terms: osteoporosis, bone mineral density, fractures, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, vasculitis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis and juvenile dermatomyositis. Osteopenia and osteoporosis respectively account for 1.4 to 68.7% and 5.0 to 61.9% of adult rheumatological diseases. Among juvenile rheumatological disorders, the frequency of low bone mass ranges from 38.7 to 70%. In general, fracture rates vary from 0 to 25%. Although glucocorticoid-induced osteoporosis has a high rate of prevalence among rheumatic diseases, a relatively low number of patients on continuous glucocorticoid treatment receive adequate diagnostic evaluation or preventive therapy. This deficit in patient care may result from a lack of clear understanding of the attributed risks by the patients and physicians, the high complexity of the treatment guidelines and poor patient compliance.

KEYWORDS: Osteoporosis; Glucocorticoids; Bone mineral density; Fractures, Rheumatic diseases.

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INTRODUCTION

Glucocorticoids (GC) are frequently used for the management of patients with rheumatological diseases. The use of GC, however, is associated with a variety of adverse effects,[1] including the development of osteoporosis and fractures. In patients who have received GCs for longer than six months, the estimated glucocorticoid-induced osteoporosis (GIO) frequency is 50%.[2] One-third to one-half of long-term GC users may develop fractures. Furthermore, the risk of fractures strongly correlates with the daily and cumulative dose of GC and does not seem to correlate with the specific underlying disease.[3] The underlying diseases for which GCs are prescribed, however, usually carry a risk of osteoporosis. The objective of the present study was to review rheumatic diseases in which GIO fractures have been described and to perform a critical analysis of the diagnostic criteria of osteoporosis and low bone mass. In addition, the current guidelines and treatment barriers for the management of GIO will be discussed.

Pathophysiology

The pathogenesis of GIO is multifaceted. Glucocorticoids have indirect effects on osteoporosis by inhibiting calcium absorption from the gastrointestinal track and decreasing the renal tubular reabsorption of calcium and consequentely secondary hyperparathyroidism. Nevertheless, hyperparathyroidism does not play a central role in the pathogenesis of GIO, snce the most of patients using chronic GC present normal levels of serum parathromone. GCs reduce growth hormone (GH) secretion and may alter the GH/insulin-like growth factor (IGF)-I axis; however, the serum levels of IGF-I are normal during osteoporosis, suggesting that alterations in the GH/IGF-I axis play a minor role in this skeletal disease. A more important role may be played by skeletal IGF-I because GCs inhibit IGF-I transcription in osteoblasts. In addition, GCs inhibit the release of gonadotrophins and the resulting hypogonadism may contribute to skeletal disease.[3]

Glucocorticoids have direct effects on bone cells. Bone histomorphometric analyses of biopsies obtained from patients with GIO reveal decreased bone turnover with a disproportionate reduction in bone formation. GCs reduce the replication, differentiation and function of osteoblasts[4] and increase the apoptosis rates of mature cells, thereby depleting the osteoblastic cell population and inhibiting the function of mature cells.[3] Furthermore, in the presence of GCs, bone marrow stromal cells do not differentiate into osteoblasts; instead, these cells differentiate toward an adipocyte cell lineage. The underlying mechanism for this change in cell fate appears to be related to an induction of CCAAT enhancer binding proteins and possibly by inhibiting Wingless (Wnt)/β-catenin signaling.[3] Moreover, GCs induce apoptosis in osteocytes and affect the functioning of

these cells. GCs increase the expression of macrophage colony stimulating factor (M-CSF) and receptor activator of Nuclear fator kappa beta (NF-kB) ligand (RANK-L). In addition, GCs decrease the expression of osteoprotegerin in stromal and osteoblastic cells. Through these mechanisms, GCs can induce the formation of osteoclasts and favor bone resorption. GCs also reduce the rate of apoptosis among mature osteoclasts.[3]

GIO in Rheumatic Diseases

The electronic database MEDLINE was searched using the date range of July 1986 to June 2009 and the following search terms: osteoporosis, bone mineral density, fractures, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis and juvenile dermatomyositis. A total of 17 studies were found regarding systemic lupus erythematosus, 16 about rheumatoid arthritis and 13 about juvenile rheumatic diseases. All of these studies included patients on GC (Tables 1, 2 and 3).[5–50] The definition of osteoporosis as determined by bone mineral density (T-score <-2.5) and osteopenia (T-score <-1.0 to -2.5) should be the definition used for postmenopausal women;[51] however, it is not applicable to GIO because patients on GCs can fracture at T-scores in the normal or osteopenic range. Along these lines, the International Society of Clinical Densitometry recommends the following definition: ''below the expected range for age'' for Z-scores lower than -2.0 and ''within the expected range for age'' for Z-scores above -2.0 for premenopausal women, children and adolescents instead of osteoporosis/osteopenia for GIO.[52] Nevertheless, published reports use different definitions for diagnosing GIO, thereby limiting the effectiveness of study comparisons. For example, the term osteoporosis may not be used for patients with fractures and a bone mineral density greater than -2.5.[53]

