

Glucocorticoid-induced osteoporosis in systemic lupus erythematosus

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Abstract

Improvement in survival of systemic lupus erythematosus has been brought about with new advancement in treatment. However, glucocorticoids remain the sole cornerstone and as patients live longer, there is a need to address long-term complications brought by long-term glucocorticoid use such as osteoporosis. In this review, glucocorticoid-induced osteoporosis in systemic lupus erythematosus will be extensively discussed. This would include prevalence of osteoporosis in systemic lupus erythematosus patients, the difficulties in measuring fracture risk and pitfalls in using conventional methods such as bone mineral density. In addition, the mechanism of actions of glucocorticoids and evidence for glucocorticoids in the treatment of specific systemic lupus erythematosus manifestations would be explored and we also discussed specific pathophysiological mechanisms in the development of glucocorticoid-induced osteoporosis in systemic lupus erythematosus. We also reviewed the latest guidelines in the treatment of glucocorticoid-induced osteoporosis and the evidence for various osteoporosis medications. Finally, we recommend an approach in monitoring bone health and the treatment of osteoporosis specifically in systemic lupus erythematosus patients.

Keywords

Systemic lupus erythematosus, glucocorticoid-induced osteoporosis, glucocorticoid, osteoporosis, treatment

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that follows a variable and unpredictable course. SLE can potentially affect multiple organ systems, leading to severe consequences. In the past, uncontrolled inflammatory process of the disease has led to high mortality, but in recent decades, mortality has improved with 10-year survival rates exceeding 90%.^{1,2}

The improvement of overall survival in patients with SLE has partly been brought about with the use of an expanding armamentarium of immunosuppressive drugs, including glucocorticoids (GCs), cyclophosphamide, mycophenolate and recently, new biologics such as rituximab and belimumab.^{3–5} GCs, however, continue to be extensively used in SLE and remain the sole cornerstone of treatment. Patients with SLE are often exposed to high-dose GC for induction therapy and are subject to long-term low to moderate GC dose for maintenance of remission. As such, there is a need to address the long-term complications

of GC use. In this review, glucocorticoid-induced osteoporosis (GIOP) will be extensively discussed, spanning from its prevalence, mechanism, impact on the health of SLE patients and potential strategies to mitigate the impact of GIOP on the well-being of patients with SLE.

Prevalence of GIOP in SLE patients

Diagnosis of osteoporosis is defined in the World Health Organization (WHO) guidelines.⁶ Dual energy

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absorptiometry (DXA) is used to measure bone mineral density (BMD) and a T-score (the number of standard deviations the measured BMD differs with reference to a young healthy adult population) of -2.5 or less is considered to be osteoporotic.⁶ Using this definition, the prevalence of osteopenia and osteoporosis differs widely in SLE patients in different geographical regions. In a British cross-sectional study of the 242 SLE patients, Yee et al.⁷ showed that the prevalence of osteoporosis and osteopenia were 10.3% and 40.5%, respectively. However, in a Chinese study of 152 SLE women, prevalence was shown to be 21.7% and 59.9%, respectively.⁸ while in a Canadian study of 81 postmenopausal SLE women, they were 12.3% and 42.1%, respectively.⁹

There are a number of concerns with the use of T-scores in SLE patients in clinical settings. First, the WHO defined osteoporosis in postmenopausal Caucasian women based on the T-scores.⁶ SLE is a disease that chiefly affects women of childbearing age. The applicability of T-scores in defining osteopenia and osteoporosis thus might not be ideal. As such, the use of Z-score has been proposed for defining secondary osteoporosis. The Z-score is the number of standard deviations the measured BMD differs from age, gender and ethnicity matched population. The Canadian Clinical Practice Guidelines defined pre-menopausal women and men below 50 years old as having BMD 'below expected range for age' if the Z-score is less than -2 .¹⁰ The American College of Rheumatology (ACR) for GIOP has recently proposed to use the Z-score for adults younger than 40 years old for predicting risk of fractures, with a threshold of less than -3 defined as moderate risk.¹¹

However, in a retrospective analysis over 247,000 individual Z-scores and patient records, McKiernan et al.¹² showed that although low Z-scores are associated with a higher prevalence of secondary osteoporosis, there was no clear inflection point. Hence, a useful clinical diagnostic threshold could not be defined. Second, fragility fractures can occur even in patients with normal BMD. In the same British cross-sectional study by Yee et al.,⁷ of the 22 SLE patients with fragility fractures, only seven (31.8%) had T-scores in the osteoporotic range. Similarly, in a cohort study of 152 SLE patients whom all had spinal radiographs, 31 were found to have morphometric vertebral fractures, of which nine (29.0%) were patients with normal BMD.⁸

In addition, SLE patients carry a higher risk of fragility fractures compared to the normal population. In a UK-based population-control study, the relative risk of fracture among SLE patients was found to be 22% higher than that of healthy individuals, and the risk increased with the duration of the disease, with it being double if the disease duration was 10 years or longer.¹³ Hence, assessment that incorporates BMD to estimate fracture risk like the popular Fracture Risk Assessment Tool (FRAX) may underestimate risks in SLE patients.¹⁴ This is likely due to SLE patients requiring

prolonged and high doses of GCs throughout their lives and while FRAX can adjust for GC use, this is only limited to a prednisolone-equivalent dose of 2.5–7.5 mg/day.¹⁵

Mechanism of action of GCs

GC produces an immunosuppressive response via two different pathways, the genomic pathway and the non-genomic pathway.^{16–18} In the genomic pathway, the highly lipophilic GC molecules pass through the cell membrane and bind to cytosolic GC receptors. The GC receptor complexes translocate into the nucleus and modulate gene expression in the cellular nucleus, resulting in inhibition of intracellular expression of pro-inflammatory molecules. The process, however, has a lag time of at least 30–60 min for changes in gene expression and protein translation to take place.¹⁷

The non-genomic pathway, on the other hand, acts more rapidly than the genomic pathway. After binding to cytosolic GC receptors, the resultant complexes activate transcription-independent mechanisms via intracellular proteins that result in inhibition of inflammatory cytokines like arachidonic acid. They can also act on cellular and mitochondrial membranes and suppress adenosine triphosphate (ATP) production, leading to alleviation of the downstream pro-inflammatory cascade.^{16,18}

The use of GCs in SLE

Treatment with GC for SLE has been described since the 1950s in case reports and case series.^{19–21} To date, no controlled trial has proven the efficacy of GC per se because trials testing the efficacy and safety of GC without combination of an immunosuppressant are ethically impossible to perform. In clinical practice, dosage of GC is often arbitrarily stratified into:^{22,23}

- Low dose: ≤ 7.5 mg prednisolone equivalent a day;
- Medium dose: > 7.5 to ≤ 30 mg prednisolone equivalent a day;
- High dose: > 30 to ≤ 100 mg prednisolone equivalent a day;
- Very high dose: > 100 mg prednisolone equivalent a day;
- Pulse: > 250 mg prednisolone equivalent a day, for a few days.

