Prevention and management of glucocorticoid-induced side effects: A comprehensive review

A review of glucocorticoid pharmacology and bone health

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Learning objectives
After completing this learning activity, participants should be able to describe key features of glucocorticoid pharmacology and anticipate, prevent, and manage complications of glucocorticoid use affecting bone health.

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Systemic glucocorticoids are an essential therapy for a range of conditions, but their multiple side effects can produce significant morbidity for patients. The objective of this review is to discuss these side effects while addressing 3 questions: 1) What dose and duration of glucocorticoid therapy should prompt concern for individual side effects?; 2) How should clinicians counsel patients about these complications?; and 3) How can these problems be prevented or managed? To accomplish these objectives, we have created a series of tables and algorithms based on a review of relevant data to guide counseling, prophylaxis, and management of 11 glucocorticoid side effects. The first article in this 4-part continuing medical education series begins with a review of glucocorticoid pharmacology followed by a discussion of bone health (ie, osteoporosis and osteonecrosis). (J Am Acad Dermatol 2017;76:1-9.)

Key words: glucocorticoids; medication monitoring; osteonecrosis; osteoporosis; pharmacology; side effects; steroids.

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GLUCOCORTICOID PHARMACOLOGY

Key points

- **Glucocorticoids are selected based on therapeutic efficacy and side effect considerations, properties that depend on pharmacokinetic and pharmacodynamic parameters**
- **Understanding these parameters may help clinicians manage glucocorticoid side effects for their patients**

There are many options when prescribing glucocorticoids. Prednisone, prednisolone, methylprednisolone, and dexamethasone are all commonly used oral formulations. High-dose pulse glucocorticoid therapy may be required in clinical emergencies or for severe, uncontrolled disease, often in the form of intravenous (IV) methylprednisolone. High-dose dexamethasone may be required in the case of central nervous system emergencies for its enhanced central nervous system penetration.[1] In dermatology, pulse IV methylprednisolone is an option for patients with severe pemphigus vulgaris, pyoderma gangrenosum, and systemic lupus erythematosus. Intraarticular and intralesional formulations, such as triamcinolone acetonide or methylprednisolone acetate, are appropriate for certain conditions. Our glucocorticoid side effect pretreatment screening, ongoing monitoring, and counseling recommendations are shown in Table I.

Glucocorticoids exert their effect by binding to the glucocorticoid receptor, which translocates to the nucleus and targets gene transcription.[2] Nongenomic mechanisms are thought to explain the efficacy of pulse-dose glucocorticoid therapy, because these doses are generally greater than the saturation dose for the glucocorticoid receptor.[1] Oral glucocorticoids are well absorbed after administration and show variable degrees of binding to corticosteroid-binding globulin and albumin.[1] Only free, unbound drug can interact with the glucocorticoid receptor.[1] Prednisone and prednisolone both have dose-dependent pharmacokinetics because of nonlinear protein binding, while methylprednisolone and dexamethasone do not have this same dose-dependency.[1]

Glucocorticoids require a carbon-11 hydroxyl group in order to have activity.[3] The enzyme 11β-hydroxysteroid dehydrogenase controls the availability of glucocorticoids for binding to receptors. Type 1 dehydrogenase converts inactive to active drug and has its greatest activity in the liver.[1] For this reason, topical glucocorticoids, such as cortisone, must be 11-hydroxyl compounds in order to be effective. Cortisone is an 11-keto compound that has no activity topically. The enzyme is also responsible for converting prednisone to its active form, prednisolone. Type 2 dehydrogenase is found in mineralocorticoid target tissue.[1]

Systemic glucocorticoids are divided into short-, medium-, and long-acting formulations on the basis of adrenocorticotropic hormone suppression after a single dose.[3] The potency of glucocorticoids is determined by affinity for the intracellular glucocorticoid receptor and duration of action.[3] There is only a weak correlation between circulating half-life, potency, and duration of action.[3,4] Glucocorticoid potencies and duration of action are shown in Table II.