Systemic Lupus Erythematosus

Studies on systemic lupus erythematosus demonstrate a frequency of osteoporosis from 4.0 to 48.8% and of osteopenia from 1.4 to 68.7%.[5–21] Fractures were evaluated in four of these reports, with a frequency of 5.0 to 21.4%.[7,11–13] A negative association between bone mass and glucocorticoid use was documented in ~60% of these studies.[5–7,13,15–17,20,21] Other possible associations with low bone mass in subjects with lupus were the chronicity of the disease, disease duration, low body mass index and weight, increased age, habitual drinking, positive serum markers of inflammation, renal dysfunction, menopause and physical dysfunction (Table 1).[6–8,10–14,17–18,20]

Rheumatoid Arthritis

The frequency of osteoporosis in patients with rheumatoid arthritis (RA) ranges from 4 to 24% and the frequency of osteopenia ranges from 28 to 61.9%.[22,26,32,36] Fractures were evaluated in four studies out of 16, which showed a prevalence of osteoporosis of 0 to 25% in patients with rheumatoid arthritis;[23,28,30,36] however, only two of these patients exhibited an association with GC use.[23–30] De Nijs *et al*., showed that each 1 mg prednisone equivalent increase in the daily dose of GC increased the risk of vertebral deformities and symptomatic vertebral fractures in patients with RA.[30] Glucocorticoid use was associated with decreased bone mass in 56.2% of subjects with RA.[28,31–35,37] Bone loss was also related to the Disease Activity Score, a change in the Health Assessment Questionnaire, radiological joint damage, age, postmenopausal state, low physical activity, body mass index, disability, functional class and anemia (Table 2).[22,23,25,26,28,31–34]

Juvenile Rheumatic Diseases

Some studies have addressed GIO in juvenile idiopathic arthritis (JIA), which includes juvenile rheumatoid arthritis (JRA), juvenile chronic arthritis (JCA), juvenile systemic lupus erythematosus and juvenile dermatomyositis.[38–50] The prevalence of low bone mineral density in children with rheumatic diseases is difficult to assess because various studies have used different cut-off points for Z-scores (e.g., < 1.0, < 2.0).[41,44–47,50] Recently, the International Society of Clinical Densitometry defined low bone mineral density as a Z-score below –2.0 in children and adolescents in an attempt to standardize clinical data.[52,54] In JIA, an association between glucocorticoid use and low bone mass was observed in four out of five studies.[39–41] Santiago *et al.*, found a relationship between pulse therapy with methylprednisolone (30 mg/kg per day for at least three days) and low bone mass in juvenile dermatomyositis.[43] An association between glucocorticoid use and low bone mass was also observed in two studies that evaluated patients with juvenile systemic lupus erythematosus[47,48] and in a study that evaluated several juvenile rheumatic diseases.[49] Seven studies evaluated the prevalence of fractures and only one[42] demonstrated an association with this complication (Table 3).[38,42,44–47,50]

Systemic Sclerosis

Several studies have assessed bone mass in patients with systemic sclerosis;[55–58] however, only two reports included patients on glucocorticoid therapy.[57,58] These authors did not find an association between osteoporosis and glucocorticoid use in this disease.[57,58]

Systemic Vasculitis

Few studies have addressed GIO in systemic vasculitis and only polymyalgia rheumatica and giant cell arteritis have been described.[59–62] The frequency of osteoporosis has been shown to vary from 14.9 to 85%.[60,61] Vertebral fractures were analyzed in a study that compared placebo with calcitonin and found an incidence of fractures between 11–14%.[59]

Guidelines for GIO

There are a number of guidelines regarding the management of GIO in patients who are receiving glucocorticoid treatment or that will be starting this therapy. We have reviewed the guidelines established by the American College of Rheumatology (ACR),[63] the Department of Veterans Affairs Medical Centers (VMACs),[64] the Dutch Society of Rheumatology (DSR)[65] and the Royal College of Physicians (RCP).[66] Various similarities among these four guidelines have been noted (Tables 4 and 5). All of these guidelines have recognized that even a short duration (3 months) of glucocorticoid use increases the risk of fracture and they recommend intervention. In addition, they suggest modification of life style risk factors (smoking cessation or avoidance, reduction of alcohol consumption if excessive and performance of weight-bearing physical exercises).[63–66]

Table 1 - GIO in systemic lupus erythematosus.

