Skeletal manifestations of systemic autoimmune diseases
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Current Opinion in Endocrinology, Diabetes & Obesity 2010, 17:540–545

Purpose of review
There is an increased risk of osteoporotic fractures and osteonecrosis often at a young age among patients with certain systemic autoimmune diseases. The loss of bone mineral density and bone integrity seen with these diseases often cannot be explained by traditional risk factors alone. In this review, we focus on rheumatoid arthritis and systemic lupus erythematosus, two systemic autoimmune diseases in which skeletal manifestations have been well described.

Recent findings
There is recent evidence that autoimmunity and its associated inflammation and vitamin D deficiency play key roles in the pathogenesis of adverse skeletal effects.

Summary
Understanding these processes carries implications for the prevention and treatment of osteoporosis and osteonecrosis among patients with autoimmune diseases.

Keywords
autoimmunity, lupus, osteoporosis, rheumatoid arthritis, vitamin D

Introduction
Several autoimmune diseases carry with them an increased risk of osteoporotic fractures and osteonecrosis, adding significantly to the morbidity and mortality of these conditions. The accelerated bone mineral density (BMD) and integrity loss seen with these diseases is often not entirely explained by traditional risk factors, and autoimmunity itself may play a role in its pathogenesis. Mechanisms for skeletal change not only include some well defined risk factors, such as corticosteroid use, but may also include chronic inflammation and immune dysregulation. The complex nature of these processes carries implications for the prevention and treatment of osteoporosis and osteonecrosis among patients with autoimmune diseases.

In this review, we will focus on the most recent studies of inflammatory effects on bone and skeletal manifestations of systemic autoimmune diseases, particularly rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). We include a discussion of vitamin D and its effects on autoimmunity, bone health and fracture outcomes. We will also include practice recommendations for providers with the goal of predicting overall fracture risk and lowering that risk in patients with autoimmune disease.

Osteoporosis in rheumatoid arthritis
RA is the leading cause of inflammatory arthritis in adults and if undertreated can lead to bone erosions and disabling loss of function of the joints [1]. RA is also an independent risk factor for osteoporosis and patients with RA develop osteoporotic fractures at an earlier age, adding significantly to the morbidity and mortality of the disease [2]. Patients with RA have an approximately two-fold risk of developing osteoporosis [3,4], two to three-fold risk of hip fracture [5–7], and two to six-fold risk of vertebral fracture compared to the general population [8]. Reduction in bone mineral density in RA may be influenced by immobility, inflammation associated with osteoclast activation, and medications used to treat the disease such as corticosteroids [9,10].

There have been several studies of the prevalence of osteoporosis in patients with RA. Using BMD measurement to diagnose osteoporosis as defined by the WHO criteria, the Italian Study Group on Bone Mass in RA found that 50% of the 925 female patients with RA had osteoporosis [11]. Assessments done in RA cohorts from Europe found inflammatory disease activity, decreased functional capacity, and corticosteroid use to be independent risk factors for osteoporosis. [12] Additionally, certain disease modifying antirheumatic drugs have been implicated in bone loss but others have a potential protective role, underscoring the need for further research in this area. One recent study reports an increase in BMD seen in RA patients after 1 year of infliximab therapy [13].

Because of the large societal impact of RA-related osteoporotic fractures, having a diagnosis of RA was
incorporated into the WHO fracture risk assessment tool, FRAX, which computes the 10-year probability of hip fracture or major osteoporotic fracture when given certain clinical risk factors. A relative fracture risk of 1.73 (95% CI 0.94–3.20) related to RA independent of BMD is included in this valuable tool [14].

Osteoporosis in systemic lupus erythematosus
Epidemiological studies have shown that patients with SLE are at greater risk for osteoporosis than the general population. Similarly, age-adjusted fracture risk is higher among SLE patients compared to the general population. Because life expectancy among SLE patients has been dramatically extended by earlier diagnosis and more effective therapies, osteoporotic fractures are becoming an even larger comorbid health concern. Recent studies estimate the prevalence of osteoporosis to be greater than 20% among the general population with SLE [15,16].