High doses and pulse therapy are often used to treat SLE patients with severe organ manifestations in order to saturate the effects of the genomic pathway and take advantage of the non-genomic pathway.²³ In practice, high-dose prednisolone is often given at 1 mg/kg/day and pulse therapy is given at 250–1000 mg of intravenous (IV) methylprednisolone for 3 days, although such doses are largely based on expert recommendations. Robust evidence supporting the

use of pulse methylprednisolone remains scarce and consists mainly of small clinical trials performed in the 1980s;^{24–26} however, clinical consensus for the use of high-dose GC for treating severe SLE has been nearly universal throughout the century and remains prominent in current guidelines.^{27–30}

Proliferative lupus nephritis is one of the most serious manifestations of SLE and if left untreated, progression to end-stage renal failure is a near certainty. Hence, use of high-dose GC remains highly prominent and is recommended in both the ACR and European League Against Rheumatism (EULAR) guidelines.^{28,29} Neuropsychiatric systemic lupus erythematosus (NPSLE) is another serious manifestation of SLE and current treatment recommendation also consists of pulse therapy with cyclophosphamide.^{27,31,32}

Pathogenesis of GIOP in SLE

Endogenous GC at physiologic concentrations may have a role in promoting osteogenesis.³³ Exogenous GC, on the other hand, induces bone loss predominantly by both increasing bone resorption and reducing bone formation.^{34,35} With long-term GC therapy, impaired bone formation usually becomes the predominant skeletal effect.³⁶ This leads to a pattern of bone loss that is most pronounced in the first few months of GC use, followed by slower but steady bone loss with chronic use. Trabecular bone loss predominates initially, with most significant changes in the lumbar spine, but over time also affects cortical bone at other sites such as the femoral neck.³⁷

The precise mechanisms of how GC affect bone are not completely understood but a number of theories have been proposed.³⁸ GC decreases intestinal calcium absorption and increases renal calcium loss by inhibiting renal tubular calcium reabsorption. GC also suppresses testosterone, oestrogens, as well as insulin-like growth factor 1, hormones crucial for skeletal growth.³⁹ In addition, Steroid-induced myopathy leads to less loading of bone, resulting in increased bone loss, and is also associated with increased falls with consequent fragility fractures.

Animal model studies have shown that high-dose GC resulted in diminished bone formation and turnover. This was determined by histomorphometric analysis of tetracycline-labelled vertebrae. Ex vivo bone marrow cell cultures have also shown impaired osteoblastogenesis and osteoclastogenesis. There was also threefold increase of apoptosis in osteoblasts in the vertebrae and apoptosis in 28% of the osteocytes in metaphyseal cortical bone, demonstrating that GC-induced bone disease arises from changes in the numbers of bone cells.⁴⁰

Further studies have also showed that GC directly induces apoptosis of osteoblasts and osteocytes. Increased cell death of osteocytes directly reduces bone strength that is independent of bone volume loss. Loss of osteocytes also disrupts the osteocyte–canalicular network, which is

responsible for signal transmission necessary for stimulating new bone formation at areas of damaged bone.⁴¹ Liu et al. demonstrated that GC directly induced apoptosis of osteoblasts by activating caspase-3.⁴² Other studies also showed that oral prednisolone as low as 2.5 mg daily could suppress serum osteocalcin, a marker of bone formation.⁴³

GC can also aggravate bone loss by reducing apoptosis of osteoclasts. GC prolongs lifespan of osteoclasts by upregulating receptor activator for nuclear factor kappa-B ligand (RANKL) and suppressing osteoprotegerin (OPG).⁴⁴ This leads to enhanced osteoclast function and increased bone resorption. Hence, markers of bone resorption are often increased in GC-treated patients.

Recent advances in understanding of the Wnt signalling pathway have highlighted its importance in bone metabolism. In short, activation of the canonical Wnt/ β -catenin pathway enhances mesenchymal stem cells along the osteoblastic lineage while suppressing their commitment to adipogenic and chondrogenic lineages.⁴⁵ The pathway also increases OPG secretion, thereby inhibiting osteoclastic activity.⁴⁶ GC however shifts differentiation the mesenchymal stem cells towards the adipocyte lineage, leading to reduced osteoblastogenesis.⁴⁷ Moreover, GC also directly increases Dickkopf expression, an antagonist that suppresses Wnt binding to its receptor.⁴⁸

It has been well established that sex hormones play a key role in bone health. Over the decades, many studies on postmenopausal women have proven the link between oestrogen deficiency to increased bone fragility. Oestrogen acts on osteoclasts to downregulate bone remodelling by first inducing apoptosis of osteocyte.⁴⁹ It also decreases bone resorption by increasing OPG while downregulating RANKL production by osteoblastic cells.⁵⁰ Recent studies have also shown that serum oestrogen level is inversely associated with sclerostin, a potent inhibitor of the Wnt pathway.⁵¹ Testosterone, on the other hand, enhances osteoblastic activity and therefore increases bone formation. Studies have shown that androgens enhance osteoblastic proliferation and inhibit apoptosis of osteoblasts.⁵² GC however directly suppresses the hypothalamic–pituitary–adrenal–gonadal axis, reducing production of gonadotropin-releasing hormone and therefore decreases sex hormone production at the gonads.⁵³

Moreover, SLE patients have altered bone geometry compared to the normal population. In an American study comparing hip geometry between SLE patients and normal controls, there were reduced section modulus and cross-sectional areas with increased buckling ratio in SLE patients.⁵⁴ This has been postulated to be due to chronic inflammation itself and while some animal studies support this,⁵⁵ there is also evidence that chronic GC use can directly disrupt bone geometry and microarchitecture. In a study using quantitative computed tomography on SLE patients with low disease activity (mean SLEDAI 2.6) but with chronic GC usage (mean duration of 9.4 years, mean

cumulative dose of 18.6 g), there were lower volumetric BMD, reduction in cortical thickness and increased porosity compared to normal controls.⁵⁶

In summary, alterations in bone turnover can contribute to microarchitectural change and result in reduced bone quality with a rapid increase in fracture risk.³⁴ This may explain why patients on GC have higher fracture risk compared to GC-naïve controls with the same BMD.⁵⁷

Other potential contributors of osteoporosis in SLE

The development of osteoporosis is not limited to GC therapy itself and SLE alone can affect bone quality.⁵⁸ The systemic inflammation of SLE induces bone loss by increasing osteoclastic bone resorption and by reducing osteoblastic bone formation.

