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Corticosteroid use in chronic dermatologic disorders and osteoporosis

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ABSTRACT

Glucocorticoid-induced osteoporosis (GIOP) is a frequently encountered and serious side effect of glucocorticoid use. Bone loss leading to an increased risk for fracture occurs early in the use of glucocorticoids, yet patients at risk for this complication are often undertreated. All physicians prescribing glucocorticoids should therefore be familiar with a basic approach to anticipating and preventing GIOP when starting patients on glucocorticoid therapy. This manuscript and its case vignettes are designed to help dermatologists assess and manage bone health to prevent GIOP in patients receiving glucocorticoid therapy.

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What is known about this subject in regard to women and their families?

- The prevalence of the use of glucocorticoids in the population is estimated to range up to 2%, with some studies finding higher percentages of women among chronic glucocorticoid users based on age and underlying disease (Briot, 2015; Fardet et al., 2011; Overman et al., 2013).
- In the International Global Longitudinal Study of Osteoporosis in Women, 2% of women with complete data over 5 years reported continuous use of glucocorticoids, yet the management of glucocorticoid-induced osteoporosis (GIOP) worldwide was noted to be suboptimal (Silverman et al., 2014).
- Postmenopausal women exposed to glucocorticoids are at greater risk for developing GIOP than other populations; however, GIOP is not limited to this population (de Gregório et al., 2006).

What is new from this article as messages for women and their families?

- Patients on chronic glucocorticoids should be screened for glucocorticoid-induced osteoporosis risk factors and initiated on preventative therapies as appropriate (Adami, 2019).
- Most often, there are no symptoms of osteoporosis until there is a fracture.
- Adequate calcium and vitamin D intake, exercise, avoidance of smoking. and limiting alcohol use are important in optimizing bone health.
- Use of anti-osteoporotic medications among postmenopausal women is associated with reduced fracture incidence compared with postmenopausal women on glucocorticoids who do not receive anti-osteoporotic medications (Overman et al., 2015).
- Women and their families should be aware that if taking chronic glucocorticoids, they may need preventative treatment to reduce the risk for fractures and should discuss this with their physician.

Background

Glucocorticoids (GCs) are widely prescribed in medical practice, including by dermatologists. Estimates suggest that approximately 2% of the population receives long-term GC therapy, and a larger number of patients receive short-term therapy (Compston, 2018; Fardet et al., 2011; Overman et al., 2013; Van Staa et al., 2000a;Waljee et al., 2017). Although glucocorticoid-induced osteoporosis (GIOP) is one of the most frequently encountered and potentially most serious side effects of GCs, at-risk patients are often undertreated (Compston, 2018; Trijau et al., 2016). All physicians prescribing GCs should be familiar with a basic approach to anticipating and preventing GIOP (Fig. 1).

GC use leads to early and rapid bone loss (primarily at the spine), elevating fracture risk before a significant decrease in bone mineral density (BMD) occurs. The risk of fragility fracture increases after the first dose of GC (Amiche et al., 2016) but becomes more substantial after 3 to 6 months of oral therapy (Van Staa et al., 2002). Approximately 33% of patients have evidence of vertebral fracture after 5 to 10 years of oral GC use, with an even higher incidence in postmenopausal women on chronic GCs (Schäcke et al., 2002). Because osteoporosis is more common in women and women are more likely to get screened for osteoporosis regardless of whether they are treated with steroids, osteoporosis in men remains largely underdiagnosed and they are less likely to receive intervention. The risk of fracture depends on the dose and duration of treatment; the higher the daily or cumulative dose and the longer GCs are used, the higher the risk. Studies have shown contrasting results regarding the strength of correlation of fracture risk to the daily or cumulative dose of GCs (De Vries et al., 2007; Van Staa et al., 2000b; 2002; 2003; Steinbuch et al., 2004). Compared with low-dose users, high-dose users (daily dose ≥15 mg prednisone equivalent and/or cumulative dose ≥1 g) have the greatest risk of fractures (Amiche et al., 2018). Bone loss was also demonstrable in individuals on alternate-day GC regimens (Gluck et al., 1981). Risk decreases after stopping GC therapy, and most of the excess risk of fracture disappears within 1 year (Van Staa et al., 2002).