Number (N) Population	Glucocorticoid association	Other associations with osteoporosis and osteopenia	Osteoporosis (%)	Osteopenia (%)	Fracture	References
N = 98, premenopausal women	Yes (cumulative GC dose with low lumbar spine BMD, and GC duration with low hip BMD)	No	6.1%	41.9%	Not described	Yeap *et al.*, 2009 (5)
N = 100, premenopausal women	Yes (low BMD at hip)	Chronic disease damage, low BMI	5.0%	40%	Not described	Mendoza-Pinto *et al.*, 2009 (6)
N = 40, men (mean age 42.6 years)	Yes (low BMD at lumbar spine)	Increased age, habitual drinking, low BMI	Not described	30%	5%	Mok *et al.*, 2008 (7)
N = 163, women (median age 47 years)	No	Age, low weight, inflammatory markers, renal dysfunction, high chronic damage	23%	Not described	Not described	Almehed *et al.*, 2007 (8)
N = 60, premenopausal women	No	No	6.6%	46.7%	Not described	Chong *et al.*, 2007 (9)
N = 307, 65% premenopausal women	No	Disease damage	Not described	Not described	Not described	Lee *et al.*, 2006 (10)
N = 70, premenopausal women (mean age 31.8 years)	No	BMD	Not described	Not described	21.4%	Borba et al, 2005 (11)
N = 107, 93% women (mean age 41.1 years)	Yes (vertebral fracture with intravenous methylprednisolone)	Low BMI Menopause Vitamin D deficiency	4%	39%	20%	Bultink et al., 2005 (12)
N = 242, 95.4% women (median age 39.9 years)	Yes (low BMD)	Age, menopause	10.3%	50.8%	9.1%	Yee et al., 2005 (13)
N = 205 patients	No	Age and damage index	48.8%	18%	Not described	Pineau *et al.*, 2004 (14)
N = 118, premenopausal women	Yes (decreased BMD at lumbar spine and trochanter)	No	Not described	1.4%	Not described	Uaratanawang et al., 2003 (15)
N = 32, women (mean age 43.2 years)	Yes (decreased BMD at lateral spine and total hip)	Not described	Not described	68.7%	Not described	Boyanov et al., 2003 (16)
N = 79, women (mean age 49 years)	Yes (daily and cumulative dose)	High functional class	23.7%	61.9%	Not described	Bhattoa *et al.*, 2002 (17)
N = 64 patients	No	Body weight, disease duration, and damage index	10.9%	Not described	Not described	Becker *et al.*, 2001 (18)
N = 23, men (mean age 45.6 years)	No	No	17.4%	Not described	Not described	Bhattoa *et al.*, 2001 (19)
N = 75, 88% women (median age 45 years)	Yes (low BMD at lumbar spine)	Age, BMI	9%	41%	Not described	Gilboe *et al.*, 2000 (20)
N = 97, women (mean age 44.2 years)	Yes (low BMD at lumbar spine)	Not described	13.4%	44.3%	Not described	Kipen et al., 1997 (21)

BMD, bone mineral density; BMI, body mass index; GC, Glucocorticoid; Osteopenia and osteoporosis defined using WHO classification.

Table 2 - GIO in rheumatoid arthritis.

	Glucocorticoid association	Other association with osteoporosis/osteopenia	Osteoporosis (%)	Osteopenia (%)	Fracture	References
N = 97, women (mean age 58 years)	No	DAS, change in HAQ	24%	36%	Not described	Book *et al.*, 2008 (22)
N = 209, 85.2% women (mean age 60.4 years)	Yes (fracture)	Functional class	Not described	Not described	11.5%	Nampei *et al.*, 2008 (23)
N = 74, premenopausal women	No	No	Not described	Not described	Not described	Hamalainen *et al.*, 2007 (24)
N = 342, 83% women (mean age 42.6 years)	No	Joint radiological damage at baseline and at progression	Not described	Not described	Not described	Guler-Yuksel *et al.*, 2008 (25)
N = 83, women (median age 47 years)	No	Age	21.4%	46.4%	Not described	Silva *et al.*, 2007 (26)
N = 16, 75% women (mean age 47.2 years)	No	Not described	Not described	Not described	Not described	Habib *et al.*, 2005 (27)
N-78, premenopausal women	Yes (osteopenia at lumbar spine)	No physical activity, low weight, high functional class, hand erosion, high ESR, anemia	Not described	Not described	0	Tourinho *et al.*, 2005 (28)
N = 81, (mean age 48 years) 30.8% female	No	No	Not described	Not described	11.1%	Van Everdingen *et al.*, 2003 (29)
N = 410, (mean age 65 years) 90% premenopausal women	Yes (vertebral fracture)	No	Not described	Not described	25%	de Nijs *et al.*, 2001 (30)
N = 76, 61% women (mean age 54.8 years)	Yes (hip bone loss)	Postmenopausal women, low physical activity	Not described	Not described	Not described	Kroot *et al.*, 2001 (31)
N = 75, 88% women (median age 45 years)	Yes (low BMD at lumbar spine)	Age and BMI	4-5%	28-44%	Not described	Gilboe et al., 2000 (32)
N = 85, 85.9% women (mean age 57 years)	Yes (decrease BMD at femoral neck)	Active and severe disease	Not described	Not described	Not described	Cortet *et al.*, 1997 (33)
N = 195, postmenopausal women	Yes (cumulative GC dose with low femoral and whole body BMD)	Disability	Not described	Not described	Not described	Hall et al., 1993 (34)
N = 30, women (mean age 54 years)	No	Not described	Not described	Not described	Not described	Sambrook et al., 1989 (35)
N = 84, women (mean age 55.5 years)	No	Not described	23.7%	61.9%	13.7%	Sambrook et al., 1986 (36)
N = 97, 90% women	Yes (distal forearm BMC)	Not described	Not described	Not described	Not described	Als *et al.*, 1985 (37)

BMD, bone mineral density; BMI, body mass index; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; ERS, erythrosedimentation rate

Table 3 - GIO in juvenile rheumatic diseases.