These concepts in pharmacology help explain the therapeutic and adverse effects of systemic glucocorticoids. For example, patients with low protein states are at increased risk of adverse effects from prednisone therapy because the amount of circulating unbound drug is increased.[1,4-6] The dose-dependent availability and clearance of prednisone and prednisolone accounts for the decreased side effects (and diminished efficacy) of alternate-day dosing.[6] Meanwhile, not all individuals metabolize drugs at the same rate; those who are slow metabolizers may suffer increased side effects.[7]

Certain diseases and drug–drug interactions alter glucocorticoid pharmacokinetics.[1] Altered pharmacokinetics are reported in patients with liver disease, renal failure, nephrotic syndrome, severe obesity, and inflammatory bowel disease, but the direction of effect is not necessarily the same for each glucocorticoid.[1] For example, in patients with severe liver disease, the conversion of prednisone to prednisolone is impaired. This effect may be partially offset by a decreased rate of elimination of prednisolone, but it may be prudent to use the active metabolite prednisolone preferentially over prednisone in these patients.[3,6] In patients with severe systemic diseases, it is wise to confer with the patient's other providers before prescribing glucocorticoids.

Clinicians should also be aware of other medications taken by the patient. The coadministration of CYP450 enzyme inducers increases the clearance and decreases the half-life of glucocorticoids, while enzyme inhibitors decrease clearance and increase half-life.[1] Complete lists of CYP450 inducers and inhibitors are readily available, and clinicians are encouraged to review all drug–drug interactions before prescribing new medications.

Glucocorticoid side effects are not limited to systemic oral or intravenous therapy. Injected glucocorticoids vary in their absorption, but high potency injections, or multiple injections that result in glucocorticoid accumulation, can cause systemic side effects. This is true of intramuscular injections, which can increase the risk of adrenal suppression

Table I. Side effect–specific pretreatment screening, ongoing monitoring, and counseling recommendations

Counseling
Choose the lowest dose and duration of therapy
Explain side effects of glucocorticoids
Document patient understanding of side effects in the health record; consider asking patient to sign consent to treatment with steroids
Consider prescribing glucocorticoid identification bracelet
Laboratory assessments and screening before initiating therapy/ongoing monitoring
Bone health
Take 1200 mg calcium and 800 IU vitamin D daily
Baseline height and bone mineral density assessment (using DEXA)
Pharmacologic therapy as indicated (see chart)
Annual DEXA scan to monitor done mineral density
Replete vitamin D and calcium before prescribing bisphosphonate if indicated
Gastrointestinal
Assess history of PUD risk factors, including nonsteroidal antiinflammatory drug use, smoking, history of *Helicobacter pylori* infection, alcohol use, age >65 years, current or previous PUD, bisphosphonates, and other medications that the increase risk of PUD
Prescribe proton pump inhibitor, if indicated
Endocrine
Screen for diabetes with baseline hemoglobin A1c level, finger stick, or basic metabolic panel
Establish baseline electrolytes and renal function with basic metabolic panel
In conjunction with primary care provider, repeat with regular laboratory monitoring
Consider prescribing a glucometer for home glucose monitoring to those taking moderate- or high-dose steroids chronically
Ocular
Ask about history of cataracts and glaucoma
Consider baseline ophthalmology examination
Repeat examinations as indicated
Cardiovascular health
Check blood pressure at every visit
Check fasting lipids as part of regular laboratory monitoring
Vaccinations (see section on vaccinations)
Take immunization history before initiating therapy
If possible, give missing or indicated vaccines before therapy; give live vaccines at least 2-4 weeks before therapy
Infectious
Hepatitis B virus, hepatitis C virus screening
HIV screening
Tuberculosis skin test or interferon-gamma release assay (eg, QuantiFERON-TB Gold) as appropriate
Strongyloides testing as appropriate
Mood and cognitive
Assess for past or current neuropsychiatric disorders
Ask all youth for history of depression and suicidality
Refer any positive findings to primary care provider or psychiatry
If concern for suicidality, urgent referral to emergency services

DEXA, Dual-energy x-ray absorptiometry; *PUD*, peptic ulcer disease.

and other systemic side effects in a largely dose- and frequency-dependent manner. It is unclear whether individual injections will lead to systemic side effects, but even a single injection can reduce cortisol levels, so clinicians are encouraged to remain aware of this possibility and treat the regular administration of intramuscular steroids as equivalent to that of oral formulations, with all the same side effect considerations. Even intralesional triamcinolone acetonide used for keloids or hypertrophic scars has been associated with the development of Cushing syndrome, especially when dosed multiple times or at high doses in pediatric patients.[8]