Increased serum levels of tumour necrosis factor (TNF)⁵⁹ and oxidized low-density lipoprotein (LDL) have been described in patients with active SLE.⁶⁰ Oxidized lipids activate T cells, increasing production of RANKL and TNF. Both RANKL and TNF stimulate osteoclast differentiation and activity.⁵⁹

Some studies have shown that SLE patients have reduced serum levels of osteocalcin, a marker for bone formation^{61,62} and osteocalcin is negatively associated with SLE disease activity.⁶² Another study also demonstrated an association between high rate of disease flares and increased bone loss in SLE.⁶³ Interestingly, anti-Ro antibody positivity and absence of Anti-Sm antibodies were shown to be associated with reduced bone mass.⁶⁴ However, such observation may be confounded by the fact that anti-Ro positive SLE patients are often advised to avoid sun exposure.⁵⁸

Besides GC, other therapies for SLE may contribute to osteoporosis. Cyclophosphamide use was shown to be an independent risk factor for femoral neck fracture in SLE in a study from Hong Kong,⁶⁵ and this can be explained by the gonadal suppressive effect of cyclophosphamide.^{66,67} In addition, animal models have demonstrated that cyclophosphamide may directly influence the Wnt / β -catenin pathway, thereby inhibiting osteoblastogenesis.⁶⁸ Another study from Taiwan showed increased serum fibroblast growth factor-23 and decreased bone turnover in SLE patients treated with cyclosporin and GC but not GC alone.⁶⁹ A cohort study from Italy reported use of anticoagulants and antiepileptic drugs as independent risk factors for symptomatic fractures in patients with SLE.⁷⁰

Circulating vitamin D levels have been shown to be reduced in patients with SLE.^{71,72} This may be contributed by photosensitivity, increased use of sunscreen, reduced sunlight exposure, and physical inactivity and chronic arthritis. Lupus nephritis can also lead to renal failure which results in reduced 1,25-(OH)-D levels. Finally, SLE patients are also subject to the same risk factors for osteoporosis

that affect the general population, including age, postmenopausal status and low body mass index (BMI).^{58,73}

Management and monitoring of osteoporosis in patients with SLE

Osteoporosis develops in patients with SLE via complex mechanisms as elucidated earlier. Hence, the management of bone loss in these patients requires a multi-pronged approach which includes (1) evaluation of SLE management that impacts bone health; (2) modification of lifestyle; (3) review of medications associated with the development of osteoporosis; (4) addressing the secondary causes of bone loss; (5) management of low bone density and (6) mitigation of fall risk in patients with SLE. Figure 1 illustrates a suggested approach to the management of osteoporosis and the reduction of fracture risk in patients with SLE.

Aspects of SLE management that impact bone health

Management of osteoporosis in patients with SLE must begin with mitigating the risk of BMD deterioration during the treatment of SLE. Because even low doses of GC can increase fracture risk, clinicians must aggressively taper the dose of GC when disease is under control.⁷⁴ Whether treating SLE disease activity to target would improve long-term outcomes in bone health needs to be addressed in future studies.

The use of cyclophosphamide is associated with premature menopause in up to 50% of patients with SLE and accounts for the accelerated bone loss in these patients.⁷⁵ Gonadotropin-releasing hormone analogues have been shown to prevent premature ovarian failure in patients with SLE receiving cyclophosphamide^{76,77} and should hence theoretically prevent BMD deterioration associated with ovarian failure. However, whether ovarian preservation with these methods truly protects against bone loss in clinical practice needs to be further studied.⁷⁸

Lifestyle modification and medication review

Physicians must also encourage patients to participate in regular aerobic, weight-bearing or resistance exercise to protect against BMD deterioration.^{79,80} Patients who maintain their body weight in the healthy range of BMI may circumvent the increased fracture risk associated with extreme BMI on both ends.^{8,81} Advice on smoking cessation and limitation of alcohol intake to 2 or less units a day is also standard practice.⁸² Where possible, medications associated with osteoporosis and fractures should be reviewed for their indications and potential substitutes. These medications include unfractionated heparin, proton

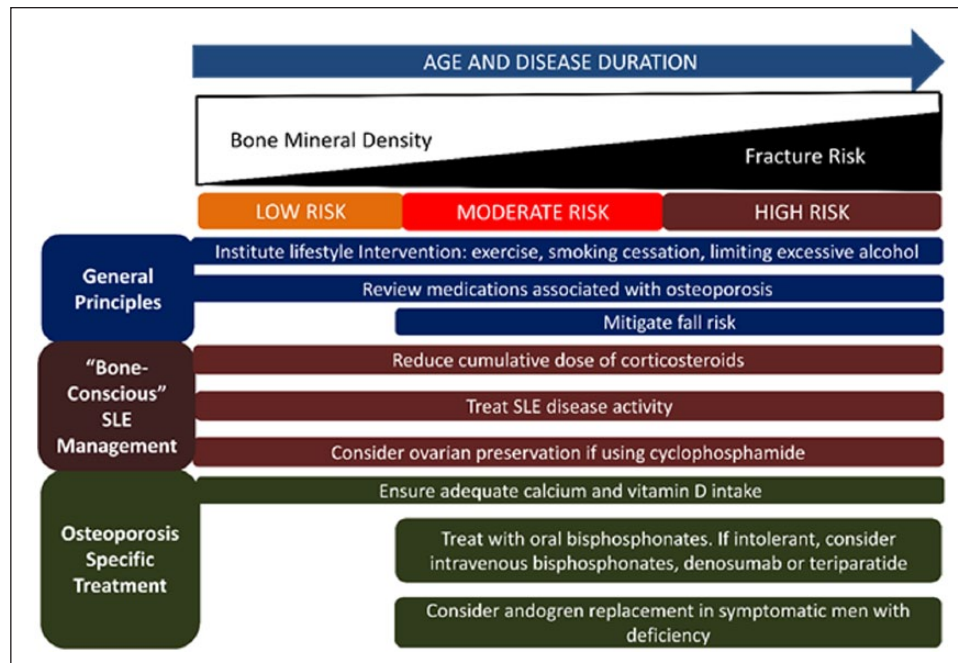


Figure 1. Approach to managing osteoporosis and fracture risk in patients with SLE.

pump inhibitors, thiazolidinediones, selective serotonin-reuptake inhibitors and calcineurin inhibitors.⁸³ While a definite relationship between these agents and osteoporosis and fractures has not been fully established, careful evaluation of their risks and benefits is warranted. Adequate intake of calcium of at least 1000 mg/day and vitamin D of at least 600 IU/day is also recommended.¹¹

Managing patients with SLE at moderate to high risk for fractures

The recently published 2017 ACR Guidelines on the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis recommended anti-resorptive treatment for patients on long-term GC if deemed moderate or high risk. Here, high risk is defined as the presence of major osteoporotic fractures in adults, a BMD of ≤ -2.5 in postmenopausal women or men aged ≥ 50 years old, or a FRAX 10-year probability of osteoporotic fracture of $\geq 20\%$ or a 10-year probability of hip fracture of $\geq 3\%$. Moderate risk is defined as a FRAX 10-year probability of major osteoporotic fracture of 10%–19% and a probability of hip fracture of $>1\%$ but $<3\%$ in adults ≥ 40 years of age. In adults <40 years, moderate risk is defined a hip or spine Z-score of <-3 or rapid bone loss of $\geq 10\%$ in hip or spine over 1 year and continuing GCs of ≥ 7.5 mg daily for ≥ 6 months. In patients receiving corticosteroids >7.5 mg daily, the FRAX score must be adjusted by multiplying the absolute 10-year major osteoporotic fracture risk by 1.15 and the hip fracture risk by 1.2.⁸⁴ It is important to note that the definition of ‘high risk’ and FRAX

intervention thresholds may differ in different countries. For example, in Japan and China, the intervention threshold for 10-year probability of major osteoporotic fracture is 15% and 4%, respectively.⁸⁵