Disease	Number (n) Population	Glucocorticoid association	Other associations with low bone mass	Low bone mass (%)	Fracture	References
JIA/JCA/JRA	N = 62, 69.4% girls (median age 11.4 years)	No	No	Not described	10%	Valta *et al*., 2007 (38)
JIA/JCA/JRA	N = 28, 57.1% girls (mean age 11 years)	Yes (low BMD at lumbar spine)	Age and age of disease onset	Not described	Not described	Celiker *et al.*, 2003 (39)
JIA/JCA/JRA	N = 18, 38.9% girls (mean age 11 years)	Yes (low BMD at lumbar spine)	No	Not described	Not described	Cetin *et al*., 1998 (40)
JIA/JCA/JRA	N = 62, 58.1% girls (5–18 years)	Yes (low BMD at distal radius and lumbar spine)	Long disease duration	50–60%	Not described	Pereira *et al*., 1998 (41)
JIA/JCA/JRA	N = 46	Yes (fracture)	Not described	Not described	50%	Varonos *et al.,* 1987 (42)
Juvenile dermatomyositis	N = 20 girls (mean age 13.4 years)	Yes (GC pulse therapy with low BMD in hip)	Lean mass	Not described	Not described	Santiago *et al*., 2008 (43)
Juvenile dermatomyositis	N = 10 girls (mean age 11.8 years)	No	Weight	70%	0	Castro *et al*., 2005 (44)
Juvenile dermatomyositis	N = 15, 60% girls (mean age 7.9 years)	No	Disease duration	66.7% (Z <-1)	33.3%	Stewart *et al*., 2003 (45)
Juvenile systemic lupus erythematosus	N = 36 girls (mean age 17.7)	No	Disease	38.7%	22.6%	Regio *et al*., 2008 (46)
Juvenile systemic lupus erythematosus	N = 70, 65% girls (mean age 26.4 years)	Yes (low bone mineral content)	Male gender	41%	6%	Lilleby et al., 2005 (47)
Juvenile systemic lupus erythematosus	N = 20, 90% girls (mean age 14.5 years)	Yes (BMD loss at lumbar spine)	No	Not described	Not described	Trapani et al., 1998 (48)
Juvenile systemic lupus erythematosus, JIA	N = 20, 65% girls (mean age 13.1 years)	No	No	Not described	Not described	Kashef et al., 2007 (49)
Juvenile dermatomyositis, juvenile systemic lupus erythematosus, vasculitis	N = 36, 91.6% girls (mean age 11.4 years)	Yes (lower BMD at lumbar spine, hip, total body)	Younger and prepubertal	40% JSLE and 27% JDM/vasculitis	0	Alsufyani et al., 2005 (50)

JIA, juvenile idiopathic arthritis; JCA, juvenile chronic arthritis; JRA, juvenile rheumatoid arthritis; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire

Table 4 - Guidelines for the prevention of GIO.

	American College of Rheumatology (49)	Department of Veterans Affairs Medical Centers (50)	Dutch Society of Rheumatology (51)	Royal College of Physicians (52)
GC dose	≥ 5mg/day	≥ 5–7.5 mg/day	≥ 7.5 mg/day	Not specified
Indication for calcium plus vitamin D	Yes	Yes	Not specified	Yes, if: - low dietary calcium intake - vitamin D insufficiency
Indication for densitometric evaluation before bisphosphonate	Yes, if: - GC therapy ≥ 6 months	Yes	Yes, if: - GC 7.5–15 mg/day - premenopausal women - men < 70 yrs	Yes, if: - < 65 yrs - no previous osteoporotic fracture
Value of T-score to initiate bisphosphonate	Not specified	Not specified	< -2.5	- 1.5
Indication for bisphosphonate	- Prednisone ≥ 5 mg/day for ≥ 6 months	- Prednisone > 5 mg/day, except if BMD is normal - DXA is not available	- Prednisone > 15 mg/day - Fracture - Post-menopausal - Men > 70 yrs	- > 65 yrs (men and women) - Previous history of fragility fracture

GC, Glucocorticoid

The Royal College of Physicians' guidelines also reinforce the necessity to use the lowest GC dose possible.[66]

Barriers in the Management of GIO

Although numerous guidelines for GIO management have been published, previous studies suggest that a relatively low percentage of patients who receive continuous glucocorticoid treatment are evaluated or administered preventive treatment for GIO. Saag *et al*., studied more than 3,000 adult men and women who had undergone long-term glucocorticoid therapy. These authors found that bone mineral density testing was performed in 19% of post-menopausal women and in 6% of women under the age of 50 years.[67] The use of antiosteoporotic medication was most common among postmenopausal women and its use approached 50% in this group. In addition, the medical specialty of the physician providing care influenced both testing and treatment regimens. Notably, testing rates were 3 to 4 times greater in rheumatology practices than in internal medicine or family medicine practices.[67,68] There are several possible explanations for these low compliance rates with current guidelines. For example, published guidelines are inconsistent regarding who should be treated. In addition, the dose and duration of glucocorticoid therapy are not standardized. Guidelines are also difficult to implement due to the physician's focus on the underlying disease. In select cases, there may be limited access to densitometry. Furthermore, patients and physicians may not have a clear perception of the risk of GIO and patients may not accept treatment. Our findings suggest that unification of guidelines regarding the glucocorticoid dose that would require treatment (such as prednisone equivalents ≥ 5 mg/day for at least 3 months), requirement of densitometric evaluation (premenopausal women and patients on GCs) and indication of bisphosphonates for prevention (postmenopausal women and men) and treatment (T-score < -1.0 or previous fragility fracture in postmenopausal women and men) could be of value to medical practioners.[69]

Treatment

Because GCs induce an overall negative calcium balance, adequate calcium and vitamin D supplementation is important. A Cochrane Database Meta-Analysis concluded that calcium and vitamin D supplementation should be started in all patients who are administered glucocorticoids because of their low toxicity, low cost and the possible benefit in terms of fracture risk.[70] Vitamin D is a hormone that increases intestinal calcium absorption and increases its reabsorption in distal renal tubules. Serum levels of at least 30 ng/mL (82 nmol/L), and optimally of 40–60 ng/mL, of 25-hydroxyvitamin D should be the target treatment regimen for GIO management. To achieve these levels, 1,000 to 2,000 IU of oral vitamin D daily may be necessary.[71]

Table 5 - Guidelines for the treatment of GIO.