General approach to preventing glucocorticoid-induced osteoporosis

A general approach to preventing GIOP involves the following steps (Fig. 1; Table 1).

Anticipate the dose and duration of expected GC therapy and identify patient-specific risk factors

Patients initiating GCs at a dose ≥2.5 mg per day prednisone or its equivalent, with an anticipated duration of >3 months, should be assessed for fracture risk through history, physical examination, and (in selected patients) BMD with dual-energy x-ray absorptiometry (DXA) scan as soon as possible, but at least within 6 months of starting GCs (and annually thereafter if GC therapy is continued). These factors enable the identification of patients at high risk for fracture who would benefit from intervention (Buckley et al., 2017). The higher the GC dose and the longer GCs are used, the higher the fracture risk; however, patient-specific risk factors must also be considered. Patient-specific risk factors include previous fracture, low body weight, current smoking status, excessive alcohol use (≥3 units/day), family history of hip fracture, rheumatoid arthritis, and other disorders that increase the risk of fractures (e.g., hypogonadism, malabsorption, premature menopause, inflammatory bowel disease, chronic liver disease; Kanis et al., 2005). Physical examination should include measurement of weight and height (>1 inch height loss may indicate vertebral fracture), testing of muscle strength, balance, and assessment for other clinical findings of undiagnosed fracture, such as spinal tenderness and kyphosis (Buckley et al., 2017).

Counsel patients about lifestyle changes to reduce fracture risk

All patients should receive counseling regarding lifestyle modifications, including maintaining a healthy body weight, smoking cessation, regular weight-bearing or resistance training exercise (30 minutes/day, 3 days/week), and limiting alcohol intake to <3 alcoholic beverages per day.