Oral bisphosphonates have been recommended as first-line treatment in this guideline. The use of bisphosphonates in GIOP has been supported by a large body of evidence, including a recently updated Cochrane systematic review which has concluded that it reduces vertebral fracture risk but not non-vertebral fracture risk.⁸⁶ In particular, the use of alendronate in patients with rheumatic diseases with GIOP has been supported by a meta-analysis of nine studies.⁸⁷ Where there are contraindications to oral bisphosphonates, IV bisphosphonates, denosumab or teriparatide can be considered. These agents are second line as they can be significantly costlier than oral bisphosphonates.¹¹ The use of oral and IV bisphosphonates, denosumab and teriparatide in SLE patients with osteoporosis was mainly extrapolated from studies in women with postmenopausal osteoporosis or patients with GIOP.⁸⁸ Only a few studies specifically investigated patients with rheumatic diseases or SLE.

More recent studies have found that denosumab is efficacious in GIOP by improving BMD, although they lack fracture outcomes.⁸⁹ Some studies have found denosumab to be more efficacious than bisphosphonates in GIOP.^{90,91} In particular, in a 24-month randomized controlled trial involving nearly 800 patients receiving GCs, denosumab was shown to be both non-inferior and superior compared to risedronate in improving BMD.⁹² Interestingly, it has been suggested that denosumab may be more efficacious in

patients with GIOP who have not received prior treatment with bisphosphonates.⁹³ One drawback, however, is the risk of fracture recurrence if denosumab is discontinued. In a review of 24 women with vertebral fractures after denosumab was stopped, fractures occurred between 8 and 16 months after last denosumab dose and patients had more fractures if they received a longer duration of denosumab before stopping.⁹⁴

Also, most studies used BMD as a surrogate end-point for fracture risk, and only a handful of studies directly addressed fracture risk reduction. The fact that better BMD improvement does not necessarily translate to greater reduction in fracture risk was highlighted in the same trial comparing denosumab with risedronate, whereby although denosumab was better at improving BMD, fracture rates were similar between them.⁹²

Teriparatide has been shown to be superior to alendronate in individuals with GIOP. A randomized controlled trial published in 2007 showed that teriparatide conferred an absolute risk reduction of 5.5% for vertebral fracture in 18 months compared to alendronate. Although hip fracture rates were similar, hip BMD improved significantly more in the teriparatide group.⁹⁵ The 18-month extension of the same trial again showed a 6% absolute risk reduction in vertebral fracture over this period with similar hip fracture rates.⁹⁶

Importantly, as a result of the young age of onset and increased longevity of patients with SLE, they are likely to be exposed to a longer duration of anti-osteoporosis therapy than postmenopausal women.⁹⁷ Therefore, the risks of long-term therapy such as atypical femoral neck fractures and osteonecrosis of the jaw, particularly in GC-treated patients, must be weighed against their benefits.⁹⁸ However, it must be noted that the risks of these adverse events are rare, and that the risk–benefit profile of bisphosphonate therapy in these patients still remain favourable. Bisphosphonates are retained in bones for extended duration and are able to cross the placenta. Although several small prospective studies have not demonstrated any teratogenic effect of bisphosphonates, clinicians must exercise caution in prescribing bisphosphonates in pre-menopausal women.^{99,100} Based on bone turnover marker studies, some authors recommended a washout period of 5 years for alendronate and zoledronate, and 2 years for ethidronate and risedronate before conception.^{99,101} A small body of case reports and case series suggest that bisphosphonate exposure before or during pregnancy does not lead to adverse foetal outcomes.^{100,102}

Raloxifene should be avoided in patients with SLE who have thrombotic tendency or history of vascular thrombosis. Notably, the benefits of raloxifene in GIOP are not fully elucidated.¹¹ While a small randomized controlled trial of 62 patients with SLE has shown that raloxifene improved lumbar spine BMD without causing disease flares, this study excluded patients with hypercoagulability or

anti-phospholipid syndrome.¹⁰³ Denosumab has been shown to be an effective agent in GIOP but it may theoretically increase the risk of infections in patients who are heavily immunosuppressed. Indeed, the ACR Guidelines for GIOP states that there is a lack of safety data on the use of denosumab in patients who are immunosuppressed.¹¹ Strontium ranelate and calcitonin are options for treatment of postmenopausal osteoporosis. However, there have been insufficient evidence for the use of these agents in the treatment of GIOP.¹⁰⁴ Moreover, due to increased cardiovascular risk associated with strontium use, it should only be used when other agents are considered unsuitable.¹⁰⁵ Calcitonin alone may not be efficacious in treating osteoporosis and is mainly being utilized for its analgesic effect in patients with compression fractures.¹⁰⁶

Recently, the ARCH trial demonstrated that an 1-year treatment of romosozumab, an anti-sclerostin antibody, followed by alendronate conferred a 5.7% absolute risk reduction of vertebral fractures over 24 months in patients with postmenopausal osteoporosis compared to patients who received alendronate alone for 24 months.¹⁰⁷ However, there was an imbalance of cardiovascular and cerebrovascular events in the romosozumab group and this agent is not currently available in many countries. In patients with severe osteoporosis, the combination of denosumab and teriparatide has also been shown to improve femoral neck and vertebral BMD more than either agents alone.¹⁰⁸ However, the utility and long-term safety of these approaches remain to be investigated in patients with GIOP. Table 1 compares the advantages and disadvantages of each class of medications for patients with SLE.^{109–125}

Because patients with SLE also suffer degraded bone microarchitecture and trabecular quality in addition to reduced bone density, it is important to consider the effects of therapy on bone quality. Anti-resorptives, including bisphosphonates and denosumab, improve bone quality by inhibiting remodelling and reducing trabecular volume loss, therefore improving connectivity. Thus, these agents exert their anti-fracture effects via improvement of both bone density and quality.¹²⁶ Teriparatide, being an osteo-anabolic agent, has been shown to improve trabecular architecture in a bone biopsy study and a randomized controlled trial.^{127,128}

It is also important to note that while both anti-resorptives and osteo-anabolic agents increase BMD and reduce fracture risk, the mechanisms of how these drugs achieve this are different. In a randomized controlled trial comparing teriparatide with zoledronic acid, measurements of bone mineralization density distribution (BMDD) were used to determine differences in mineralization kinetics. The authors demonstrated that teriparatide increased bone turnover rate with heterogenous mineralization while zoledronic acid slowed bone turnover rate but resulted in higher and more homogeneous mineralization of the bone matrix.¹²⁹

Table 1. Comparison of anti-osteoporotic agents.