	American College of Rheumatology (49)	Department of Veterans Affairs Medical Centers (50)	Dutch Society of Rheumatology (51)	Royal College of Physicians (52)
GC dose	≥ 5mg/day	Not specified	Not specified	Not specified
Indication for calcium plus vitamin D	Yes	Yes	Not specified	Yes
Indication for densitometric evaluation before bisphosphonates	Yes	Yes	Not specified	Yes
Indication for bisphosphonate	BMD <-1.0	- low BMD - history of fracture	Not specified	BMD <-1.5 or a reduction in BMD > 4% after 1 year

GC, Glucocorticoid; BMD, bone mineral density

Bisphosphonates are indicated for the prevention and treatment of GIO and most guidelines recommend the use of these drugs.[63–66] The prevention and treatment goals of bisphosphonate use are stabilized or increased bone mineral density, as well as reduced frequency of fractures. A study using risedronate showed a decrease in vertebral fractures after one year of treatment.[72] Currently, alendronate (70 mg/week or 10 mg/day) and risedronate (35 mg/week or 5 mg/day) are the only oral antiresorptive drugs that are recommended in GIO. Recently, zoledronic acid was approved for the prevention and treatment of GIO. In a multicenter, double-blind, double-dummy, randomized controlled trial that included 833 patients, a single 5 mg intravenous infusion of zoledronic caused a greater increase in bone mineral density than oral risedronate at 5 mg daily.[73] Bisphosphonate treatment is recommended while patients are on glucocorticoids; however, in subjects with significant bone loss, therapy may need to be continued following the discontinuation of glucocorticoids.

Caution needs to be exercised when considering the use of bisphosphonates in women of childbearing age with GIO,[63,74,75] given that bisphosphonates have an extended half-life and may cross the placenta with potentially unfavorable effects on fetal skeletal development. A recent review of 51 human cases examining exposure to bisphosphonates before or during pregnancy did not demonstrate skeletal abnormalities or other congenital malformations in the infants.[75] Similarly, a related case-controlled study suggested that preconceptional and first-trimester use of bisphosphonates may pose limited fetal risk.[76] Nevertheless, these studies included a small number of subjects and the safety of bisphosphonates in women of childbearing age, during pregnancy or while lactating is unknown. Therefore, physicians should carefully weigh the risks and benefits of bisphosphonate therapy in premenopausal women.

Although the guidelines do not address the use of anabolic therapies in GIO, this approach appears to be ideal because glucocorticoids reduce bone formation. Saag *et al.*, published a randomized multicenter trial to compare use of oral alendronate (10 mg/day) and subcutaneous teriparatide (20 μg/day) over 18 months in patients with established GIO. The study showed that among patients with osteoporosis with a high risk for fracture, the bone mineral density increase in patients receiving teriparatide was greater than in those receiving alendronate.[77] The study did not possess enough statistical power to detect differences in the incidence of fractures, although the number of vertebral fractures was significantly lower in the teriparatide arm than in the alendronate arm. Subsequently, the study was extended to 36 months and these results confirmed a higher increase in bone mineral density and fewer new vertebral fractures in subjects treated with teriparatide as compared to alendronate.[78]

CONCLUSION

After an extensive review of the literature, it was observed that the frequency of GIO varies due to different study designs and the lack of a uniform definition of GIO. Similarly, currently available guidelines use different recommendations for the prevention and treatment of GIO, thereby creating practical difficulties. Consequently, patients who are frequently exposed to GCs are not assessed or treated.