Topical therapy can result in skin thinning, and both topical and inhaled therapy may also result in systemic side effects, such as Cushing syndrome or hypothalamic–pituitary–adrenal axis suppression. The potency of topical corticosteroids depends on the particular molecule and its absorption through the skin, a feature of penetration, concentration,

Table II. Glucocorticoid potencies and duration of action

Name	Equivalent dose (mg)	Anti-inflammatory potency	Duration of action (hrs)*
Cortisol (hydrocortisone)	20	1	8-12
Cortisone	25	0.8	8-12
Prednisone	5	4	12-36
Prednisolone	5	4	12-36
Methylprednisolone	4	5	12-36
Triamcinolone	4	5	12-36
Betamethasone	0.75	25	36-72
Dexamethasone	0.75	25	36-72
Fludrocortisone†	—	10	12-36

Data from Axelrod[3] and Nierman.[52]
*Short acting, 8-12 hours; intermediate acting, 12-36 hours; and long acting, 36-72 hours.
†Not used for glucocorticoid effects.

saturation, and elimination,[9] as well as the location of application.[10] A recent consensus statement and literature review suggested that topical glucocorticoids may rarely be associated with striae, ophthalmologic disease, and short-term hypothalamic–pituitary–adrenal suppression in pediatric patients with eczema. Systemic side effects may also be seen with intraarticular glucocorticoids, although this is encountered more rarely than with systemic formulations and is most likely with repeat exposures and high potency steroids.[11]

Dose and duration

Specific side effects may develop at different doses and durations of glucocorticoid therapy. In general, the European League Against Rheumatism (EULAR) defines dosing as: low if ≤ 7.5 mg prednisone equivalent per day; medium if > 7.5 mg but ≤30 mg prednisone equivalent per day; high if > 30 mg but ≤100 mg prednisone equivalent per day; very high if > 100 mg prednisone equivalent per day; and pulse dose if ≥250 mg prednisone equivalent per day for 1 or a few days.[12] Similarly, the definitions of "chronic," "long-term," or "short-term" therapy also vary. One study defines dosing as short-term if <3 months, medium-term if 3 to 6 months, and long-term if > 6 months.[13] Information regarding dose and duration pertaining to specific side effects is discussed within each section.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Key points

- **Loss of bone mineral density occurs early in the course of glucocorticoid therapy**
- **All patients regardless of age, sex, dose, and duration of glucocorticoid therapy require counseling, screening, and prophylaxis for glucocorticoid-induced osteoporosis**

Background

Glucocorticoid therapy is the leading iatrogenic cause of secondary osteoporosis.[14,15] Loss of bone mineral density (BMD) in patients who are taking glucocorticoids occurs primarily in the first 6 months of therapy and slows after 1 year.[16] Within the first 3 months of therapy, the risk of fracture increases by as much as 75%, before a significant decrease in BMD.[14]

Epidemiology and risk factors

Glucocorticoid-induced osteoporosis (GIOP) may occur in 30% to 50% of patients undergoing glucocorticoid therapy.[17] Fractures occur predominantly in regions with a high amount of cancellous bone, especially the lumbar spine and proximal femur, and they may be asymptomatic in a large number of patients.[15,18] The incidence of fracture is strongly associated with daily dose and duration of glucocorticoids.[18] In 1 study, patients taking doses of prednisone ≥7.5 mg/day had a risk of hip and nonvertebral fracture double that of patients taking prednisone 2.5 mg/day.[19] In the same study, however, there was no threshold dose at which glucocorticoids could be considered safe.[19] Fractures can occur on doses as low as 2.5 to 7.5 mg of prednisone (or equivalent) per day.[20] Alternate-day and intermittent dosing do not decrease the risk of fracture.[21-23] Conversely, there is currently no evidence that osteoporosis medication is needed to prevent fractures for patients on occasional dose-pack prescription glucocorticoids, replacement therapy for hypopituitarism or adrenal insufficiency, or short term high-dose intravenous or oral therapy with <1 g of cumulative annual exposure.[14] For cumulative prednisolone doses of >1 g prescribed in short bursts even over the course of 1 year, significant bone loss has been seen.[24] Cumulative corticosteroid dose strongly correlates with loss of bone mineral density.[19,25]