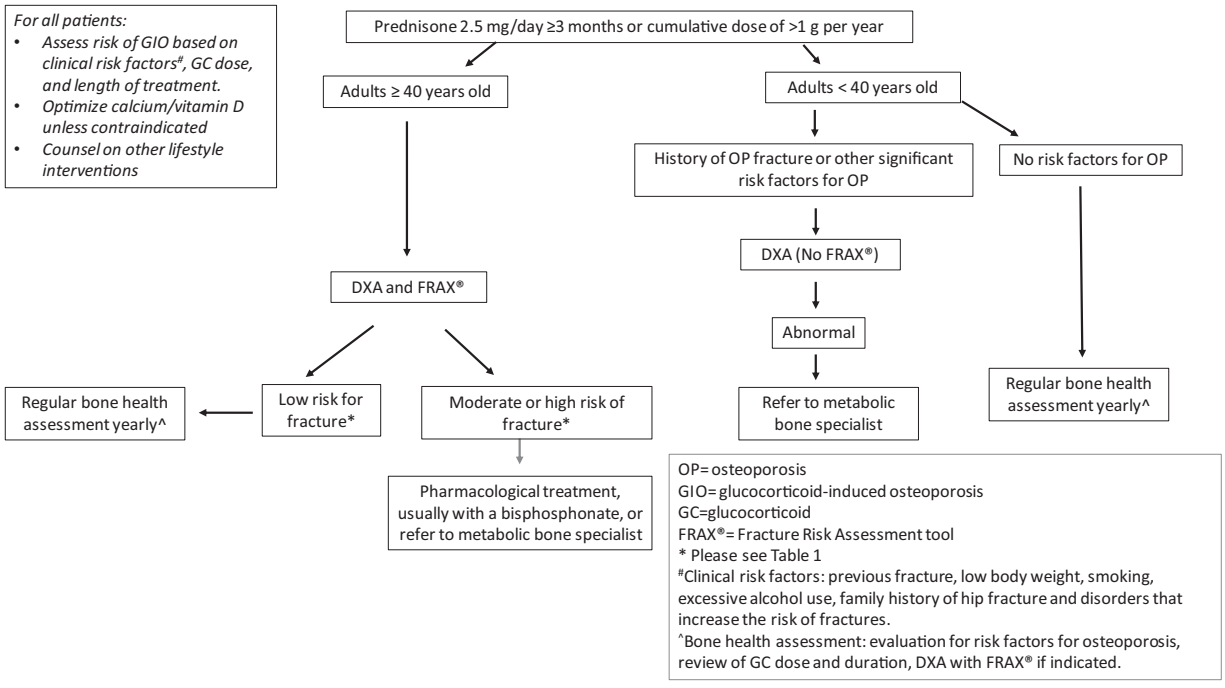

Fig. 1. Fracture Risk Assessment and Intervention Algorithm.

Table 1
Fracture risk categories in glucocorticoid-treated patients (adapted from Buckley et al., 2017)

Adults age ≥40 years	**High risk for fracture**	Prior osteoporotic fracture(s) Hip or spine T-score ≤ −2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted) 10-year risk of major osteoporotic fracture ≥20% FRAX* (GC-adjusted) 10-year risk of hip fracture ≥3%
	Moderate risk for fracture	FRAX* (GC-adjusted) 10-year risk of major osteoporotic fracture 10%-19% FRAX* (GC-adjusted) 10-year risk of hip fracture >1% and <3%
	Low risk for fracture	FRAX* (GC-adjusted) 10-year risk of major osteoporotic fracture <10% FRAX* (GC-adjusted) 10-year risk of hip fracture ≤1%
Adults age <40 years	**High risk for fracture**	Prior osteoporotic fracture(s)
	Moderate risk for fracture	Hip or spine Z-score < −3 **or** rapid bone loss (≥10% at the hip or spine >1 year) AND Continuing GC treatment at a prednisone dose of ≥7.5 mg/day or its equivalent for ≥6 months Adults age ≥30 years taking very high dose GCs (prednisone ≥30 mg daily) or cumulative use (>5 g in 1 year)
	Low risk for fracture	No risk factors other than GC treatment

FRAX, Fracture Risk Assessment Tool; GC, glucocorticoid
* FRAX calculator can be found at https//www.shef.ac.uk/FRAX/tool.jsp. The risk calculated by FRAX should be multiplied by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if the GC dose is >7.5 mg/day of prednisone or its equivalent.

Optimize calcium and vitamin D intake, unless contraindicated

All patients expected to be on GCs at any dose for ≥3 months should have their calcium and vitamin D intake optimized, unless contraindicated. A daily intake of 1000 to 1200 mg of calcium and 600 to 800 IU of vitamin D is recommended. Dietary calcium (primarily through dairy products) is encouraged, but calcium supplements can be used when there is inadequate dietary intake. The 25-hydroxyvitamin D level should be checked to assess for vitamin D deficiency; if low, the level should be repleted if not contraindicated. The optimal 25-hydroxyvitamin D level is controversial, but for bone health maintaining a 25-hydroxyvitamin D level of at least 30 ng/dl is reasonable (Cosman et al., 2014). Calcium and vitamin D supplementation should be used with caution in special populations, including those with chronic kidney disease, sarcoidosis, and primary hyperparathyroidism.

Identify patients who would benefit from additional pharmacologic interventions

Patients expected to receive steroids at a dose of ≥2.5 mg/day prednisone (or its equivalent) for ≥3 months should have a risk stratification performed by calculating the Fracture Risk Assessment Tool (FRAX) score (not for use in patients age <40 years) or BMD by DXA.

Fracture Risk Assessment Tool

For adults age ≥40 years, the absolute risk of fracture can be calculated using the FRAX (Centre for Metabolic Bone Disease, 2021). FRAX is an online tool used to predict the 10-year probability of major osteoporosis-related fracture (hip, forearm, proximal humerus, and cervical spine) and the 10-year probability of hip fracture. It incorporates clinical risk factors for fractures, as well

as femoral neck BMD obtained via DXA scan. FRAX can be used for both men and women and is country-specific. FRAX can be adjusted to account for daily dosage of GCs (prednisone ≥5 mg for >3 months), but not for cumulative dosage or length of use. When GC use is added as a risk factor in the FRAX tool, the fracture estimate reflects the risk associated with prednisone at a dose of 2.5 to 7.5 mg per day. For patients taking prednisone >7.5 mg per day or its equivalent, the risk estimate needs to be corrected upward, generally by 15% for major osteoporotic fracture and by 20% for hip fracture (Buckley et al., 2017). The FRAX tool does not provide fracture risk estimates for young patients age <40 years.