Agent	Pros compared to other agents	Cons compared to other agents	Evidence for use in GIOP	Included in the 2017 ACR Guideline on the prevention and treatment of glucocorticoid-induced osteoporosis	Investigated in patients with SLE
Oral bisphosphonates	These agents are most-studied and have the best long-term data	These agents are associated with gastroesophageal reflux and a small risk of osteonecrosis of the jaw and atypical femoral neck fractures. ¹⁰⁹ Compliance of these agents may be poorer compared to parenteral options. ¹¹⁰	Yes, based on meta-analysis and randomized controlled trials	Yes	A meta-analysis has shown benefit in patients with rheumatic diseases. ¹¹¹ In addition, SLE patients were included in alendronate and risedronate clinical trials ^{112,113}
Intravenous bisphosphonates	Compliance to these agents may be better compared to oral bisphosphonates. ¹¹⁰	There is a risk of hypocalcaemia, acute reaction and atrial fibrillation, ^{114,115} and they are more costly than oral options	Yes, based on randomized controlled trials	Yes	The HORIZON trial for zoledronic acid had included a small proportion of SLE patients. ¹¹⁶
Denosumab	With denosumab, continuous improvement of bone density is possible up to 10 years. ¹¹⁷ It also has a short washout period compared to bisphosphonates. ^{118,119} May be more efficacious than bisphosphonates. ⁹¹	There is a risk of hypocalcaemia. Some concerns were raised about infective risk in patients on concurrent immunosuppression. ¹¹ Also, BMD deteriorates when stopped. ¹¹⁹	Yes, based on randomized controlled trials	Yes	Yes. A small Japanese study of 29 patients with GIOP included 19 patients with SLE and showed efficacy in improving spine and hip BMD. ⁸⁹
Teriparatide	Teriparatide may be more efficacious for spine and hip BMD than oral bisphosphonates. ⁹⁵	This agent is costly and associated with a potential risk of osteosarcoma in animal studies only. ¹²⁰	Yes, based on randomized controlled trials	Yes	No
Denosumab with teriparatide	Combination therapy may confer greater BMD improvement than either agent alone. ¹⁰⁸	Cost effectiveness of this strategy has not been studied	No	Not included	No
Raloxifene	Raloxifene leads to an absolute risk reduction of invasive breast cancer by 0.79% in postmenopausal women over a median of 40 months. ¹²¹	There is an increased risk of venous thrombosis, and hence must be avoided in patients with anti-phospholipid syndrome. ¹²²	Yes, based on a small randomized controlled trial	Yes	A randomized controlled trial of 62 patients with SLE showed that raloxifene improved spine BMD. ¹⁰³
Romosozumab	Romosozumab may be more efficacious for spine and hip BMD if given for 1 year before transitioning to oral bisphosphonates compared to bisphosphonates at onset. ¹⁰⁷	This agent has not been studied in patients with GIOP, and insufficient long-term data are available	No	Not included	No
Strontium	This agent has not been associated with osteonecrosis of the jaw or atypical femoral neck fractures. In fact, there are some reports of its utility to treat atypical femoral fractures. ¹²³	Strontium is associated with an increased cardiovascular risk. ¹⁰⁵ Also, there is not enough evidence for use in GIOP	No	Not included	No
Calcitonin	This agent has not been associated with osteonecrosis of the jaw or atypical femoral neck fractures	Calcitonin may be less efficacious than bisphosphonates and there is not enough evidence for use in GIOP. ¹²⁴	No	Not included	No
Androgen replacement	Androgen replacement may improve other signs and symptoms associated with hypoandrogenism, for example, fatigue and loss of libido. ¹²⁵	Testing for androgen deficiency is difficult: screening must occur at low disease activity and while patient is on low dose corticosteroids. It cannot be used alone for GIOP	Yes, based on randomized controlled trial	Not included	No

ACR: American College of Rheumatology; SLE: systemic lupus erythematosus; BMD: bone mineral density; GIOP: glucocorticoid-induced osteoporosis.

There is also evidence that combination therapy performs better than monotherapy. In a randomized controlled trial comparing denosumab, teriparatide and the combination of denosumab and teriparatide, combination therapy improved radial trabecular volumetric BMD more than either agent alone.¹³⁰

Hypotestosteronism afflicts up to 60% of males with SLE, particularly as a result of exposure to cyclophosphamide or GC.¹³¹ A small body of evidence suggests that testosterone replacement in men deficit of the hormone may modestly improve spine BMD, although it is unclear whether this leads to reduced fracture risk.¹³² The 2018 Endocrine Society guidelines recommend ‘testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct testosterone deficiency’.¹²⁵ In patients with SLE, serum androgen levels have been found to correlate with BMD.¹³³ Testing and treatment should also be considered in patients who exhibit signs and symptoms of hypoandrogenism, such as erectile dysfunction and low libido.¹²⁵ As active SLE disease and GC may both interfere with the pituitary–gonadal axis, measurement of free and total testosterone levels is only meaningful when SLE disease activity is low and GC is tapered to a low dose.¹²⁵ Interestingly, in vitro studies demonstrated that testosterone inhibited B-cell activity and decreased anti-dsDNA production by peripheral blood mononuclear cells.¹³⁴ A small open-label study also demonstrated that dehydroepiandrosterone replacement in females is associated with lower lupus disease activity measured by SLEDAI.¹³⁵ However, testosterone replacement has several important contraindications which are not discussed in the scope of this review. Clinicians should therefore work with endocrinologists to discuss the risks and benefits of androgen replacement for the individual patient.

Monitoring bone health and fracture risk in patients with SLE

The 2017 American College of Rheumatology Guideline for the Prevention and Treatment of GIOP recommend that all patients older than 40 years should receive a fracture risk assessment ideally with an assessment of BMD upon GC initiation.¹¹ BMD testing within 6 months of initiation of GC is recommended for patients younger than 40 years with risk factors of osteoporosis.¹¹

Patients with SLE should be assessed for fracture risk annually. The FRAX tool is the most commonly used instrument for fracture assessment.¹¹ Nevertheless, clinicians must acknowledge the important limitations of using FRAX in patients with SLE, including the fact that (1) it has not been validated in patients who are receiving anti-osteoporotic treatment; (2) it does not take into account the dose of GC for fracture risk calculation; (3) it does not incorporate fall risk, which may be elevated in patients with SLE; (4) it may underestimate fracture risk in patients with

SLE; (5) the fracture risk can only be imputed in patients above the age of 40 and (6) different FRAX intervention threshold exists for different countries.^{85,88,136} Whether imputing a trabecular bone score with the FRAX calculation improves fracture risk estimation for patients with SLE remains unclear. The Qfracture tool and Garvan risk assessment tools allow imputation of fall risk but they do not take into account the BMD and their use in patients with rheumatic diseases is limited.^{137,138}

Conclusion and future perspectives

GCs remain an indispensable therapeutic agent in the treatment of SLE. Given at high doses, it allows control of acute flares with severe manifestations and used at low doses to achieve long-term disease control. Unfortunately, its use comes with cost of multiple side effects, and one of the most significant being GIOP. Hence, given the excellent survival of most patients, management of GIOP must be incorporated into routine care of SLE. Looking forward, ongoing development of newer immunosuppressive agents has led to more novel approaches against SLE. This will hopefully reduce our dependence on GCs and its associated complications in the future. On the other hand, treatment of osteoporosis has often been limited to the use of mainly anti-resorptive agents with few ‘bone-building’ agents. More data with the use of newer therapeutic options such as romosozumab for SLE patients remains awaited.

