

Journal Pre-proof

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

Peter D. Arkwright, FRCPCH, D Phil, M. Zulf Mughal, MBChB, FRCP, FRCPCH



PII: S0091-6749(19)31476-9

DOI: <https://doi.org/10.1016/j.jaci.2019.10.029>

Reference: YMAI 14248

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 21 October 2019

Accepted Date: 25 October 2019

Please cite this article as: Arkwright PD, Mughal MZ, Vertebral, pelvic and hip fracture risk in adults with severe atopic dermatitis, *Journal of Allergy and Clinical Immunology* (2019), doi: <https://doi.org/10.1016/j.jaci.2019.10.029>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Editorial

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

Peter D. Arkwright, FRCPCH, D Phil^a, M. Zulf Mughal, MBChB, FRCP, FRCPCH^b

^aLydia Becker Institute of Immunology and Inflammation, University of Manchester, UK,

^bDepartment of Paediatric Endocrinology, Royal Manchester Children's Hospital, UK

Declaration of interests: PDA and MZM declare no relevant conflicts of interest.

Corresponding author: Dr Peter Arkwright, MD, D Phil, Lydia Becker Institute of Immunology and Inflammation, University of Manchester, 48 Grafton St., Manchester, M13 9XX Manchester, United Kingdom. Telephone: +441617010678; E-mail: peter.arkwright@manchester.ac.uk

Key words: atopic dermatitis; osteoporosis; fractures; peak bone mass; corticosteroids

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, low mood, poorer concentration and productivity. Long-term sequelae are however important to consider and include those directly related to the atopic march (asthma, allergic rhinoconjunctivitis, food allergies), the consequences of suffering from a chronic disease and potential side-effects of therapy, particularly of topical corticosteroids. Regarding the latter, a proportion of patients with concerns about the long-term consequences of corticosteroids 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* investigated the prevalence of vertebral, pelvic, femoral, humoral and wrist bony fractures in adults. Data was collated from electronic health and hospital admissions records from half a million British patients with AD and 2.5 million controls. The study found a 7–18% higher risk of hip, pelvis, spine and wrist fractures in the AD group as a whole, which was independent of age, gender, history of asthma and oral corticosteroid use. The higher fracture risk was largely confined to patients with severe disease, defined as those receiving systemic therapies (azathioprine, ciclosporin, methotrexate, or mycophenolate mofetil), phototherapy and those under specialist care from a dermatologist. In this subset of patients, the overall risk of fractures was 50–109% higher than patients without AD. Vertebral fracture risk was more than doubled, the risk of pelvic fractures was 70% higher, and the risk of hip fractures was 50% higher than healthy controls. After adjusting for confounding factors, wrist and proximal humoral fractures were not significantly associated with even severe AD.

Previous population studies undertaken in the US and Taiwan have also shown a significant association between AD and osteoporosis, 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 higher fracture prevalence, particularly of the vertebrae and femora.^{3,4} The risk was higher in older people, women, those with depression and patients prescribed oral corticosteroids. In the USA, the ICD-9 733.0 code for diagnosing osteoporosis is based on finding a T-score of ≤ -2.5 at the lumbar spine, femur neck, or total hip by bone mineral density (BMD) testing, compared with a person's bone density with that of a healthy 30-year-old of the same gender. Because of the cost and time required, bone density (dual energy X-ray absorption (DXA)) scanning has only been performed in a few studies and 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 bone mineral density (BMD) and clinical risk factors. Populations 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* (Figure 1).

1. **Type-2 inflammation** associated with AD may actually protect against, rather than increase fracture risk, as Th2 (and Th1) cytokines are recognized to have an osteoprotective effect by inhibition of osteoclastogenesis, enhancing the anabolic effects of parathormone, and lowering the RANKL/OPG ratio leading to inhibition of bone resorption.⁸
2. **Peak bone mass (PBM)** acquired by 30 - 40 years old, is known to be an important determinant of osteoporotic fracture risk later in life. PBM is regulated by genes,

hormones, supply of nutrients (calcium, phosphorous, protein, 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 lower PBM. As such they may have contributed to the increased fracture risk in adults with severe AD, where disease onset is likely to have been in early in childhood and associated with concomitant food allergies.
- b. **Reduce moderate physical activity** might also have contributed to osteopenia in patients with severe AD, as 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. Lowe *et al* however did not find a significant association between oral steroid use and fracture risk, possibly because of the small number of participants who had been on long-term steroids for their AD. There is little or no evidence to suggest that topical steroids, even potent topical steroids, increase the risk of fractures.⁹ Severe AD is associated with asthma, and thus the potential that inhaled corticosteroids used to treat asthma may have contributed to the fracture risk. However, this and previous studies have failed to confirm a link between inhaled corticosteroids used in asthma and fractures in children and adults, although the period of study was only two years.¹⁰