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REFERENCES

1. Cutolo M, Seriolo B, Pizzorni C, Secchi ME, Soldano S, Paolino S, et al. Use of glucocorticoids and risk of infections. Autoimmun Rev. 2008;8:153-5, doi: 10.1016/j.autrev.2008.07.010.
2. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002;13:777-87, doi: 10.1007/s001980200108.
3. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18:1319-28, doi: 10.1007/s00198-007-0394-0.
4. Pereira RM, Delany AM, Canalis E. Cortisol inhibits the differentiation and apoptosis of osteoblasts in culture. Bone 2001;28:484-90, doi: 10.1016/S8756-3282(01)00422-7.
5. Yeap S, Fauzi A, Kong N, Halim A, Soehardy Z, Rahimah S, et al. Influences on bone mineral density in Malaysian premenopausal systemic lupus erythematosus patients on corticosteroids. Lupus 2009;18:178-81, doi: 10.1177/0961203308094995.
6. Mendoza-Pinto C, García-Carrasco M, Sandoval-Cruz H, Escárcega RO, Jiménez-Hernández M, Etchegaray-Morales I, et al. Risks factors for low bone mineral density in pre-menopausal Mexican women with systemic lupus erythematosus. Clin Rheumatol. 2009;28:65-70, doi: 10.1007/s10067-008-0984-z.
7. Mok CC, Cheung MY, Ho LY, Yu KL, To CH. Risk and predictors of work disability in Chinese patients with systemic lupus erythematosus. Lupus. 2008;17:1103-7, doi: 10.1177/0961203308094280.
8. Almehed K, Forsblad d'Elia H, Kvist G, Ohlsson C, Carlsten H. Prevalence and risk factors of osteoporosis in female SLE patients-extended report. Rheumatology Oxford. 2007;46:1185-90, doi: 10.1093/rheumatology/kem105.
9. Chong HC, Chee SS, Goh EM, Chow SK, Yeap SS. Dietary calcium and bone mineral density in premenopausal women with systemic lupus erythematosus. Clin Rheumatol. 2007;26:182-5, doi: 10.1007/s10067-006-0258-6.
10. Lee C, Almagor O, Dunlop DD, Manzi S, Spies S, Chadha AB, et al. Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. Rheumatology. (Oxford) 2006;45:53-60, doi: 10.1093/rheumatology/kei079.
11. Borba VZ, Matos PG, da Silva Viana PR, Fernandes A, Sato EI, Lazaretti-Castro M. High prevalence of vertebral deformity in premenopausal systemic lúpus erythematosus patients. Lupus. 2005;14:529-33, doi: 10.1191/0961203305lu2154oa.
12. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum. 2005;52:2044-50, doi: 10.1002/art.21110.
13. Yee CS, Crabtree N, Skan J, Amft N, Bowman S, Situnayake D, et al. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:111-3, doi: 10.1136/ard.2003.018127.
14. Pineau CA, Urowitz MB, Fortin PJ, Ibanez D, Gladman DD. Osteoporosis in systemic lupus erythematosus: factors associated with referral for bone mineral density studies, prevalence of osteoporosis and factors associated with reduced bone density. Lupus. 2004;13:436-41, doi: 10.1191/0961203303lu1036oa.
15. Uaratanawong S, Deesomchoke U, Lertmaharit S, Uaratanawong S. Bone mineral density in premenopausal women with systemic lupus erythematosus. J Rheumatol 2003;30:2365-8.
16. Boyanov M, Robeva R, Popivanov P. Bone mineral density changes in women with systemic lupus erythematosus. Clin Rheumatol. 2003;22:318-23, doi: 10.1007/s10067-003-0743-0.
17. Bhattoa HP, Bettembuk P, Balogh A, Szegedi G, Kiss E. Bone mineral density in women with systemic lupus erythematosus. Clin Rheumatol. 2002;21:135-41, doi: 10.1007/s10067-002-8272-9.
18. Becker A, Fischer R, Scherbaum WA, Schneider M. Osteoporosis screening in systemic lupus erythematosus: impact of disease duration and organ damage. Lupus. 2001;10:809-14, doi: 10.1177/096120330101001108.
19. Bhattoa HP, Kiss E, Bettembuk P, Balogh A. Bone mineral density, biochemical markers of bone turnover, and hormonal status in men with systemic lupus erythematosus. Rheumatol Int. 2001;21:97-102, doi: 10.1007/s00296-001-0149-8.
20. Gilboe IM, Kvien TK, Haugeberg G, Husby G. Bone mineral density in systemic lupus erythematosus: comparison with rheumatoid arthritis and healthy controls. Ann Rheum Dis. 2000;59:110-5, doi: 10.1136/ard.59.2.110.