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References

1. Mills JA. Systemic lupus erythematosus. *N Engl J Med* 1994; 330: 1871–1879.
2. Mak A, Cheung MW, Chiew HJ, et al. Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. *Semin Arthritis Rheum* 2012; 41: 830–839.
3. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3918–3930.
4. Jordan N and D’Cruz D. Current and emerging treatment options in the management of lupus. *Immunotargets Ther* 2016; 5: 9–20.
5. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus

- erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 721–731.
6. Kanis JA, Melton LJ, Christiansen C, et al. The diagnosis of osteoporosis. *J Bone Miner Res* 1994; 9: 1137–1141.
 7. Yee CS, Crabtree N, Skan J, et al. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. *Ann Rheum Dis* 2005; 64: 111–113.
 8. Li EK, Tam LS, Griffith JF, et al. High prevalence of asymptomatic vertebral fractures in Chinese women with systemic lupus erythematosus. *J Rheumatol* 2009; 36: 1646–1652.
 9. Cramarossa G, Urowitz MB, Su J, et al. Prevalence and associated factors of low bone mass in adults with systemic lupus erythematosus. *Lupus* 2017; 26: 365–372.
 10. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010; 182: 1864–1873.
 11. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol* 2017; 69: 1521–1537.
 12. McKiernan FE, Berg RL and Linneman JG. The utility of BMD Z-score diagnostic thresholds for secondary causes of osteoporosis. *Osteoporos Int* 2011; 22: 1069–1077.
 13. Bultink IE, Harvey NC, Lalmohamed A, et al. Elevated risk of clinical fractures and associated risk factors in patients with systemic lupus erythematosus versus matched controls: a population-based study in the United Kingdom. *Osteoporos Int* 2014; 25: 1275–1283.
 14. Unnanuntana A, Gladnick BP, Donnelly E, et al. The assessment of fracture risk. *J Bone Joint Surg Am* 2010; 92: 743–753.
 15. Leib ES, Saag KG, Adachi JD, et al. Official positions for FRAX(®) clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX(®) of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(®). *J Clin Densitom* 2011; 14: 212–219.
 16. Ruiz-Irastorza G, Danza A and Khamashta M. Glucocorticoid use and abuse in SLE. *Rheumatology (Oxford)* 2012; 51: 1145–1153.
 17. Stahn C and Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008; 4: 525–533.
 18. Kleiman A and Tuckermann JP. Glucocorticoid receptor action in beneficial and side effects of steroid therapy: lessons from conditional knockout mice. *Mol Cell Endocrinol* 2007; 275: 98–108.
 19. Treatment of systemic lupus erythematosus with steroids: report to the Medical Research Council by the Collagen Diseases Hypersensitivity Panel. *Br Med J* 1961; 2: 915–920.
 20. Richards DG. Three cases of collagen disease treated with corticoids. *Br Med J* 1954; 2: 777–780.
 21. Dubois EL. High dosage steroid therapy for systemic lupus erythematosus. *Arthritis Rheum* 1962; 5: 250–260.
 22. Buttgerit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002; 61: 718–722.
 23. Parker BJ and Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. *Lupus* 2007; 16: 387–393.
 24. Mackworth-Young CG, David J, Morgan SH, et al. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. *Ann Rheum Dis* 1988; 47: 496–502.
 25. Isenberg DA, Morrow WJ and Snaith ML. Methyl prednisolone pulse therapy in the treatment of systemic lupus erythematosus. *Ann Rheum Dis* 1982; 41: 347–351.
 26. Liebling MR, McLaughlin K, Boonsue S, et al. Monthly pulses of methylprednisolone in SLE nephritis. *J Rheumatol* 1982; 9: 543–548.
 27. Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* 2010; 69: 2074–2082.
 28. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71: 1771–1782.
 29. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)* 2012; 64: 797–808.
 30. Mok CC, Yap DY, Navarra SV, et al. Overview of lupus nephritis management guidelines and perspective from Asia. *Nephrology (Carlton)* 2014; 19: 11–20.
 31. Fernandes Moça Trevisani V, Castro AA, Ferreira Neves Neto J, et al. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. *Cochrane Database Syst Rev* 2013; 2: CD002265.
 32. Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheum Dis* 2005; 64: 620–625.
 33. Kalak R, Zhou H, Street J, et al. Endogenous glucocorticoid signalling in osteoblasts is necessary to maintain normal bone structure in mice. *Bone* 2009; 45: 61–67.
 34. Van Staa TP, Leufkens HG, Abenham L, et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; 15: 993–1000.
 35. Reid IR and Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. *Arch Intern Med* 1990; 150: 2545–2548.
 36. Lukert BP and Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; 112: 352–364.
 37. Natsui K, Tanaka K, Suda M, et al. High-dose glucocorticoid treatment induces rapid loss of trabecular bone mineral density and lean body mass. *Osteoporos Int* 2006; 17: 105–108.