Evaluation

All clinicians prescribing glucocorticoids should, at the outset of therapy, counsel their patients about osteoporosis and screen for the GIOP risk factors listed in Table III. Those with anticipated therapy lasting ≥3 months should be screened for osteoporosis (T-score ≤−2.5) and osteopenia (T-score between −1 and −2.5) at baseline with a

dual-energy x-ray absorptiometry (DEXA) scan, which estimates BMD. Using this information, the patient's risk of fracture should then be estimated. In many instances, clinical history and DEXA findings are sufficient to guide management without the use of specific risk equations. When necessary, however, several tools exist to predict GIOP risk.[14,27,28] The World Health Organization fracture prevention algorithm (FRAX) is a widely used fracture prediction tool (available at: http://www.shef.ac.uk/FRAX/). FRAX calculates the 10-year risk of fracture with or without BMD. Importantly, FRAX underestimates fracture risk associated with glucocorticoid use,[14,29] so clinicians who use FRAX should modify the results based on the dose and duration of glucocorticoid exposure and the additional risk factors listed in Table III. Note that because of a lack of data, no current model accurately predicts fracture risk in premenopausal women or men <50 years of age.[30,31] Clinical judgment is required to estimate risk in these patients. Our approach is outlined in Fig 1.

Table III. Factors associated with glucocorticoid-induced osteoporosis

Advanced age
Low body mass index
Underlying disease
Previous fracture
Smoking
Excessive alcohol use
Falls
Family history of fracture
High-dose glucocorticoid use
Duration of therapy
Low bone mineral density (as measured by dual-energy x-ray absorptiometry)
Hypovitaminosis D

Prevention and treatment

Clinicians should choose the lowest effective daily dose of steroids for the shortest duration possible and offer lifestyle counseling focused on reducing GIOP risk factors. It is important to emphasize that because significant changes occur within the first 3 months of therapy, clinicians cannot safely wait 3 months to initiate therapies aimed at preventing bone loss and fractures. These measures should be implemented at the outset of glucocorticoid therapy.

Treatment

Calcium and vitamin D. All patients taking any dose of glucocorticoids with an anticipated duration of ≥3 months should maintain, through diet or supplementation, a total daily calcium intake of 800 to 1200 mg daily and vitamin D of 800 to 2000 units daily with rare exceptions (eg, patients with sarcoidosis may have high levels of activated vitamin D at baseline and may require disease-specific adjustments; patients with a history of hypercalcemia, hypercalcuria, or hypervitaminosis D may warrant adjustment as well; in patients with chronic kidney disease, calcium supplementation should be discussed with a nephrologist).[30,32]

Bisphosphonates. Bisphosphonates are first-line therapy for treating GIOP. There is substantial evidence of their effectiveness in preventing and treating bone loss in these patients.[33] Patients most likely to benefit from bisphosphonates are those at highest fracture risk. This includes postmenopausal women and men ≥50 years of age with established osteoporosis (a T-score ≤ −2.5 or a history of fragility fracture), osteopenia (a T-score ranging from 1-2.5) taking ≥7.5 mg/day prednisone for ≥3 months, and osteopenia taking <7.5 mg/day prednisone who are considered high risk using the FRAX equation. Bisphosphonate therapy in premenopausal women and younger men is less well defined and must be balanced against potential long-term risks and teratogenicity. Nevertheless, it should be considered in patients who are taking glucocorticoids chronically who have accelerated BMD loss or a history of fragility fractures.

Alendronate or risedronate are preferred first-line agents. For patients who cannot tolerate oral medications, IV zoledronic acid may be considered. Bisphosphonates should be avoided in patients with a creatinine clearance of <30 mL/minute; such patients should be referred to a bone metabolism expert for additional management. Bisphosphonate-specific dosing, administration, and counseling recommendations can be found in Table IV. Of note, bisphosphonates are lipid soluble and may be stored in body fat for months to years; animal studies suggest the potential for fetal harm with abnormal bone development, and clinicians should therefore use caution when considering these medications for premenopausal women who may still become pregnant.[30,34,35]

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures are 2 rare side effects of bisphosphonate therapy of which clinicians should be aware. ONJ is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification.[36] The estimated incidence among those taking bisphosphonates is between 1 in 10,000 and 1 in 100,000 patients, but is higher for cancer patients who receive larger

