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# Psoriasis and atopic dermatitis: similarities and differences

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## ABSTRACT

*Psoriasis and atopic dermatitis (AD) are systemic inflammatory skin disorders that share many clinical characteristics and are T-cell-driven diseases, but are marked by clear pathological differences and environmental triggers. Both conditions have significant impact on patient quality of life and, therefore, demand a thorough understanding of disease burden, associated comorbidities, and treatments. In 2016, the International Psoriasis Council and the International Eczema Council held a joint symposium entitled, "Psoriasis and Atopic Dermatitis: Two Diseases or One Spectrum?" at the European Academy of Dermatology and Venereology Congress in Vienna, Austria. The symposium debated whether the diseases are on a continuum or if the evidence presented supported the classification of each disease state as a distinct entity. Presenters provided key epidemiological and clinical differences between psoriasis and atopic dermatitis and discussed immune mechanisms and the new targeted therapies for each condition. In addition, overlapping and disparate comorbidities were examined, recognizing the need to better subclassify the diseases based on underlying immunophenotype. A session dedicated to pediatric psoriasis and atopic dermatitis highlighted important gaps in knowledge and treatment challenges.*



From left to right: Matthias Augustin, Germany; Eric Simpson, United States; Carsten Flohr and Chris Griffiths, United Kingdom; Amy Paller, Emma Guttman-Yassky and James Krueger, United States; Darren Ashcroft, United Kingdom; and Thomas Bieber, Germany. Not pictured is Peter van de Kerkhof, the Netherlands.

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## Psoriasis epidemiology

The 2016 World Health Organization (WHO) global report on psoriasis recognized the disease as a common, chronic, and noncommunicable disorder and emphasized that many patients with psoriasis suffer from significant physical and mental health comorbidities.<sup>1</sup> Strong evidence demonstrates the importance of genetic susceptibility in psoriasis pathogenesis, but from an epidemiological perspective, a number of environmental risk factors trigger its onset or exacerbation, including smoking, obesity, alcohol consumption, infections, medication, and stressful life events.

Darren Ashcroft, University of Manchester, United Kingdom, described a detailed systematic review of the literature, including 53 studies that reported on the incidence and/or prevalence of psoriasis in the general population.<sup>2</sup> This review and a 2017 report published in the *British Journal of Dermatology* concluded that important gaps in knowledge of both the epidemiology and the natural history of psoriasis still exist and highlighted a number of ongoing methodological issues.<sup>3</sup>

A 2017 population-based cohort study in the United Kingdom aimed to determine trends in incidence, prevalence, and mortality of patients with psoriasis over 15 years, and examined how epidemiological factors changed over time.<sup>4</sup> The investigators observed a steady increase in prevalence over time from 2.3% (2,297 cases per 100,000) in 1999 to 2.8% (2,815 per 100,000) in 2013. The observed increase in prevalence did not appear to be attributable to changes in incidence rates. Peaks in age bands characteristic of early- and late-onset psoriasis were noted. Another interesting finding was an increase in incidence and prevalence with increasing latitude in the United Kingdom. All-cause mortality rates for the general population and for patients with psoriasis have decreased over the last 15 years. However, the risk of all-cause mortality for psoriasis remains elevated compared to people without psoriasis, and no significant change in this premature mortality gap was seen over time. This study identified an increasing population living longer with psoriasis in the United Kingdom, which has important implications for health care service delivery and resource allocation. Further understanding of the determinants of the premature mortality gap in psoriasis is required, which may help to identify modifiable targets for intervention.

## Atopic dermatitis epidemiology

In contrast to psoriasis, much more is known about the epidemiology of atopic dermatitis (AD) and, in particular, within children. Although the disease starts

in patients under 2 years of age in the majority of cases, it is the later-onset disease that is linked with higher disease persistence. Carsten Flohr, St. John's Institute of Dermatology, London, United Kingdom, described predictors of disease persistence, including severity of disease, concomitant food and respiratory allergies, and family history of atopic diseases. Much of the association with family history is due to inheritance of filaggrin skin barrier gene mutations, which increase the risk of carriers developing AD by approximately 4 times that of the general population. However, the population-attributable risk of filaggrin mutations in AD is only 10%, highlighting the importance of the environmental component in disease etiology.