Dual-energy x-ray absorptiometry

DXA scan is the gold standard test for evaluating BMD and effectively discriminates high-risk patients from low-risk patients. Screening DXA scan is recommended in adults age ≥40 years taking prednisone ≥2.5 mg daily, or its equivalent, with an anticipated duration of >3 months, as well as adults age <40 years taking GCs with a history of fragility fracture or other significant risk factors for fracture (Buckley et al., 2017). DXA scan should be repeated every 1 to 3 years depending on the clinical risk factors, baseline bone density, and dose and duration of GC treatment. A vertebral fracture assessment can be performed at the same time a routine DXA scan is obtained, depending on the type and model of the scanner. A vertebral fracture assessment can detect clinically significant prevalent vertebral fractures (Lewiecki, 2010).

According to the American College of Rheumatology guidelines, based on BMD assessment through DXA scan, the presence of clinical risk factors for fractures, FRAX estimation, and GC dose, patients can be classified as at low, moderate, or high risk for fracture (Table 1; Buckley et al., 2017). Generally, patients at moderate or high risk for fracture benefit from pharmacological intervention.

Prescribe fracture prevention medications or refer patients to a metabolic bone disorder expert

First-line therapy for osteoporosis treatment and prevention is typically an oral bisphosphonate (e.g., alendronate, risedronate). Second-line therapies include intravenous bisphosphonates, teriparatide, denosumab, and raloxifene (in postmenopausal women when other second-line medications are not appropriate; Buckley et al., 2017). Patients taking oral bisphosphonates should follow specific administration instructions. Individuals who have contraindications to oral bisphosphonates, such as underlying esophageal disorders, cannot tolerate oral bisphosphonates because of acid reflux disease, or are unable to follow the administration instructions are candidates for intravenous bisphosphonates (zoledronic acid). Bisphosphonates are not recommended for patients with creatinine clearance <30 to 35 mL/min. The usual length of oral bisphosphonate treatment is 5 years; however, treatment can be prolonged if the patient continues to receive GCs and is still considered to be at moderate to high risk for fractures.

Some patients may benefit from early referral to a physician with particular expertise in managing metabolic bone disease (typically an endocrinologist or rheumatologist), including patients with fragility fractures and baseline osteopenia or osteoporosis (who would require evaluation for secondary causes of low BMD), premenopausal women or young men with low BMD, patients intolerant of oral bisphosphonates or patients with low kidney function in whom bisphosphonates would be contraindicated, patients with complex calcium and vitamin D metabolism (e.g., patients with sarcoidosis), or patients who have fractures or ongoing bone loss while on anti-osteoporotic therapy despite good adherence.

Case vignettes

Case vignette 1

A 60-year-old woman receives prednisone 5 mg daily for maintenance therapy of bullous pemphigoid for 6 months. Should she receive pharmacologic intervention to reduce fracture risk?

Our patient is a postmenopausal woman and has been taking prednisone 5 mg daily for >3 months; thus, she is at risk for GIOP. Clinical evaluation should start with a thorough history and physical examination. Aside from GC use, risk factors for fracture should be identified (e.g., history of fracture, falls, or family history of osteoporosis). The patient should receive lifestyle counseling and instructions on how to optimize her calcium and vitamin D intake. Obtaining a DXA scan to evaluate her BMD is indicated.

Her DXA scan shows osteopenia of the spine, total hip, and femoral neck (T-score between –1.0 and –2.5). How should you proceed?