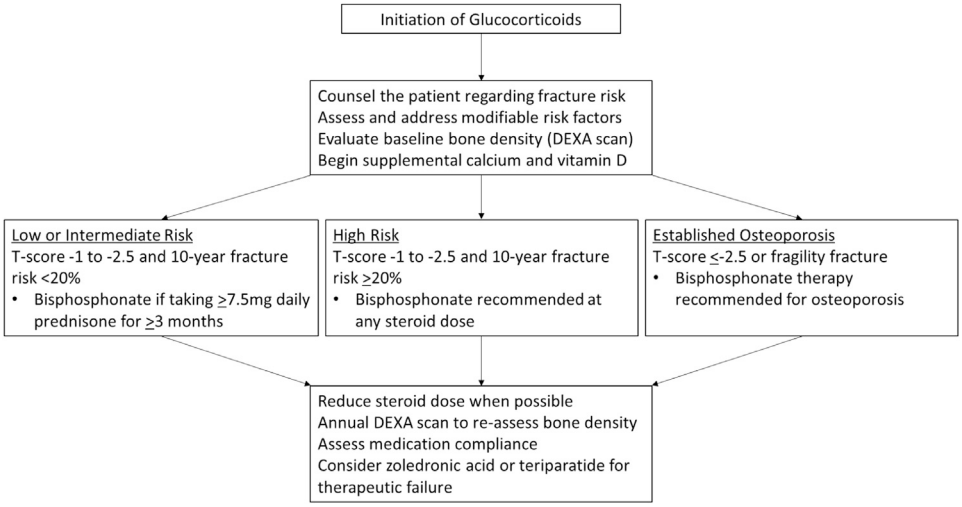

Fig 1. Approach to treating glucocorticoid-induced osteoporosis using bisphosphonates. These recommendations are most applicable to postmenopausal women and men >50 years of age. Bisphosphonate therapy in premenopausal women and younger men is less well defined. *DEXA*, Dual-energy x-ray absorptiometry. Adapted from Grossman et al.[26]

Table IV. Bisphosphonate therapy

Options for bisphosphonate therapy
Alendronate: 5 mg daily, 70 mg weekly, or 150 mg monthly (generally the 70-mg weekly dose for treatment is favored)
Risedronate: 5 mg daily or 35 mg weekly
Ibandronate: 150 mg/month (only weak recommendation for this medication in glucocorticoid-induced osteoporosis)
Zoledronic acid: 5 mg once yearly as an intravenous infusion for patients who cannot tolerate oral bisphosphonates (monitor for flu-like symptoms 2-3 days after first injection; can treat with acetaminophen or nonsteroidal antiinflammatory drugs; use with caution in patients with history of atrial fibrillation)
Before initiating therapy
Consider referring all patients for dental examination; avoid bisphosphonate therapy when dental work is needed
Correct hypocalcemia and vitamin D deficiencies
Assess for comorbidities that may preclude bisphosphonate use
Measure serum creatinine: avoid bisphosphonate use if creatinine clearance is <30-35 mL/min, and consider referral to endocrinology or nephrology for additional management
Ensure patient has no swallowing difficulties and can remain upright for 30 min after taking a bisphosphonate
Avoid use in patients with active upper gastrointestinal disease
Administration
Take alone on an empty stomach first thing in the morning with 8 oz of water*
Avoid food and drink and other medications or supplements for 30 min after taking alendronate or risedronate and 1 hr after taking ibandronate
Remain upright for 30 min after taking
Discontinue if patients develop esophagitis
Do not prescribe for any patients with swallowing difficulties or with active upper gastrointestinal disease

*Enteric coated, delayed-release risedronate is taken immediately after breakfast with 4 oz of water.

doses of IV bisphosphonates.[36] Most cases have been reported in patients with underlying osteolytic breast cancer or multiple myeloma.[14] The American Association of Oral and Maxillofacial Surgeons recommends stopping oral bisphosphonates 3 months before and 3 months after a dental procedure if systemic conditions permit.[37] However, stopping bisphosphonates while on glucocorticoids greatly increases the loss of BMD, and ONJ is rare. To provide perspective, clinicians may consider the following data: to prevent 1 vertebral fracture, the number needed to treat for 8 years is 3; to prevent 1 nonvertebral fracture, the number needed to treat for 8 years is 7; the number needed to harm over 8 years for ONJ is 1000 to 100,000.[38-40] The American Dental Association Council on Scientific Affairs issued an

executive summary in which they stated that the benefit of antiresorptive therapy outweighs the low risk of ONJ.[41]