Risk factors for osteoporosis in patients with SLE include high disease activity, vitamin D deficiency, renal disease, corticosteroid use, and premature ovarian failure from cytotoxic medications such as cyclophosphamide [17]. Because patients with SLE are told to avoid the sun, a common trigger of disease flares, vitamin D deficiency is even more prevalent than in the general population. A recent study found that screening, prophylaxis, and treatment of osteoporosis among community-based patients with SLE was suboptimal, with 69–74% of patients being screened and 56–58% taking calcium and vitamin D even among patients with risk factors for BMD loss [18]. Only 47% of patients with documented osteoporosis were taking an antiresorptive or anabolic agent [18].

Because most SLE patients have multiple disease-associated and traditional osteoporosis risk factors, bone loss tends to run a rapid course, resulting in the early onset of osteoporosis. Unlike what is seen in the general population, decreased bone mineral density in patients with SLE tends to be diagnosed in premenopausal women, and African–American ethnicity tends not to be protective. Overall, disease features such as disease duration, organ damage accumulation and cumulative steroid dose have been shown to predict low BMD and fracture, highlighting the role played by the ‘lupus-milieu’ in the disruption of skeletal health.

Osteonecrosis in autoimmune diseases
Osteonecrosis of bone is a cause of significant morbidity and is frequently seen in patients with SLE. Among patients with SLE, the prevalence is 10–13% for symptomatic and approaches 50% in studies which include asymptomatic osteonecrosis detected by MRI. Even 10–13% is a higher prevalence than what one would expect from the elevated risk of corticosteroid use alone [19]. In a study of 868 patients with SLE, 49 patients had clinically apparent osteonecrosis, with femoral heads being the most common site and 83% of them had bilateral involvement [20]. Risk factors for osteonecrosis included corticosteroid dose within the past 4 months and cumulative prednisolone dose [20]. Other risk factors include Raynaud phenomenon, hyperlipidemia, and male sex [20,21]. An association with the presence of antiphospholipid antibodies has been seen in a few studies but others have looked and not seen a correlation [22].

The most likely cause of osteonecrosis involves the compromise of bone vasculature leading to the death of bone and marrow cells leading ultimately to mechanical failure. Patients most commonly present with pain in the area of the affected joint with weight-bearing or movement. Plain films are good for initial evaluation but if unrevealing and clinical suspicion remains high an MRI is more than 90% sensitive and diagnostically helpful [23].

The role of vitamin D in autoimmunity and the skeleton
Vitamin D is derived from UVB-catalyzed skin synthesis and from dietary sources and is carried in the circulation bound to the vitamin D-binding protein. Vitamin D is activated by 25-hydroxylation and 1-alpha-hydroxylation in the liver and kidney, respectively. Active vitamin D brings about its effects by binding the vitamin D receptor (VDR), a member of the nuclear receptor super family that has now been identified in many tissues including bone, parathyroid gland, gastrointestinal tract, muscle, and immune cells. Adequate vitamin D stores are needed to help maintain immune system homeostasis, yet vitamin D deficiency is highly prevalent among patients with RA and SLE and compounds the already elevated fracture risk seen in these disorders (Fig. 1) [24].

The vitamin D axis is intimately involved in calcium metabolism and skeletal health. Under average nutritional circumstances, the gastrointestinal absorption of calcium is not sufficient to counterbalance obligatory losses in urine and sweat and at the same time support skeletal health in the absence of active (vitamin D-mediated) gastrointestinal transport [25]. This vitamin D-related enhancement of calcium absorption has largely been attributed to calcitriol but recent studies have demonstrated that 25-hydroxyvitamin D is also involved and that 25-hydroxyvitamin D levels matter [25]. Although this position has been recently contradicted [26], the study of Bischoff-Ferrari et al. [27] demonstrated that a higher calcium intake is needed to maintain
BMD among patients in the lowest quartile of 25-hydroxyvitamin D.

Several studies have provided evidence linking vitamin D status with surrogates of bone material and structure. Indeed, vitamin D supplementation has been associated with fracture reduction in many clinical studies, supporting the assertion that vitamin D status has a direct bearing on bone strength [28].