If the patient has osteoporosis on her DXA scan, she should receive anti-osteoporotic medication and/or be referred to a metabolic bone disorder expert for further evaluation and treatment. Our patient has osteopenia, and further risk stratification should occur based on clinical risk factors and calculation of the FRAX score to determine her absolute risk for major osteoporotic-related fracture and hip fracture. Pharmacologic intervention with anti-osteoporotic medication is indicated if she is considered to be at moderate or high risk for fracture (see Table 1 for definitions of risk-based on FRAX score). If the patient is at low risk based on her FRAX score, she should be monitored carefully while on GCs. Of note, referring these patients to a metabolic bone disorder expert for evaluation may still be appropriate (Fig. 1).

You decrease the patient's prednisone dose to 2.5 mg daily. Is this a safe dose of steroids with regard to bone health?

GC-induced bone loss and increase in fracture risk during GC treatment are dose-dependent. Based on data in 244,235 patients and 244,235 controls, the hip fracture risk was 0.99 (range, 0.82-1.20) relative to controls with a daily prednisone dose of <2.5 mg, increasing to 1.77 (range, 1.55-2.02) with daily doses of 2.5 to 7.5 mg and 2.27 (range, 1.94-2.66) at doses of ≥7.5 mg. For vertebral fracture, the relative rates were 1.55 (range, 1.20-2.01), 2.59 (range, 2.16-3.10), and 5.18 (range, 4.25-6.31), respectively (Van Staa et al., 2000c). There is likely no dose of steroids that can be considered completely safe, because even doses as low as 2.5 mg prednisone per day used continuously have been associated with increased fracture risk

You change the patient's steroid dose to 5 mg every other day. Do alternate-day dosing regimens decrease the risk for osteoporosis?

Alternate-day dosing GC regimens may decrease the risk of hypothalamic pituitary adrenal axis suppression (Ackerman and Nolan, 1968) but do not decrease the risk for GIOP (Gluck et al., 1981), and monitoring for bone loss should be approached in the same manner as for patients on daily dosing GC regimens.

Case vignette 2

A 54-year-old woman is seen for severe atopic dermatitis. In addition to prescribing potent topical steroids, you provide a 3-week prednisone taper. The patient previously required short courses of systemic

steroids and has used potent topical steroids. In this patient who receives intermittent doses of prednisone rather than continuous therapy, what counseling and interventions are recommended for protection of bone health?

Assessing fracture risk in this patient is challenging because she is receiving short and intermittent courses of GCs. Knowing a patient's prescription history to identify cumulative exposure to oral GCs is important in helping clinicians identify patients at high risk of fracture.

The minimum cumulative GC dose necessary to produce bone loss in adults has not been established, but based on available data, if the patient's cumulative dose is >1 g in a year, she may be at increased fracture risk and would benefit from risk assessment with a DXA and/or FRAX. Of note, the FRAX algorithm does not account for the cumulative dosage of GCs and may underestimate the patient's fracture risk. Her calcium and vitamin D intake should be optimized, and she should receive lifestyle modification counseling. If the patient is at moderate or high risk for fracture based on clinical evaluation and BMD measurement, anti-osteoporotic treatment should be considered to prevent bone loss and decrease fracture risk.

Are there any risks associated with the long-term use of potent topical steroids?

The risk of osteoporosis and major osteoporotic fracture after application of topical GCs has not been extensively explored. In a recent cohort study of 723,251 users of potent or very potent topical GCs, the use of these medications was associated with an increased risk of osteoporosis and major osteoporotic fracture, with a dose-response association for cumulative use. A 3% relative-risk increase of osteoporosis and fractures was observed with doubling of the cumulative topical GC dose, but much of this risk was driven by the small subset of individuals requiring the highest doses (>10,000 g; Egeberg et al., 2021). Despite demonstrating a dose-response relationship of topical GCs with bone health, the number of patient-years of topical GC use needed for 1 fracture is almost 4-fold higher than that reported for high-dose oral GCs (40 mg oral prednisolone for ≥30 days), suggesting that topical GCs are preferable to high-dose systemic GC when both options are efficacious (Jackson, 2021). However, for patients requiring potent topical GC treatment on large body surfaces for prolonged periods, clinicians may consider GC-sparing therapeutic options to limit the risk of osteoporosis.