The International Study of Asthma and Allergies in Childhood (ISAAC), with approximately 2 million children from more than 50 countries, demonstrated significant variations in the prevalence of AD, with >15% affected in the United Kingdom and Scandinavia, and much lower prevalence in southern European countries and developing nations in Asia, East Asia, and Africa.<sup>5</sup> ISAAC was repeated with the same methodology 5-7 years later in the same centers with children of the same ages. Where there had been a higher prevalence of AD in the first survey, there tended to be a plateauing effect. In contrast, previous low- and middle-bracket prevalence settings tended to see an increase in burden. This suggests that only those who are genetically susceptible to environmental factors will develop the disease and that environmental factors are important disease drivers.<sup>6</sup>

Cross-sectional studies found a positive association between domestic water hardness (high calcium carbonate (CaCO<sub>3</sub>) levels) and AD risk in schoolchildren.<sup>7-9</sup> More recently, high domestic water CaCO<sub>3</sub> levels were shown to be associated with a 45% increased risk of AD by 3 months of age, with stronger associations seen in those with a filaggrin mutation, thus suggesting a direct detrimental effect of hard water on skin barrier function and risk modification through filaggrin genotype.<sup>10</sup>

Climate is another important environmental factor to consider. In general, the closer to the equator, the lower the prevalence of AD.<sup>5</sup> However, ultraviolet (UV) light exposure may not have a simple linear relationship with developing AD, as some studies have reported a higher risk of AD at the extreme ends of UV exposure.<sup>11</sup>

Furthermore, hygiene-related factors have attracted research interest. Some data show that an increase in frequency of washing as well as the use of soaps and

detergents increases AD risk, potentially due to a direct detrimental effect on skin barrier function. Another potential explanation would be changes in the bacterial skin flora, as there is evidence that a reduced diversity in the bacterial microbiome of the skin predisposes to a higher risk of AD development.<sup>12</sup> There is similar evidence showing that a reduced diversity of the gut bacterial flora predicts later onset of AD, corroborated by the increased risk seen with early-life antibiotic exposure and the observation that consumption of unpasteurized cow's milk and direct contact with farm animals reduce the risk of AD development.<sup>13</sup>

Based on the above observations, the most promising preventative measures are intensive emollient application to prevent skin barrier breakdown and probiotic (*Lactobacilli* and *Bifidobacteria*) supplementation during the last trimester of pregnancy and in early life. A trial with a water softening device installed before delivery in hard-water areas is currently underway in the United Kingdom to see whether this can additionally contribute to AD prevention.

Other research has focused on the possibility of preventing AD by simple measures such as using emollients soon after birth. Two studies to date have shown this intervention to be effective in reducing the development of AD in high-risk children.<sup>14,15</sup> How to identify children who will benefit from this early intervention has yet to be defined.

### Psoriasis immune pathway

Both psoriasis and AD are immune-mediated conditions driven by specific T-cell subsets and cytokines. Dr. James Krueger, The Rockefeller University, New York, United States, reviewed evidence supporting psoriasis as a disease predominately driven by interleukin (IL) 23/T helper (Th)17 with co-activation of other T-cell subsets.<sup>16,17</sup> The discovery of the role of Th17 cells has significantly advanced our knowledge of psoriasis pathogenesis. Th17 cells are under the direction of IL-23, a dimeric cytokine. IL-23 binds to the IL-23 receptor, activates STAT3 (Signal Transducer and Activator of Transcription), and drives the IL-17 response. Psoriasis was first linked with this particular cytokine axis in 2004 in a study that used mRNA profiling to measure levels of the two IL-23 subunits, p40 and p19, in lesional and nonlesional skin of psoriasis patients.<sup>18</sup> In this study, increased expression of IL-23 p19 and p40 was found in lesional skin of patients with psoriasis. In 2006, it was found that high levels of IL-22 in psoriatic skin were associated with enhanced expression of cutaneous S100A8, S100A9, matrix metalloproteinase 1, and psoriasin (S100A7, which was previously discovered in psoriatic

scale). Gamma interferon was not associated with these increases in expression.<sup>19</sup> Subsequently, IL-17 was also found to increase expression of psoriasin.