Atypical subtrochanteric and femoral fractures are also associated with bisphosphonate use. Atypical femoral fractures present with groin or thigh pain unassociated with trauma.[42] According to a report of The American Society for Bone Mineral Research, atypical fractures appear to be more common in patients who have been taking bisphosphonates for >3 years. They also note multiple case series in which patients who are not taking bisphosphonates developed atypical femur fractures.[42] Any patient taking glucocorticoids and presenting with new, dull, or aching pain in the groin, thigh, or hip should have a plain radiograph of the affected side, and the prescribing clinician should communicate with radiology the concern for atypical femoral fracture. Fortunately, this complication is rare; the number needed to harm for atypical femoral fracture is 1282 if receiving bisphosphonates for 8 years.[38-40]

Bisphosphonate drug holidays are not recommended for patients who are at risk for GIOP. Studies guiding such recommendations did not include GIOP, and the results are therefore not generalizable.[14,43-45] A retrospective observational study of patients on extended bisphosphonates for GIOP found that patients who discontinued alendronate after 1 year while remaining on ≥6 mg/day of prednisone had significantly decreased BMD compared to those who remained on alendronate.[46] We recommend continuing bisphosphonates for GIOP while taking glucocorticoids, with annual repeat DEXA scans to monitor BMD.

Other therapies. Teriperatide, recombinant human parathyroid hormone; denosumab, a human monoclonal antibody to RANKL; and calcitonin, a parathyroid hormone antagonist, may be considered for patients who cannot tolerate bisphosphonates or who require long-term therapy.[47] These medications should be prescribed by clinicians who are experienced in managing bone disease. Data on hormone-replacement therapy are insufficient to make specific recommendations.

Monitoring. In addition to annual DEXA scans to monitor BMD, compliance with bisphosphonate therapy and calcium and vitamin D intake should be regularly reviewed. The importance of smoking cessation, decreased alcohol consumption, and weight-bearing exercise should be discussed. The serum 25-hydroxy vitamin D level should be measured annually.

OSTEONECROSIS

Key points

- **The risk for developing osteonecrosis increases with cumulative and daily dose of glucocorticoids; however, patients taking any dose of glucocorticoid therapy may develop this side effect**
- **In patients taking glucocorticoids, clinicians must take note of any complaint of pain, especially in the hip, knee, or shoulder**

Background

Osteonecrosis of the femoral neck, distal femur, and proximal tibia may occur in as many as 40% of patients on long-term or high-dose glucocorticoid therapy.[23] The total cumulative dose and daily dose of glucocorticoids, and likely the underlying condition, affect the risk of developing osteonecrosis.[48] Very short-course, low-dose protocols are only rarely associated with osteonecrosis.[49] In 1 study, the mean daily dose of prednisone exceeded 40 mg/day for ≥1 month in 93% of patients and 20 mg/day in 100% of patients who developed osteonecrosis.[50] In addition, the association between osteonecrosis and Cushingoid features was highly significant.

Pathogenesis and clinical presentation. The pathogenesis of osteonecrosis (also called aseptic, avascular, or ischemic necrosis or bone infarct) is not known. However, fat embolism, vascular thrombosis, fatigue (stress) fractures, and osteocyte apoptosis triggered by glucocorticoids have all been suggested as underlying mechanisms.[48] Osteonecrosis most commonly occurs in the femoral and humeral heads. Pain is usually the first symptom, but the clinical presentation is variable and depends on the site and size of the infarct.[51] Worsening pain occurs with movement of the affected joint, and as symptoms progress, patients may experience nocturnal pain. Symptoms may present within weeks to months on high-dose oral, intravenous, or intraarticular steroids or with chronic use over time.[49,51]

Management. Patients taking any dose of glucocorticoids must be monitored for osteonecrosis, because damage may be irreversible in later stages of disease. Clinicians must take note of any hip, knee, or shoulder pain with or without reduced range of motion. Complaints of joint pain should prompt consideration of osteonecrosis and, if concerned, referral for magnetic resonance imaging of the affected joint and evaluation by the patient's primary care provider, orthopedics, or rheumatology.

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