Because our patient required very high potency topical GCs on a large body surface for many years, optimizing her calcium and vitamin D intake is reasonable.

Case vignette 3

A 27-year-old premenopausal woman has been taking 5 mg prednisone per day chronically for about 3 years for management of cutaneous lupus. A DXA scan is performed and notable for a Z-score of –2.6. How should young patients be evaluated for GIOP?

In premenopausal women, the diagnosis of osteoporosis should not be made on the basis of densitometric criteria alone. The International Society for Clinical Densitometry recommends that instead of T-scores, ethnic- or race-adjusted Z-scores should be used, with Z-scores of −2.0 or lower defined as either low BMD for chronological age or below the expected range for age and those above −2.0 being within the expected range for age (The International Society of Clinical Densitometry, 2021).

Low BMD in premenopausal women can be due to low-peak bone mass (e.g., in patients with underlying chronic disease) or secondary to a medical condition that causes accelerated bone loss (e.g., primary hyperparathyroidism, hyperthyroidism, vitamin D deficiency). A large proportion of young patients have a secondary cause as the reason for their low BMD (Khan and Syed, 2004), which precedes GC use. These patients do not necessarily have a high risk of fracture and are best managed in conjunction with a specialist in bone metabolism. In this patient with low BMD for her chronological age, a careful history and physical examination should be conducted, and she should be referred to a bone specialist to be evaluated for secondary causes of low bone density.

Should the patient be prescribed a bisphosphonate?

Because our patient has a Z-score of > −3, no evidence of accelerated bone loss, has not had fragility fractures, and takes only 5 mg of prednisone daily, she is considered at low risk for fracture. The American College of Rheumatology guidelines recommend treating adults age <40 years who are at moderate or high risk for fracture with anti-osteoporotic medications (Buckley et al., 2017). Although our patient does not need pharmacological treatment, she should be counseled on adequate intake of calcium and vitamin D, as well as other lifestyle interventions, such as physical activity, fall precautions, smoking cessation, and limiting alcohol intake. The patient remains on GCs, but a DXA scan should be performed every 1 to 2 years to assess for ongoing bone loss.

Six months later, the patient fractures her wrist. Should anti-osteoporotic treatment be reconsidered?

A fragility fracture, such as a fracture sustained from falling from standing height, is a marker of increased bone fragility and increased risk of future fractures. Because our patient has sustained a fragility fracture, she is now deemed to be at high risk of fractures, and initiation of an anti-osteoporotic medication should be considered.

There has been a reluctance to treat premenopausal women with bisphosphonates because of concerns that the long-term retention of these agents in bone may later affect the fetal skeleton. When treatment is needed in women of childbearing age, agents such as risedronate and teriparatide that have shorter half-lives and less retention in bone are generally preferred (Buckley and Humphrey, 2018). Therapy with teriparatide requires subsequent treatment with a bisphosphonate to consolidate gains in bone density. These patients would benefit from referral to a metabolic bone disorder expert.

The patient expresses a desire to become pregnant. How should the patient be counseled?

There are limited data on the safety of anti-osteoporotic therapies in pregnant women. Pharmacologic treatment to prevent fractures is not recommended during pregnancy. Our patient is planning to get pregnant; thus, the anti-osteoporotic medication should be discontinued, and strategies to minimize her exposure to systemic steroids should be implemented to decrease the negative effects on bone health (e.g., topical or intralesional steroid injections, or the use of steroid-sparing systemic medications).

Case vignette 4

A 42-year-old woman takes prednisone chronically for management of sarcoidosis. Her 25-hydroxyvitamin D level is low.

How should the patient be counseled with regard to her calcium and vitamin D intake?

Approximately 30 to 50% of patients with sarcoidosis have hypercalciuria, and 10 to 20% have hypercalcemia. These abnormalities of calcium metabolism are due to increased activity of 1α-hydroxylase in the macrophages of the granuloma, increasing the production of 1,25-dihydroxyvitamin D (calcitriol). Untreated hypercalcemia and hypercalciuria can cause nephrocalcinosis, renal stones, and renal failure. Treatment with GCs suppresses the 1,25-dihydroxyvitamin D production and reverses the metabolic defect (Sharma, 1996).