In addition to these cytokine pathways, co-activation of multiple immune axes contributes to a more complex pathogenic pathway in psoriasis. Myeloid dendritic cells produce high levels of IL-12 and IL-23, which drive a number of T-cell axes (Th1, Th17, Th22). The primary cytokines activate transcription factors in keratinocytes (including STAT1, STAT3, and CEBP/NFκB), which amplify an immune response and create other inflammatory molecules.<sup>16</sup>

Specific antagonists to IL-17 and IL-23 have been developed. Ixekizumab and secukinumab are both monoclonal antibodies to IL-17A, and brodalumab is an anti-IL-17 receptor antibody. Currently, these IL-17 inhibitors are approved for the treatment of moderate to severe psoriasis in the United States and Europe, and have demonstrated superiority against older agents, including ustekinumab and etanercept, in psoriasis treatment.<sup>20-22</sup>

The first in-human, proof-of-concept study that supported a central role for IL-23 in psoriasis was published in 2015. The clinical and biological effects of risankizumab (BI 655066), a monoclonal antibody specific to the p19 subunit of IL-23, were evaluated in patients with moderate to severe plaque psoriasis. At the 12-week primary endpoint, 87% of patients had achieved a Psoriasis Area Severity Index (PASI) 75 response in comparison with no patients in the placebo group ( $p < 0.01$ ). Further improvements were noted beyond the primary endpoint.<sup>23</sup> Following this, guselkumab and tildrakizumab have demonstrated excellent efficacy in phase 2 studies.<sup>24,25</sup> The first anti-IL-23 agent, guselkumab, is approved for the treatment of psoriasis in the United States and Europe.<sup>26,27</sup> Tildrakizumab is also approved for the treatment of psoriasis in the United States and Europe; risankizumab has recently received approval in Japan while approval is pending the United States and Europe. The increased understanding of disease-specific immune pathways in psoriasis has spurred the development of highly effective pathway-targeted therapeutics in recent years, with psoriasis now representing the most effectively-treated human autoimmune disease.<sup>28,29</sup>

### Atopic dermatitis immune pathway

Dr. Emma Guttman-Yassky, Mount Sinai Medical Center, New York, United States, described the recent paradigm shift in the pathogenesis of AD, which has very important implications for treatment.<sup>30</sup> The spectrum of AD

phenotypes (intrinsic AD, Asian AD, pediatric AD, and European-American AD) is driven by multiple immune pathways;<sup>17</sup> however, Th2 and Th22 cells are activated across all phenotypes. In AD, Th2 cytokines include IL-4 and IL-13, which have been shown in vitro to inhibit antimicrobial peptide and disrupt the skin barrier with reduction of filaggrin, loricrin, involucrin, lipids, and many other markers. IL-22, which has been linked to epidermal hyperproliferation, also disrupts the skin barrier and, together with IL-17, results in an increase in S100.<sup>30,31</sup> The itch cytokine IL-31 is also implicated in AD and contributes to the development of the itch-scratch lichenification cycle. There is an intensification of cytokine effects in the disease's chronic stage.

This immune hypothesis was tested in a phase 1b study using dupilumab, a specific immune antagonist targeting IL-4 receptor alpha ( $\alpha$ ) which inhibits both IL-4 and IL-13, in 67 patients with moderate to severe AD.<sup>32</sup> At 4 weeks, 71.4% of patients receiving 300 mg dupilumab weekly achieved a 50% reduction in Eczema Area and Severity Index (EASI 50).<sup>32</sup> Importantly, there were no differences in responses between patients who had increased IgE and patients who had filaggrin mutations. Dupilumab has been shown to be effective in pivotal phase 3 trials, including with long-term treatment, and is now approved for the treatment of AD in the United States and Europe. In mechanistic studies using skin biopsies, dupilumab was found to significantly reduce epidermal hyperplasia, as measured by expression of KRT16 (encoding keratin 16) in a dose-dependent manner after only 4 weeks of treatment, with placebo found to exacerbate epidermal hyperplasia.<sup>32,33</sup> Dupilumab 300 mg resulted in downregulation of the mRNA expression of not only Th2 markers, but also of Th17/IL-23 and Th22 markers, including elafin, IL-23p19 and p40, IL-17A, S100A8/9/12 and several others that may be involved in epidermal proliferation and inflammation.<sup>33</sup> Global gene expression studies of lesional skin demonstrated significant downregulation of inflammatory genes with 300 mg of dupilumab. Together, the clinical and expression studies establish IL-4 and IL-13 as pathogenic cytokines in AD, and add to the evidence that AD is a reversible, immune-driven disease.<sup>32,33</sup>

