Editorial

Systemic Lupus Erythematosus, Osteoporosis, and Fractures

Osteoporosis is a common yet less-recognized complication of systemic lupus erythematosus (SLE) that has been brought to our attention by Zhu, *et al*'s article in this issue of *The Journal*[1]. Recent studies, however, have highlighted the high prevalence of fractures in a relatively young population of women suffering from SLE[1,2,3,4,5,6,7]. There have been many studies reporting different results. This might be explained by the complex relationship between SLE, complications of the disease itself or its treatment, duration of disease, bone loss, and fractures. Indeed the systemic inflammation associated with SLE and the resultant end-organ damage may all play a role[1,2,3]. Combine this with the traditional risk factors for fracture and it is easy to understand why the study of osteoporosis and fractures in SLE is complex.

Confounders include active inflammation and treatment of inflammation with glucocorticoids[1,2,3], menopausal status, and disease-associated complications such as renal bone disease and neuropsychiatric disease[3]. Other non-SLE risk factors including age, medications such as selective serotonin receptor inhibitors (SSRI) and possibly proton pump inhibitors (PPI) may all confound the relationship between SLE and fractures. The effect of treatment with bone-active drugs to prevent bone loss and fractures must also be taken into consideration in studies of SLE.

Risk Factors

Inflammation. There is a well-recognized association between inflammatory diseases, bone loss, and fractures. The classic example is rheumatoid arthritis. Other conditions such as inflammatory bowel and lung disease are also associated with increased fracture risk. Tumor necrosis factor-α, interleukin 1 (IL-1), and IL-6 are well known activators of osteoclasts, leading to increased bone turnover and fractures[8].

Renal disease. Of particular importance is the presence of renal disease in a large proportion of individuals with SLE. Renal disease is associated with fractures and osteoporosis, with greater renal dysfunction resulting in greater risk[9]. Even those with moderate chronic kidney disease have abnormalities in bone metabolism that predispose to bone loss and fractures.

Neurologic disease. Those with neurologic disease are often predisposed to falls and if their neuropsychiatric disease manifests as seizures and resultant falls, the risk of fractures increases. In those with neuropsychiatric SLE, there is an increased risk[3]. In addition to seizures, the use of anticonvulsants may be associated with fractures[10].

Medications. There are a number of commonly used medications that may affect fracture risk in patients with SLE.

Glucocorticoids. Glucocorticoids are a well-recognized cause of bone loss[11]. They affect both premenopausal and postmenopausal women as well as men. Glucocorticoids lead to early rapid bone loss with increased fracture risk occurring shortly after initiation of therapy. There are many factors contributing to the loss of bone and fractures including direct effects on osteoblasts, osteoclasts, and osteocytes and indirect effects on calcium absorption, renal handling of calcium, reduced gonadal hormones, and decreased neuromuscular function[12].

SSRI. SSRI use is ubiquitous in general[13] and is commonly used in those with SLE, particularly when they have neuropsychiatric disease. SSRI have been associated with increased fracture risk and the risk of fractures may be increased if they are used in combination with glucocorticoids[14].

PPI. A number of studies including a metaanalysis have reported a modest association between PPI and fractures[15], with 1 report suggesting that PPI may negate the beneficial effects seen with alendronate therapy[16].

Other drugs that are associated with fractures and may be used in the SLE population include anticonvulsants[10], and benzodiazepines[17].

Menopause. Menopause and irregular menstrual cycles may

confound the bone loss seen in SLE. With active disease there are many young women with menstrual irregularities that may contribute to bone loss. Fractures are seldom seen in young populations because their youth and general health are protective. However, in the SLE population, fractures occur even in this young age group. Bone loss in older women who have gone through menopause occurs as would be seen in any postmenopausal women.

Treatment

Treatment may be divided into that which controls SLE disease and that which directly targets osteoporosis. Given the pathophysiology of bone loss and fractures in SLE, intervention that results in reduction of inflammation, with the exception of glucocorticoids, and control of disease are likely of benefit in reducing bone loss and increasing mobility and overall health. In principle this may be important in reducing fracture risk. Therapy with demonstrated efficacy in osteoporosis and fracture prevention for the most part includes the use of bisphosphonates. While other therapies are available, their use has not been well reported in this population.

The strengths of the current study include the identification and characterization of SLE as well as the traditional risk factors for fracturing. SLE disease activity was well documented using SLE Disease Activity Index. The documentation of flares and the severity of the flare, new organ damage, and the prospective capture of medications including antifracture medications are unique to this study of SLE and bone disease. Further strengths are the duration of followup and the examination of traditional risk factors for fracture including bone mineral density (BMD) measurements, measurement of vitamin D, and the documentation of the cumulative dose and duration of glucocorticoid use. Unfortunately, the sample size is still relatively small, and as a result, it is not possible to adjust for the many potential confounders that may be seen in those with SLE. The age distribution included younger individuals, as would be expected in SLE; however, 62.4% were older postmenopausal women. Unfortunately, because of the lack of a control group, the important effects of age could not be examined relative to bone loss that might normally be seen in those without SLE. The effects of menopause were studied; however, the incidence of menstrual irregularities was not reported in this study. Factors such as comorbid disease, frailty, and falls, which are confounders that tend to be seen in an older population, were not reported. Renal function and new renal disease was associated with larger declines in BMD than other new organ damage. What is apparent from this study and consistent with earlier studies is the negative effect that glucocorticoids have on bone in this population. The association of greater declines in BMD with disease flare, renal disease, and new organ damage are important findings; and

the fact that osteoporosis therapy prevents bone loss is reassuring.

The discrepancies in fracture risk seen among the various studies of SLE may be explained by many of the different risk factors seen in different SLE populations, different study durations, designs (cross-sectional vs prospective cohorts), sample sizes, and primary outcome measures. To elucidate the association of SLE to fractures and osteoporosis, larger studies must be completed to be able to control for many of the confounders that make the study of fractures in SLE difficult. The current study contributes to the literature by increasing the growing body of evidence required to further understand the association among SLE, BMD, and the potential for fractures.

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