38. Bultink IE, Baden M and Lems WF. Glucocorticoid-induced osteoporosis: an update on current pharmacotherapy and future directions. *Exp Opin Pharmacother* 2013; 14: 185–197.
39. Canalis E, Centrella M, Burch W, et al. Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. *J Clin Invest* 1989; 83: 60–65.
40. Weinstein RS, Jilka RL, Parfitt AM, et al. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998; 102: 274–282.
41. O'Brien CA, Jia D, Plotkin LI, et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. *Endocrinology* 2004; 145: 1835–1841.
42. Liu Y, Porta A, Peng X, et al. Prevention of glucocorticoid-induced apoptosis in osteocytes and osteoblasts by calbindin-D28k. *J Bone Miner Res* 2004; 19: 479–490.
43. Nielsen HK, Charles P and Mosekilde L. The effect of single oral doses of prednisone on the circadian rhythm of serum osteocalcin in normal subjects. *J Clin Endocrinol Metab* 1988; 67: 1025–1030.
44. Hofbauer LC, Gori F, Riggs BL, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. *Endocrinology* 1999; 140: 4382–4389.
45. Baron R and Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. *Nat Med* 2013; 19: 179–192.
46. Glass DA, Bialek P, Ahn JD, et al. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. *Dev Cell* 2005; 8: 751–764.
47. Canalis E, Mazzuoli G, Giustina A, et al. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* 2007; 18: 1319–1328.
48. Ohnaka K, Tanabe M, Kawate H, et al. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. *Biochem Biophys Res Commun* 2005; 329: 177–181.
49. Khosla S, Melton LJ and Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner Res* 2011; 26: 441–451.
50. Hofbauer LC, Khosla S, Dunstan CR, et al. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. *Endocrinology* 1999; 140: 4367–4370.
51. Mödder UI, Clowes JA, Hoey K, et al. Regulation of circulating sclerostin levels by sex steroids in women and in men. *J Bone Miner Res* 2011; 26: 27–34.
52. Mohamad NV, Soelaiman IN and Chin KY. A concise review of testosterone and bone health. *Clin Interv Aging* 2016; 11: 1317–1324.
53. Whirlledge S and Cidlowski JA. Glucocorticoids, stress, and fertility. *Minerva Endocrinol* 2010; 35: 109–125.
54. Alele JD, Kamen DL, Hunt KJ, et al. Bone geometry profiles in women with and without SLE. *J Bone Miner Res* 2011; 26: 2719–2726.
55. Caetano-Lopes J, Nery AM, Henriques R, et al. Chronic arthritis directly induces quantitative and qualitative bone disturbances leading to compromised biomechanical properties. *Clin Exp Rheumatol* 2009; 27: 475–482.
56. Tang XL, Qin L, Kwok AW, et al. Alterations of bone geometry, density, microarchitecture, and biomechanical properties in systemic lupus erythematosus on long-term glucocorticoid: a case-control study using HR-pQCT. *Osteoporos Int* 2013; 24: 1817–1826.
57. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum* 2003; 48: 3224–3229.
58. Bultink IEM. Bone disease in connective tissue disease/systemic lupus erythematosus. *Calcif Tissue Int* 2017; 102: 575–591.
59. Svenungsson E, Fei GZ, Jensen-Urstad K, et al. TNF-alpha: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. *Lupus* 2003; 12: 454–461.
60. Frostegard J, Svenungsson E, Wu R, et al. Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. *Arthritis Rheum* 2005; 52: 192–200.
61. Teichmann J, Lange U, Stracke H, et al. Bone metabolism and bone mineral density of systemic lupus erythematosus at the time of diagnosis. *Rheumatol Int* 1999; 18: 137–140.
62. Guo Q, Fan P, Luo J, et al. Assessment of bone mineral density and bone metabolism in young male adults recently diagnosed with systemic lupus erythematosus in China. *Lupus* 2017; 26: 289–293.
63. Zhu TY, Griffith JF, Au SK, et al. Bone mineral density change in systemic lupus erythematosus: a 5-year followup study. *J Rheumatol* 2014; 41: 1990–1997.
64. Mok CC, Mak A and Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. *Lupus* 2005; 14: 106–112.
65. Mok CC, Ying SK, To CH, et al. Bone mineral density and body composition in men with systemic lupus erythematosus: a case control study. *Bone* 2008; 43: 327–331.
66. Hadji P, Ziller M, Maskow C, et al. The influence of chemotherapy on bone mineral density, quantitative ultrasonometry and bone turnover in pre-menopausal women with breast cancer. *Eur J Cancer* 2009; 45: 3205–3212.
67. Wetzels JF. Cyclophosphamide-induced gonadal toxicity: a treatment dilemma in patients with lupus nephritis? *Neth J Med* 2004; 62: 347–352.
68. Zhao D, Wang C, Zhao Y, et al. Cyclophosphamide causes osteoporosis in C57BL/6 male mice: suppressive effects of cyclophosphamide on osteoblastogenesis and osteoclastogenesis. *Oncotarget* 2017; 8: 98163–98183.
69. Lai CC, Chen WS, Chang DM, et al. Increased serum fibroblast growth factor-23 and decreased bone turnover in patients with systemic lupus erythematosus under treatment with cyclosporine and steroid but not steroid only. *Osteoporos Int* 2015; 26: 601–610.
70. Carli L, Tani C, Spera V, et al. Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus. *Lupus Sci Med* 2016; 3: e000098.
71. Toloza SM, Cole DE, Gladman DD, et al. Vitamin D insufficiency in a large female SLE cohort. *Lupus* 2010; 19: 13–19.

72. Borba VZ, Vieira JG, Kasamatsu T, et al. Vitamin D deficiency in patients with active systemic lupus erythematosus. *Osteoporos Int* 2009; 20: 427–433.
73. Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. *Arthritis Care Res* 1995; 8: 137–145.
74. Laan RF, van Riel PL, van de Putte LB, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med* 1993; 119: 963–968.
75. Di Munno O, Mazzantini M, Delle Sedie A, et al. Risk factors for osteoporosis in female patients with systemic lupus erythematosus. *Lupus* 2004; 13: 724–730.
76. Somers EC, Marder W, Christman GM, et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005; 52: 2761–2767.
77. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017; 76: 476–485.
78. Van Vollenhoven RF, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014; 73: 958–967.
79. Kipen Y, Briganti E, Strauss B, et al. Three year followup of bone mineral density change in premenopausal women with systemic lupus erythematosus. *J Rheumatol* 1999; 26: 310–317.
80. Bonaiuti D, Shea B, Iovine R, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2002; 3: CD000333.
81. Bultink IE, Lems WF, Kostense PJ, et al. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. *Arthritis Rheum* 2005; 52: 2044–2050.
82. Fernando MM and Isenberg DA. How to monitor SLE in routine clinical practice. *Ann Rheum Dis* 2005; 64: 524–527.
83. Panday K, Gona A and Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. *Ther Adv Musculoskelet Dis* 2014; 6: 185–202.
84. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2017; 69: 1095–1110.
85. Kanis JA, Harvey NC, Cooper C, et al. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos* 2016; 11: 25.
86. Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev* 2016; 10: CD001347.
87. Kan SL, Yuan ZF, Li Y, et al. Alendronate prevents glucocorticoid-induced osteoporosis in patients with rheumatic diseases: a meta-analysis. *Medicine* 2016; 95: e3990.
88. Bultink IEM. Osteoporosis and fractures in systemic lupus erythematosus. *Arthritis Care Res* 2012; 64: 2–8.
89. Sawamura M, Komatsuda A, Togashi M, et al. Effects of denosumab on bone metabolic markers and bone mineral density in patients treated with glucocorticoids. *Intern Med (Tokyo, Japan)* 2017; 56: 631–636.
90. Mok CC, Ho LY and Ma KM. Switching of oral bisphosphonates to denosumab in chronic glucocorticoid users: a 12-month randomized controlled trial. *Bone* 2015; 75: 222–228.
91. Saag K, Wagman R, Geusens P, et al. OP0010 Effect of denosumab compared with risedronate in glucocorticoid-treated individuals: results from the 12-month primary analysis of a randomized, double-blind, active-controlled study. *Ann of the Rheum Dis* 2017; 76: 54.
92. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol* 2018; 6: 445–454.
93. Suzuki T, Nakamura Y and Kato H. Significant improvement of bone mineral density by denosumab without bisphosphonate pre-treatment in glucocorticoid-induced osteoporosis. *Mod Rheumatol* 2018; 22: 1–5.
94. Anastasilakis AD, Polyzos SA, Makras P, et al. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res* 2017; 32: 1291–1296.
95. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 2007; 357: 2028–2039.
96. Saag KG, Zanchetta JR, Devogelaer JP, 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: 3346–3355.
97. Carter EE, Barr SG and Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol* 2016; 12: 605–620.
98. Hermann AP and Abrahamsen B. The bisphosphonates: risks and benefits of long term use. *Curr Opin Pharmacol* 2013; 13: 435–439.
99. Losada I, Sartori L, Di Gianantonio E, et al. Bisphosphonates in patients with autoimmune rheumatic diseases: can they be used in women of childbearing age? *Autoimmun Rev* 2010; 9: 547–552.
100. Sokal A, Elefant-Amoura E, Leturcq T, et al. OP0101 Bisphosphonates during pregnancy: a prospective study. *Ann Rheum Dis* 2016; 75: 93.
101. Russell RG, Watts NB, Ebetino FH, et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008; 19: 733–759.
102. Green SB and Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm* 2014; 71: 2029–2036.
103. Mok CC, To CH, Mak A, et al. Raloxifene for postmenopausal women with systemic lupus erythematosus: a pilot