Additionally, the VDR has been identified in muscle tissue, where its activation has been associated with de-novo protein synthesis, muscle growth and improved muscle function; clinical, epidemiologic and laboratory studies have provided evidence in support of a direct effect of vitamin D on muscle function [29]. Using tests that predict risks of fall-related hip fracture and disability, Bischoff-Ferrari et al. [30] have demonstrated an association between 25-hydroxyvitamin D level and lower extremity muscle function among ambulatory subjects within the US population. Considering that most fractures are a direct consequence of falls, this study demonstrates that the treatment of vitamin D deficiency represents a unique opportunity to reduce fracture risk among the osteoporosis population.

Finally, vitamin D is thought to have an immunomodulatory function, with deficient levels associated with impaired innate immune function and overexuberant adaptive immune function [31]. Markers of inflammation have been associated with increased bone turnover and bone loss, a factor that is thought to be particularly at play among patients with inflammatory diseases. Consequently, low vitamin D levels can lead to accelerated bone loss among patients with inflammatory diseases. Put together, these observations move us beyond the calcitropic effects of vitamin D deficiency among patients with inflammatory diseases, and argue in favor of higher serum levels than are currently accepted [32].

Vitamin D supplementation has been recommended to prevent osteoporosis in SLE but there is no consensus on dosage, and optimal levels of 25-hydroxyvitamin D for bone health in SLE have not been established. The current Recommended Daily Intake (RDI) in adults of 200–600 international unit of vitamin D daily has been shown to be suboptimal for maintaining normal serum levels of 25-hydroxyvitamin D and inadequate for preserving BMD [32–34].

**Relationship between inflammation and skeletal damage**

Several studies have found an association between pro-inflammatory cytokines which play a role in bone resorption, such as TNF-α, IL-1 and IL-6, and the development of osteoporosis [35,36]. Epidemiologic studies have shown levels of systemic inflammation to predict bone loss and future fracture [37]. It is becoming clear that T cells play a pivotal role in regulating bone homeostasis through direct interactions with bone marrow, stromal cells and osteoblasts. Once activated, these T cells release osteoclastogenic cytokines and Wnt ligands [38].

Under normal circumstances, fracture prevention is a consequence of two surface-specific processes that function to adapt skeletal structure to prevailing loads (skeletal modeling) or repair damage when it inevitably happens (skeletal remodeling). These cellular processes are very successful early in life due to a tight regulatory system, which unfortunately fails with aging, resulting in skeletal fragility [39].

There is a growing body of evidence suggesting similar disruption of skeletal remodeling and possibly modeling within the context of inflammation leading to increased fragility. In this regard, the study of Teichmann et al. [40] is particularly enlightening. Among a cohort of 20 patients with SLE who had never been on steroids, osteocalcin levels were significantly lower, the urinary excretion of cross-links were significantly higher than in a non-SLE cohort, suggesting that there is decreased bone formation and increased bone resorption among steroid-naive SLE patients. Although these findings were attributed to the underlying disease, comparable results were detected among a steroid-treated cohort implying that steroid treatment does not undo the skeletal effects of inflammation in SLE as was speculated by some researchers.
This uncoupling of osteoclast from osteoblast activity can be associated with reduced bone deposition relative to bone removal with each remodeling cycle, leading to net bone loss over time [41].

Consistent with this hypothesis, Korczowska et al. [42] recently reported finding statistically significant correlation between the markers of inflammation (α-1-acid glycoprotein and C-reactive protein) and carboxy-terminal collagen cross-links, a marker of bone resorption among a steroid-treated cohort of SLE patients. Bone resorption was positively (significantly) correlated with levels of interleukin 6 (IL-6) among these patients. In subgroup analysis, there were statistically significant differences in the levels of IL-6, AP-B and Dpd between SLE patients who had osteoporosis compared to those that did not. These findings suggest that patients with more active inflammation are at greater risk for bone loss [43**].

Another factor responsible for negative bone balance in SLE and RA is exposure to corticosteroids, a class of drugs commonly and effectively used for treating the underlying inflammation. However, steroids have many adverse skeletal effects that can lead to bone loss, osteonecrosis and ultimately to fracture and/or collapse [44**]. These effects include the suppression of osteoblastogenesis along with increased apoptosis of osteoblasts and osteocytes, leading to reduced bone formation [45]. Steroids also downregulate osteoprotegerin expression while stimulating RANKL expression leading to increased osteoclast activity. Because OPG is inhibitory to osteoclast formation/activity, but RANKL has the very opposite effect, this action of steroids can lead to increased bone resorption [44*]. In addition, steroids alter calcium metabolism by vitamin D-dependent and vitamin D-independent mechanisms [44*].