Further work is required to unravel the key risk factors for fractures in patients with severe AD. Some factors may 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 may be possible to extract these data from primary care physician records from the health records used by Lowe *et al*, 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, as patients with darker skin, particularly those living in countries with long winters and modest sunlight, might be expected to have a higher fracture risk because of poorer vitamin D metabolism and lower PBM.

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

99 **References**

- 100 1. Li AW, Yin ES, Antaya RJ. Topical Corticosteroid Phobia in Atopic Dermatitis: A
101 Systematic Review. *JAMA Dermatol.* 2017;153:1036-1042.
- 102 2. Lowe KE, Mansfield KE, Delmestri A, Smeeth L, Roberts A, Abuabara K, et al. Atopic
103 eczema and fracture risk in adults: A population-based cohort study. *J Allergy Clin*
104 *Immunology.* 2019;XXX
- 105 3. Shaheen MS, Silverberg JI. Atopic dermatitis is associated with osteoporosis
106 and osteopenia in older adults. *J Am Acad Dermatol.* 2019;80:550-551.
- 107 4. Wu CY, Lu YY, Lu CC, Su YF, Tsai TH, Wu CH. Osteoporosis in adult patients with
108 atopic dermatitis: a nationwide population-based study. *PLoS One.* 2017;12:e0171667.
- 109 5. Haeck, I.M., Hamdy, N.A., Timmer-de Mik, L., Lentjes, E.G., Verhaar, H.J., Knol, M.J.
110 et al. Low bone mineral density in adult patients with moderate to severe atopic
111 dermatitis. *Br J Dermatol.* 2009; 161: 1248–1254
- 112 6. van Velsen SG, Knol MJ, van Eijk RL, de Vroede MA, de Wit TC, Lam MG, et al.
113 Bone mineral density in children with moderate to severe atopic dermatitis. *J Am Acad*
114 *Dermatol.* 2010;63:824-31.
- 115 7. Garg NK, Silverberg JI. Eczema is associated with osteoporosis and fractures in adults: a
116 US population-based study. *J Allergy Clin Immunol.* 2015;135:1085-1087.e2.
- 117 8. Srivastava RK, Dar HY, Mishra PK. Immunoporosis: Immunology of osteoporosis – role
118 of T-cells. *Front Immunol* 2018;9:657.
- 119 9. van Velsen SG, Haeck IM, Knol MJ, Lam MG, Bruijnzeel-Koomen CA. Two-year
120 assessment of effect of topical corticosteroids on bone mineral density in adults with
121 moderate to severe atopic dermatitis. *J Am Acad Dermatol.* 2012;66:691-693.

- 122 **10.** Loke YK, Gilbert D, Thavarajah M, Blanco P, Wilson AM. Bone mineral density and
123 fracture risk with long-term use of inhaled corticosteroids in patients with asthma:
124 systematic review and meta-analysis. *BMJ Open*. 2015;5:e008554.

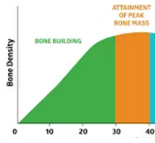
125 **Figure legends**

126 **Figure 1 Factors that may promote and protect against osteoporosis and bony fractures**

127 **in patients with atopic dermatitis.**

OSTEOPOROSIS / FRACTURES

DISEASE PROMOTING



reduction in
peak bone mass

chronic vitamin D def./
suboptimal Ca^{+2} intake,
reduced physical activity



concomitant
allergic diseases

e.g. inhaled steroids
in asthmatics
nutritional deficiency
with food allergy



oral steroids



topical
steroids



skin
color

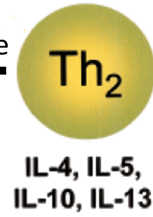
disease onset



UNKNOWN

DISEASE PROTECTING

Th2 response



IL-4, IL-5,
IL-10, IL-13