21. Kipen Y, Buchbinder R, Forbes A, Strauss B, Littlejohn G, Morand E. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. J Rheumatol. 1997;24:1922-9.
22. Book C, Karlsson M, Akesson K, Jacobsson L. Disease activity and disability but probably not glucocorticoid treatment predicts loss in bone mineral density in women with early rheumatoid arthritis. Scand J Rheumatol. 2008;37:248-54, doi: 10.1080/03009740801998747.
23. Nampei A, Hashimoto J, Koyanagi J, Ono T, Hashimoto H, Tsumaki N, et al. Characteristics of fracture and related factors in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18:170-6, doi: 10.1007/s10165-008-0032-5.
24. Hämäläinen H, Kaarela K, Kröger H, Kauppi M, Järvenpää S, Hakala M, et al. Changes in bone mineral density in premenopausal women with rheumatoid arthritis during a two-year follow-up. Joint Bone Spine. 2007;74:482-7, doi: 10.1016/j.jbspin.2007.01.021.
25. Güler-Yüksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Hulsmans HM, de Beus WM, et al. Changes in bone mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis. 2008;67:823-8, doi: 10.1136/ard.2007.073817.
26. Silva RG, Pippa MG, Zerbini CA. Evaluation of body composition and bone mineral density in women with rheumatoid arthritis. Rev Assoc Med Bras. 2007;53:135-41, doi: 10.1590/S0104-42302007000200018.
27. Habib GS, Haj S. Bone mineral density in patients with early rheumatoid arthritis treated with corticosteroids. Clin Rheumatol. 2005;24:129-33, doi: 10.1007/s10067-004-0989-1.
28. Tourinho TF, Stein A, Castro JA, Brenol JC. Rheumatoid arthritis: evidence for bone loss in premenopausal women. J Rheumatol. 2005;32:1020-5.
29. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, Bijlsma JW. Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures? Clin Exp Rheumatol. 2003;21:155-60.
30. de Nijs RN, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, et al. Osteoporosis Working Group, Dutch Society for Rheumaology. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology. (Oxford) 2001;40:1375-83, doi: 10.1093/rheumatology/40.12.1375.
31. Kroot EJ, Nieuwenhuizen MG, de Waal Malefijt MC, van Riel PL, Pasker-de Jong PC, Laan RF. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. Arthritis Rheum. 2001;44:1254-60, doi: 10.1002/1529-0131(200106)44:6<1254::AID-ART216>3.0.CO;2-G.
32. Gilboe IM, Kvien TK, Haugeberg G, Husby G. Bone mineral density in systemic lupus erythematosus: comparison with rheumatoid arthritis and healthy controls. Ann Rheum Dis. 2000;59:110-5, doi: 10.1136/ard.59.2.110.
33. Cortet B, Flipo RM, Blanckaert F, Duquesnoy B, Marchandise X, Delcambre B. Evaluation of bone mineral density in patients with rheumatoid arthritis. Influence of disease activity and glucocorticoid therapy. Rev Rhum Engl Ed. 1997;64:451-8.
34. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum. 1993;36:1510-6, doi: 10.1002/art.1780361105.
35. Sambrook PN, Cohen ML, Eisman JA, Pocock NA, Champion GD, Yeates MG. Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. Ann Rheum Dis. 1989;48:535-8, doi: 10.1136/ard.48.7.535.
36. Sambrook PN, Eisman JA, Yeates MG, Pocock NA, Eberl S, Champion GD. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. Ann Rheum Dis. 1986;45:950-3, doi: 10.1136/ard.45.11.950.
37. Als OS, Gotfredsen A, Christiansen C. The effect of glucocorticoids on bone mass in rheumatoid arthritis patients. Influence of menopausal state. Arthritis Rheum. 1985;28:369-75, doi: 10.1002/art.1780280403.
38. Valta H, Lahdenne P, Jalanko H, Aalto K, Mäkitie O. Bone health and growth in glucocorticoid-treated patients with juvenile idiopathic arthritis. J Rheumatol 2007;34:831-6.
39. Celiker R, Bal S, Bakkaloğlu A, Ozaydin E, Coskun T, Cetin A, et al. Factors playing a role in the development of decreased bone mineral density in juvenile chronic arthritis. Rheumatol Int. 2003;23:127-9.
40. Cetin A, Celiker R, Dinçer F, Ariyürek M. Bone mineral density in children with juvenile chronic arthritis. Clin Rheumatol. 1998;17:551-3, doi: 10.1007/BF01451301.
41. Pereira RM, Corrente JE, Chahade WH, Yoshinari NH. Evaluation by dual X-ray absorptiometry (DXA) of bone mineral density in children with juvenile chronic arthritis. Clin Exp Rheumatol. 1998;16:495-501.
42. Varonos S, Ansell BM, Reeve J. Vertebral collapse in juvenile chronic arthritis: its relationship with glucocorticoid therapy. Calcif Tissue Int. 1987;41:75-8, doi: 10.1007/BF02555248.
43. Santiago RA, Silva CA, Caparbo VF, Sallum AM, Pereira RM. Bone mineral apparent density in juvenile dermatomyositis: the role of lean body mass and glucocorticoid use. Scand J Rheumatol. 2008;37:40-7, doi: 10.1080/03009740701687226.
44. Castro TC, Terreri MT, Szejnfeld VL, Len C, Fonseca AS, Hilário MO. Bone mineral density of Brazilian girls with juvenile dermatomyositis. Braz J Med Biol Res. 2005;38:309-13.
45. Stewart WA, Acott PD, Salisbury SR, Lang BA. Bone mineral density in juvenile dermatomyositis: assessment using dual x-ray absorptiometry. Arthritis Rheum. 2003;48:2294-8, doi: 10.1002/art.11211.
46. Regio P, Bonfá E, Takayama L, Pereira RM. The influence of lean mass in trabecular and cortical bone in juvenile onset systemic lupus erythematosus. Lupus. 2008;17:787-92, doi: 10.1177/0961203308089446.
47. Lilleby V, Lien G, Frey Frøslie K, Haugen M, Flatø B, et al. Frequency of osteopenia in children and young adults with childhood-onset systemic lupus erythematosus. Arthritis Rheum. 2005;52:2051-9, doi: 10.1002/art.21115.
48. Trapani S, Civinini R, Ermini M, Paci E, Falcini F. Osteoporosis in juvenile systemic lupus erythematosus: a longitudinal study on the effect of steroids on bone mineral density. Rheumatol Int. 1998;18:45-9, doi: 10.1007/s002960050056.
49. Kashef S, Saki F, Karamizadeh Z, Kashef MA. Bone mineral density in children wth systemic lupus erythematosus and juvenile rheumatoid arthritis. Ann Saudi Med. 2007;27:427-31, doi: 10.4103/0256-4947.51458.
50. Alsufyani KA, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, et al. Bone mineral density in children and adolescents with systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. J Rheumatol. 2005;32:729-33.
51. (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization; 1994. Technical Report Series, No. 843.
52. Official positions of the International Society for Clinical Densitometry Updated 2007. Available at www.iscd.org/Visitors/positions/OfficialPositionsText.cfm Accessed July 5, 2009.
53. Langsetmo L, Goltzman D, Kovacs CS, Adachi JD, Hanley DA, Kreiger N, et al. Repeat Low-Trauma Fractures Occur Frequently Among Men and Women who have Osteopenic Bone Mineral Density. J Bone Miner Res. 2009;24:1515-22, doi: 10.1359/jbmr.090319.
54. Khan AA, Bachrach L, Brown JP, Hanley DA, Josse RG, Kendler DL, et al. Standards and guidelines for performing central dual-energy X-ray absorptiometry in premenopausal women, men, and children. J Clin Densitom. 2004;51-63, doi: 10.1385/JCD:7:1:51.
55. Souza RB, Borges CT, Takayama L, Aldrighi JM, Pereira RM. Systemic sclerosis and bone loss: the role of the disease and body composition. Scand J Rheumatol. 2006;35:384-7, doi: 10.1080/03009740600704296.
56. Frediani B, Baldi F, Falsetti P, Acciai C, Filippou G, Spreafico A, et al. Clinical determinants of bone mass and bone ultrasonometry in patients with systemic sclerosis. Clin Exp Rheumatol. 2004;22:313-8.
57. Yuen SY, Rochwerg B, Ouimet J, Pope JE. Patients with scleroderma may have increased risk of osteoporosis. A comparison to rheumatoid arthritis and noninflammatory musculoskeletal conditions. J Rheumatol. 2008;35:1073-8.
58. Sampaio-Barros PD, Costa-Paiva L, Filardi S, Sachetto Z, Samara AM, Marques-Neto JF. Prognostic factors of low bone mineral density in systemic sclerosis. Clin Exp Rheumatol. 2005;23:180-4.
59. Healey JH, Paget SA, Williams-Russo P, Szatrowski TP, Schneider R, Spiera H, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. Calcif Tissue Int. 1996;58:73-80, doi: 10.1007/BF02529727.
60. Andersson R, Rundgren A, Rosengren K, Bengtsson BA, Malmvall BE, Mellström D. Osteoporosis after long-term corticosteroid treatment of giant cell arteritis. J Intern Med. 1990;227:391-5, doi: 10.1111/j.1365-2796.1990.tb00177.x.
61. Hatz HJ, Helmke K. Polymyalgia rheumatica and giant cell arteritis; diagnosis and side effects of low-dose long-term glucocorticoid therapy. Z Rheumatol 1992;51:213-21.
62. Pearce G, Ryan PF, Delmas PD, Tabensky DA, Seeman E. The deleterious effects of low-dose corticosteroids on bone density in patients with polymyalgia rheumatica. Br J Rheumatol. 1998;37:292-9, doi: 10.1093/rheumatology/37.3.292.
63. (2001) American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. Arthritis Rheum. 2001;44:1496-503, doi: 10.1002/1529-0131(200107)44:7<1496::AID-ART271>3.0.CO;2-5.
64. Adler RA, Hochberg MC. Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the Department of Veterans Affairs. Arch Intern Med. 2003;163:2619-24, doi: 10.1001/archinte.163.21.2619.
65. Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. Ann Rheum Dis. 2004; 63:324-5, doi: 10.1136/ard.2003.008060.
66. National Osteoporosis Society & Royal College of Physicians guidelines working group for Bone and Tooth Society. Glucocorticoid-induced