Although corticosteroids continue to occupy a central role in the management of inflammatory autoimmune conditions, several targeted biologic therapies and nonsteroidal disease modifying agents are now in use. It remains to be seen whether these agents will ameliorate the skeletal consequences of autoimmune diseases.

**Recommendations for monitoring and risk factor reduction**

Because of the enormous health impact of osteoporotic fractures, several organizations, including the National Osteoporosis Foundation [46], American College of Rheumatology (ACR) [47], and SLE Quality Indicators Project Expert Panel [48], have set guidelines for screening, prevention, and treatment of osteoporosis. The current guidelines from the ACR for patients starting corticosteroids recommend calcium and vitamin D supplementation for all, and initiation of bisphosphonate therapy if treatment with at least 5 mg daily of prednisone or equivalent for greater than 3 months is anticipated [47]. For those already on long-term corticosteroids but not on a bisphosphonate, it is recommended to follow annual or biannual BMD measurements.

Effective and well tolerated therapies for osteoporosis exist which reduce fracture rates [49–52]; however, studies have shown underuse of these therapies even in the highest-risk patients with a history of prior fragility fracture [53–56]. Bisphosphonates have not been widely accepted for use among premenopausal patients, and patients with SLE or RA are often still young when they have the greatest need to protect their BMD. Teriparatide is an effective anabolic therapy but despite being approved for steroid-induced osteoporosis, it also remains underutilized possibly due to the need for daily injections. Most recently, denosumab has been approved for the treatment of postmenopausal osteoporosis. Denosumab works by binding to RANK ligand, preventing interaction with its receptor on the surface of osteoclasts and their precursors, which makes it a promising treatment for inflammation-related osteoporosis in particular [57]. Although there is no doubt that the use of oral corticosteroids contribute to the elevated fracture risk seen among patients with systemic autoimmune diseases, recent studies have also found a potentially beneficial effect on BMD of low-dose short-term corticosteroids in RA, due to their anti-inflammatory effects [58]. These reports should be interpreted with caution given the observation that corticosteroid-associated fracture can occur with minimal BMD reduction.

In light of the alarming prevalence of vitamin D deficiency seen worldwide, all patients with autoimmune disease should have at least a baseline screening 25-hydroxyvitamin level to screen for vitamin D deficiency [24]. The only laboratory test usually required to ascertain the patient’s status is the 25-hydroxyvitamin D level with a goal of at least greater than 30 ng/ml.

**Conclusion**

Bone loss and damage commonly occurs in patients with systemic autoimmune diseases. We are improving in our ability to diagnose and treat autoimmune diseases and their complications; yet osteoporosis and osteonecrosis remain growing comorbid conditions.

Guidelines set forth by the professional societies are clear in their emphasis on preventive measures with calcium and vitamin D supplementation prophylaxis and potential initiation of a bisphosphonate in patients with autoimmune diseases requiring even low-dose
corticosteroids [46–48]. Improvement in adherence to these guidelines will substantially reduce the risk of fractures, subsequently improving quality of life, disability rate, healthcare cost, and mortality.

Acknowledgement
This work was supported by the National Institutes of Health K23 grant (AR052364) to Dr Kamen titled ‘The Role of Vitamin D in Systemic Lupus Erythematosus’.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 572–573).


This paper reviews current literature on vitamin D deficiency and provides an estimate for the true fracture preventive impact of vitamin D sufficiency in the population.


This article is an in-depth examination of the connection between T cells and bone health.


This paper discusses in great detail the central role played by skeletal modeling and skeletal remodeling in the maintenance of skeletal integrity. Mechanisms of origin of fragility are also discussed in detail.


This paper reviews recent studies on osteoporosis in SLE, including the role of inflammation.


In this paper, recent data on SLE-associated osteoporosis are discussed, with a detailed review of the impact of corticosteroids.