- randomized controlled study. *Arthritis Rheum* 2005; 52: 3997–4002.
104. Fraser LA and Adachi JD. Glucocorticoid-induced osteoporosis: treatment update and review. *Ther Adv Musculoskelet Dis* 2009; 1: 71–85.
105. Abrahamsen B, Grove EL and Vestergaard P. Nationwide registry-based analysis of cardiovascular risk factors and adverse outcomes in patients treated with strontium ranelate. *Osteoporos Int* 2014; 25: 757–762.
106. Knopp-Sihota JA, Newburn-Cook CV, Homik J, et al. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. *Osteoporos Int* 2012; 23: 17–38.
107. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; 377: 1417–1427.
108. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013; 382: 50–56.
109. Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. *J Clin Endocrinol Metab* 2012; 97: 2272–2282.
110. Hadji P, Felsenberg D, Amling M, et al. The non-interventional BonViva Intravenous Versus Alendronate (VIVA) study: real-world adherence and persistence to medication, efficacy, and safety, in patients with postmenopausal osteoporosis. *Osteoporos Int* 2014; 25: 339–347.
111. Feng Z, Zeng S, Wang Y, et al. Bisphosphonates for the prevention and treatment of osteoporosis in patients with rheumatic diseases: a systematic review and meta-analysis. *PLoS ONE* 2013; 8: e80890.
112. Mok CC, Tong KH, To CH, et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. *Osteoporos Int* 2008; 19: 357–364.
113. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001; 44: 202–211.
114. Sharma A, Einstein AJ, Vallakati A, et al. Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. *Am J Cardiol* 2014; 113: 1815–1821.
115. Mak A, Cheung MW, Ho RC, et al. Bisphosphonates and atrial fibrillation: Bayesian meta-analyses of randomized controlled trials and observational studies. *BMC Musculoskelet Disord* 2009; 10: 113.
116. Reid DM, Devogelaer JP, Saag K, 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: 1253–1263.
117. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017; 5: 513–523.
118. Papapoulos S, Lippuner K, Roux C, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. *Osteoporos Int* 2015; 26: 2773–2783.
119. Torring O. Effects of denosumab on bone density, mass and strength in women with postmenopausal osteoporosis. *Ther Adv Musculoskelet Dis* 2015; 7: 88–102.
120. Miller PD. Safety of parathyroid hormone for the treatment of osteoporosis. *Curr Osteoporos Rep* 2008; 6: 12–16.
121. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. *JAMA* 1999; 281: 2189–2197.
122. Adomaityte J, Farooq M and Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. *Thromb Haemost* 2008; 99: 338–342.
123. Carvalho NNC, Voss LA, Almeida MOP, et al. Atypical femoral fractures during prolonged use of bisphosphonates: short-term responses to strontium ranelate and teriparatide. *J Clin Endocrinol Metab* 2011; 96: 2675–2680.
124. Tascioglu F, Colak O, Armagan O, et al. The treatment of osteoporosis in patients with rheumatoid arthritis receiving glucocorticoids: a comparison of alendronate and intranasal salmon calcitonin. *Rheumatol Int* 2005; 26: 21–29.
125. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2018; 103: 1715–1744.
126. Recker RR and Armas L. The effect of antiresorptives on bone quality. *Clin Orthopaed Relat Res* 2011; 469: 2207–2214.
127. Jiang Y, Zhao JJ, Mitlak BH, et al. Recombinant human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res* 2003; 18: 1932–1941.
128. Saag KG, Agnusdei D, Hans D, et al. Trabecular Bone Score in patients with chronic glucocorticoid therapy-induced osteoporosis treated with alendronate or teriparatide. *Arthritis Rheumatol* 2016; 68: 2122–2128.
129. Dempster DW, Roschger P, Misof BM, et al. Differential effects of teriparatide and zoledronic acid on bone mineralization density distribution at 6 and 24 months in the SHOTZ study. *J Bone Miner Res* 2016; 31: 1527–1535.
130. Tsai JN, Uihlein AV, Burnett-Bowie SM, et al. Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRpQCT study). *J Clin Endocrinol Metab* 2016; 101: 2023–2030.
131. Arnaud L, Nordin A, Lundholm H, et al. Effect of corticosteroids and cyclophosphamide on sex hormone profiles in male patients with systemic lupus erythematosus or systemic sclerosis. *Arthritis Rheumatol (Hoboken, NJ)* 2017; 69: 1272–1279.
132. Hoppé E, Bouvard B, Royer M, et al. Is androgen therapy indicated in men with osteoporosis? *Joint Bone Spine* 2013; 80: 459–465.
133. Formiga F, Moga I, Nolla JM, et al. The association of dehydroepiandrosterone sulphate levels with bone mineral

- density in systemic lupus erythematosus. *Clin Exp Rheumatol* 1997; 15: 387–392.
134. Kanda N, Tsuchida T and Tamaki K. Testosterone suppresses anti-DNA antibody production in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1703–1711.
135. Van Vollenhoven RF, Morabito LM, Engleman EG, et al. Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 1998; 25: 285–289.
136. Edens C and Robinson AB. Systemic lupus erythematosus, bone health, and osteoporosis. *Curr Opin Endocrinol Diabetes Obes* 2015; 22: 422–431.
137. Hippisley-Cox J and Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ* 2012; 344: 18.
138. Bolland MJ, Siu ATY, Mason BH, et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. *J Bone Miner Res* 2011; 26: 420–427.