Balancing the need to avoid the consequences of hypercalcemia while maintaining bone health is complicated in patients with sarcoidosis treated with GCs. Patients with underlying sarcoidosis at risk for osteoporosis because of chronic GC use should get a baseline biochemical evaluation by measuring serum total calcium (with correction for albumin level), serum ionized calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and a 24-hour urine collection for calcium. Patients with hypercalcemia or hypercalciuria should not receive supplemental calcium. If the 25-hydroxyvitamin D level is normal, vitamin D supplementation is not necessary. Evaluation for fracture risk through clinical assessment of risk factors, DXA scan, and FRAX calculation should be done as in other patients receiving chronic GCs. Due to the complexity of altered calcium metabolism in patients with sarcoidosis, these individuals are best referred for bone health assessment and management by a metabolic bone specialist.

Vitamin D supplementation for patients with sarcoidosis and a low vitamin D level is controversial. Because studies have not consistently shown a clear association between vitamin D supplementation and the risk of hypercalcemia (Capolongo et al., 2016; Kamphuis et al., 2014; Sodhi and Aldrich, 2016), it is reasonable to consider vitamin D supplementation (particularly with small doses of 200-400 IU/day) in patients with sarcoidosis and low 25-hydroxyvitamin D levels who have low BMD or fracture history and who have no hypercalcemia, hypercalciuria, or high calcitriol levels. A 1,25-dihydroxyvitamin D level should be checked first, and if elevated, the patient should be referred to a metabolic bone disorder expert.

Case vignette 5

A 26-year-old woman has alopecia areata and receives intralesional triamcinolone monthly. What are the risks to bone health with monthly intralesional triamcinolone injections?

Intralesional injections of GCs are an important part of dermatologic therapy for various skin conditions. Triamcinolone acetonide is the most common GC used for intralesional injections. The number of injections depends on the disease, location of the lesions, age of the patient, and response to previous injections. The maximum dosage of triamcinolone acetonide should not exceed 20 mg/ml/session (although some experts may be comfortable with a monthly dose not exceeding 40 mg) and should be tailored specifically to the site to limit the risk of cutaneous atrophy

Systemic adverse effects of intralesional GCs are infrequent, especially when GCs are used in low doses and at intervals of $\geq$3 weeks. A study on administration of intralesional GCs for several dermatoses showed that doses of triamcinolone diacetate of $\leq$25 mg were unlikely to produce systemic effects (McGugan and Shuster, 1963). Cushing syndrome resulting from intralesional triamcinolone acetonide has been rarely reported, with most cases occurring in children treated with 30 mg per month (Fredman and Tenenhaus, 2013).

Low bone density has been rarely reported to result from the use of intralesional GCs (Samrao et al., 2013). If an individual treated with intralesional GCs for many years reaches high cumulative doses, it would be reasonable to consider performing baseline and periodic DXA scans (Richards, 2010).

Conclusion

GIOP is one of the most serious side effects of prednisone therapy, increasing fracture risk early in the course of treatment prior to a significant decrease in BMD. There is likely no safe dose of GCs below which patients do not experience increased fracture risk. Therefore, all patients starting GC therapy with an anticipated duration of $\geq$3 months should undergo a risk assessment for GIOP. A general strategy to assess and prevent GIOP includes assessing for patient-specific fracture risk factors, obtaining a DXA scan, and/or FRAX score where appropriate, optimizing vitamin D and calcium intake, and referring patients who would benefit from pharmacologic intervention (those at the highest risk for fracture) to a metabolic bone disorder expert. Patients who do not have osteoporosis on DXA scans may still benefit from pharmacologic intervention and can be risk-stratified by FRAX score. Patients age <40 years require additional evaluation and consideration, especially women of childbearing potential. Referral to a metabolic bone disorder expert is always a reasonable consideration in challenging situations where management is not straightforward.

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Conflicts of interest

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