Osteoporosis: guidelines for prevention and treatment. London, Royal College of Physicians. 2002.
67. Saag KG, Gehlbach SH, Curtis JR, Youket TE, Worley K, Lange JL. Trends in prevention of glucocorticoid-induced osteoporosis. J Rheumatol. 2006;33:1651-7.
68. Guzman-Clark JR, Fang MA, Sehl ME, Traylor L, Hahn TJ. Barriers in the management of glucocorticoid-induced osteoporosis. Arthritis Rheum. 2007;57:140-6, doi: 10.1002/art.22462.
69. Solomon DH, Morris C, Cheng H, Cabral D, Katz JN, Finkelstein JS, et al. Medication use patterns for osteoporosis: an assessment of guidelines, treatment rates, and quality improvement interventions. Mayo Clin Proc. 2005;80:194-202, doi: 10.4065/80.2.194.
70. Berris KK, Repp AL, Kleerekoper M. Glucocorticoid-induced osteoporosis. Curr Opin Endocrinol Diabetes Obes. 2007;14:446-50.
71. Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol Biol. 2005;97:13-9, doi: 10.1016/j.jsbmb.2005.06.020.
72. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000;67:277-85, doi: 10.1007/s002230001146.
73. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2009;373:1253-63, doi: 10.1016/S0140-6736(09)60250-6
74. Franchimont N, Canalis E. Management of glucocorticoid induced osteoporosis in premenopausal women with autoimmune disease. Autoimmun Rev. 2003;2:224-8, doi: 10.1016/S1568-9972(03)00056-9.
75. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can. 2008;30:1146-8.
76. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone. 2009;44:428-30, doi: 10.1016/j.bone.2008.11.001.
77. Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357:2028-39, doi: 10.1056/NEJMoa071408.
78. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009;60:3346-55, doi: 10.1002/art.24879.