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COMORBIDITIES IN ADULT ECZEMA: WHAT'S REAL? WHAT MATTERS?

The observation that psoriasis may be an independent risk factor for myocardial infarction (MI) most famously elucidated in a population-based study from the UK published in JAMA,¹ has been followed by a steady flow of studies on comorbidities of dermatologic diseases.

Psoriasis, atopic dermatitis (eczema), hidradenitis suppurativa, alopecia areata and more have been studied in relation to various extracutaneous comorbidities. Eczema, in particular, has been studied in relation to mental health and sleep disorders, cardiovascular disease and osteoporosis and fracture risk. In this article, I will review the evidence for selected adult eczema comorbidities and provide an opinion on whether each of them might change the way we manage patients. In other words, do they matter?

Sleep disorders

Large population-based studies in the US have shown that adults with eczema have three times the rates of insomnia compared with the general population.² It makes sense, then, that they also have increased rates of daytime sleepiness and fatigue. Studies have shown that this poor sleep has other consequences; namely that the combination of eczema with sleep disruption has been associated with poor self-ratings of overall health and increased rates of injury.^{2,3} These findings make sense clinically. Many of my patients with eczema report that their itch is worse at night, leading to nocturnal scratching and difficulty falling asleep, as well as nighttime awakenings. This leads to fatigue and a general sense of feeling unwell. Additionally, poor sleep and fatigue could lead to decreased concentration and an increased propensity to injury.

In short, sleep disruption in patients with eczema matters. We should ask our patients when we see them in the clinic about their sleep as a secondary measure of disease control. It is part of standardized assessments of eczema symptoms such as the Patient-Oriented Eczema Measure (POEM),⁴ but clinicians may opt instead to ask the simple question: “how has your sleep been lately?” In either case, the more formal assessment-method or the routine questioning can both help to illuminate sleep issues that may be impacting our eczema patients. The good news is that for patients whose sleep is adversely impacted by their eczema, we can help. Clinical trials have shown that when eczema is treated effectively, sleep improves as well.^{5,6}

Depression

The association between eczema and depression is one of the best established and replicated comorbidities. In a meta-analysis, atopic dermatitis was associated with twice the odds of depression compared to controls.⁷ We conducted a case-control study of the risk of suicide associated with eczema using population-based data from Ontario and found that having persistent eczema, defined as five or more physician visits for eczema within 5 years, was associated with a 20% increased risk of dying from suicide compared to the general population.⁸ Further, we found that, in the month before their death, two-thirds of eczema patients who

died from suicide had visited a physician and 13% visited a physician specifically for their skin condition.

Depression, like sleep disruption, can be thought of as a comorbidity and as a symptom of the disease itself. The constant itch and poor sleep experienced by people with severe eczema can lower mood in the absence of a clinical diagnosis of major depressive disorder. Along those lines, in clinical trials, depressive symptoms improve when eczema improves.

We should assess our patients' affect and mood in clinic, and if there is low mood, assess for risk of self-harm. This can be done informally or using validated tools like the 2-question PHQ-2.⁹ If, after this assessment, we are concerned, coordinating care with the patient's family doctor and/or directing them to emergency care may be warranted.

Cardiovascular disease

Cardiovascular disease and its risk factors are considered to be more controversial comorbidities associated with eczema. A systematic review of the association between eczema and cardiovascular disease found significant heterogeneity between studies, including cross-sectional, case-control and cohort studies, with some studies showing an increased risk and others showing a decreased risk for cardiovascular outcomes like myocardial infarction and stroke.¹⁰ A more recent meta-

analysis found that when limiting to cohort studies (the best study design for this research topic), there was an increased risk of cardiovascular outcomes associated with eczema such as an increased risk of myocardial infarction (n = 4; relative risk [RR], 1.12; 95% CI, 1.00-1.25), stroke (n = 4; RR, 1.10; 95% CI, 1.03-1.17), ischemic stroke n = 4; RR, 1.17; 95% CI, 1.14-1.20), angina (n = 2; RR, 1.18; 95% CI, 1.13-1.24), and heart failure (n = 2; RR, 1.26; 95% CI, 1.05-1.51). This same meta-analysis found that increasing atopic eczema severity was associated with increased risk of cardiovascular outcomes.¹¹ However, these observational studies all suffer from confounding and other biases, which may temper our interpretation of the results. Additionally, even in well-done cohort studies that have found an association between severe eczema and cardiovascular disease, the absolute risk has been low, on the order of 25 extra strokes per 100,000 person-years with eczema.¹²

Explanations for a potential association between eczema and cardiovascular disease include a systemic inflammatory state, decreased exercise due to the risk of eczema flares with sweating and heat and other lifestyle factors such as obesity and smoking. Eczema has been associated with increased rates of obesity and smoking, with positive associations seen in multiple meta-analyses.^{13,14} However, those associations do not correlate with my own clinical experience.

In my opinion, either eczema is not a true cardiovascular risk factor, or it is a very minor and not clinically actionable one.¹⁵ As such, I believe eczema patients should receive age-appropriate cardiovascular risk screening and treatment without any modification related to their skin disease. In patients who are overweight or who smoke, a healthy lifestyle should be encouraged independent of their eczema.

Osteoporosis and fractures

Associations between eczema and bone health are less well-studied. We conducted a systematic review (in press) and found 15 studies on the topic; unfortunately, most were cross-sectional and of poor-quality. Recently, though, a large cohort study using data from the UK was published which found eczema to be associated with an increased risk for various types of fractures commonly associated with osteoporosis, including an increased risk of hip (HR, 1.10; 99% CI, 1.06-1.14), pelvic (HR, 1.10; 99% CI, 1.02-1.19), spinal (HR, 1.18; 99% CI, 1.10-1.27), and wrist (HR, 1.07; 99% CI, 1.03-1.11) fractures.¹⁶ As with cardiovascular disease, the risk was accentuated in people with more severe eczema. Severe eczema was associated with double the risk for spinal fractures and 1.5 times the risk for hip fractures compared with the general population.

There are many potential reasons for an association between eczema and poor bone health and fractures.

Poor sleep leading to fatigue could increase the risk for injury overall. Systemic inflammation associated with severe eczema could lead to aberrant bone turnover. My suspicion is that the relationship seen with severe eczema may relate to intermittent treatment with systemic corticosteroids such as prednisone. Systemic corticosteroids, which are known to increase fracture risk, are often prescribed for eczema despite recommendations to limit their use.¹⁷

While the association between eczema and fractures is poorly understood, taking a general medical history including, history of fractures is worthwhile, as is assessing previous and current use of systemic corticosteroids. If there is a significant history of systemic steroid use, a referral for bone mineral density testing or fracture preventive treatment may be indicated.

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Comorbidity	Clinical takeaways
Sleep disorders	<ul style="list-style-type: none"> • Ask patients about the effect of eczema on their sleep • Effective treatment can improve sleep
Depression	<ul style="list-style-type: none"> • Assess patient's mood in clinic • Assess for self-harm in clinic
Cardiovascular disease	<ul style="list-style-type: none"> • No specific action required • Patients should have age-appropriate screening as in the general population
Osteoporosis and fractures	<ul style="list-style-type: none"> • Ask about history of systemic corticosteroid exposure • Refer for bone testing or fracture prevention if indicated

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