Vertebral, pelvic and hip fracture risk in adults with severe atopic dermatitis

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Editorial

Vertebral, pelvic, and hip fracture risk in adults with severe atopic dermatitis

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The immediate priority for clinicians managing patients with atopic dermatitis (AD) is treating the disease, particularly the constant itch and sleep disturbance, with its consequential disruption of both home and work life and association with low mood, poorer concentration, and productivity. However, long-term sequelae are important to consider and include those directly related to the atopic march (asthma, allergic rhinoconjunctivitis, and food allergies), the consequences of having a chronic disease, and potential side effects of therapy, particularly topical corticosteroids. Regarding the latter, concern about the long-term consequences of corticosteroids among a proportion of patients leads to noncompliance with this first-line topical therapy and more poorly controlled disease.[1]

An article published in this issue of the *Journal* focuses on a less well recognized long-term sequelae of AD: osteoporosis and fracture risk.[2] In their matched cohort study set in primary care, Lowe et al[2] investigated the prevalence of vertebral, pelvic, femoral, humoral, and wrist bony fractures in adults. Data were collated from electronic health and hospital admissions records from half a million British patients with AD and 2.5 million control subjects. The study found a 7% to 18% greater risk of hip, pelvis, spine, and wrist fractures in the AD group as a whole, which was independent of age, sex, history of asthma, and oral corticosteroid use. The greater fracture risk was largely confined to patients with severe disease, defined as those receiving systemic therapies (azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil) and phototherapy and those receiving specialist care from a dermatologist. In this subset of patients, the overall risk of fractures was 50% to 109% greater than in patients without AD. Vertebral fracture risk more than doubled, the risk of pelvic fractures was 70% greater, and the risk of hip fractures was 50% greater compared with risks in healthy control subjects. After adjusting for confounding factors, wrist and proximal humoral fractures were not significantly associated with even severe AD.

Previous population studies undertaken in the United States and Taiwan have also shown a significant association between AD and osteoporosis, which is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased fracture risk. In most of these studies, osteoporosis was not measured directly but assumed based on a greater fracture prevalence, particularly of the vertebrae and femora.[3,4] The risk was greater in older persons, women, those with depression, and patients prescribed oral corticosteroids. In the United States the International Classification of Diseases, Ninth Edition, code 733.0 for diagnosing osteoporosis is based on a T-score of −2.5 or less at the lumbar spine, femur neck, or total hip determined by using bone mineral density (BMD) testing and comparison of a subject's bone density with that of a healthy 30-year-old of the same sex. Because of the cost and time required, bone density (dual-energy X-ray absorption) scanning has only been performed in a few studies, and results were found to be significantly lower in adults but not children with AD.[5,6] An integrated Fracture Risk Assessment Tool (FRAX) was developed in 2008 to combine BMD and clinical risk factors. Population studies linking low BMD and clinical fracture risk have previously shown an association with AD in adults.[7]

There are a number of potential reasons for the observed association between AD and fractures in adults highlighted in study by Lowe et al[2] (Fig 1).

1. Type 2 inflammation associated with AD might actually protect against, rather than increase, fracture risk because T_H2 (and T_H1) cytokines are recognized to have an osteoprotective effect through inhibition of osteoclastogenesis, enhancing the anabolic effects of parathormone and decreasing the receptor activator of nuclear factor-κB ligand/osteoprotegerin ratio, leading to inhibition of bone resorption.[8]
2. Peak bone mass (PBM) acquired by 30 to 40 years of age is known to be an important determinant of osteoporotic fracture risk later in life. PBM is regulated by genes, hormones, nutrient supply (calcium, phosphorous, protein, and vitamin D),

and physical activity.

A. Dietary restrictions at critical periods of bone mineralization can lead to suboptimal calcium and vitamin D intake and thus decreased PBM. As such, they might have contributed to the increased fracture risk in adults with severe AD, in whom disease onset is likely to have been in early in childhood and associated with concomitant food allergies.

B. Reduced moderate physical activity might also have contributed to osteopenia in patients with severe AD because these patients often find it hard to mobilize. Regular exercise is an important factor contributing to and maintaining skeletal calcification and strength.

3. Corticosteroids are well recognized as a major risk factor for osteoporosis and bony fractures. However, Lowe et al[2] did not find a significant association between oral steroid use and fracture risk, possibly because of the small number of participants who had been receiving long-term steroids for their AD. There is little or no evidence to suggest that topical steroids, even potent topical steroids, increase fracture risk.[9] Severe AD is associated with asthma, and thus there is potential that inhaled corticosteroids used to treat asthma might have contributed to the fracture risk. However, this and previous studies have not confirmed a link between inhaled corticosteroids used in asthmatic patients and fractures in children and adults, although the period of study was only 2 years.[10]

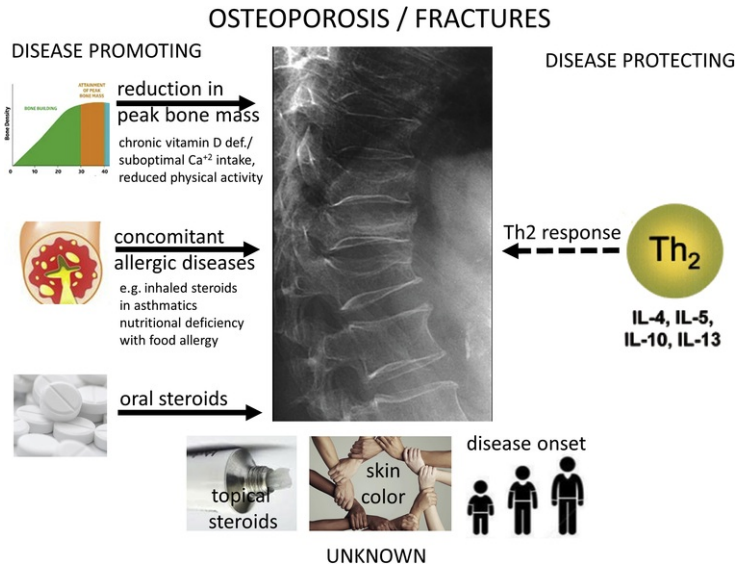

Fig 1 Factors that might promote and protect against osteoporosis and bony fractures in patients with AD.

Further work is required to unravel the key risk factors for fractures in patients with severe AD. Some factors might be difficult to study, but an obvious place to start might be to investigate the association between fracture risk and long-term burden of potent topical corticosteroids. It might be possible to extract these data from primary care physicians' records from those used by Lowe et al[2] by studying the association between the number of prescriptions for potent steroids and fracture risk in patients with severe AD. Onset and duration of AD in relation to fracture risk would be another variable worth investigating, particularly in relation to our understanding of PBM and the risk of fractures later in life. In this regard it would also be interesting to examine the association between severe AD and fractures in relation to skin color/ethnicity because patients with darker skin, particularly those living in countries with long winters and modest sunlight, might be expected to have a greater fracture risk because of poorer vitamin D metabolism and lower PBM.

In summary, although the effect of the findings in patients with mild-to-moderate AD is less clear, the current study published in this issue of the *Journal* highlights the greater risk of vertebral, pelvic, and hip fractures in patients with severe AD. Unpacking the reasons for this association will be a challenge for the future.

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