Both AD and psoriasis are characterized by T-cell activation in the skin. However, their comparable systemic T-cell activation has been unclear until recently, when it was demonstrated that patients with AD have excessive systemic activation among central and effector CD4+ and CD8+ CLA+ and CLA- memory subsets ( $p < 0.01$ ) compared with both patients with psoriasis and controls.<sup>34</sup> This may

represent why marked increases in cytokine activation are observed in nonlesional skin of patients with AD.<sup>35</sup> These findings may suggest the need for systemic treatment approaches for severe AD patients.

### Classical therapies and pathogenesis-based treatment

Professor Peter CM van de Kerkhof, Radboud University, Nijmegen, the Netherlands, and Professor Thomas Bieber, University of Bonn, Germany, reviewed classical and targeted treatment modalities for psoriasis and AD (Table 1). The major unmet need in the majority of patients treated with conventional systemic agents is long-term, safe control of disease. Targeted immunosuppressive agents may be contraindicated in some patients, for example, in malignancy, and some of the older systemic treatments still play an important role in these patients who are unsuitable for newer biologic agents. Professor van de Kerkhof emphasized that treatment decisions should be made on an individual basis, taking into account a patient's clinical characteristics of disease as well as comorbidities.

The advent of biologic agents such as tumor necrosis factor (TNF) $\alpha$  inhibitors and ustekinumab have revolutionized the treatment of psoriasis, providing long-term, safe control of the disease. With increased knowledge of the molecular pathways of psoriasis, more targeted therapies have been developed, including the anti-IL-17 and anti-IL-23 agents. Additionally, inhibition of inflammatory response can be achieved by oral therapies, such as apremilast (selective inhibitor of phosphodiesterase-4) and a new class of inhibitors, currently being evaluated for psoriasis and AD, that target the janus kinases (JAK inhibitors). Although AD lags behind psoriasis in terms of translational research, the recent approval of dupilumab has advanced treatment for adults and adolescent patients.

### Psoriasis comorbidities

Professor Matthias Augustin, University Clinics of Hamburg, Germany, reviewed common and emerging psoriasis comorbidities. Table 2 lists psoriasis-associated comorbidities, including psoriatic arthritis, which occurs in approximately one-third of patients with psoriasis. There is a substantial number of studies on comorbidities in psoriasis, but the impact of screening on long-term outcomes has not been published to date. Comorbidities add significantly to the resource utilization and economic burden associated with psoriasis.<sup>36</sup> Some of the emerging comorbidities include celiac disease, erectile dysfunction,

**Table 1. Classical treatments and innovative therapies for psoriasis and atopic dermatitis**

	Psoriasis	Atopic dermatitis
<b>Basis therapy</b>	Emollients	Emollients
<b>Topical anti-inflammatory therapy</b>	Dithranol Coal tar TCS TCI* Vitamin D3 Tazarotene	Crisaborole Coal tar TCS TCI
<b>UV therapy</b>	UVB 311nm PUVA	UVA UVB 311nm
<b>Systemic retinoids</b>	Acitretin	Alitretinoin**
<b>Immunosuppressors</b>	Methotrexate Cyclosporin	Methotrexate Cyclosporin Azathioprine MMF
<b>Oral treatments</b>	Fumaric acid esters Apremilast	
<b>Biologic agents</b>	Etanercept Adalimumab Infliximab Ustekinumab Secukinumab Ixekizumab Brodalumab Guselkumab Certolizumab pegol Tildrakizumab Risankizumab	Dupilumab

\*for face/flexures, \*\* for hand dermatitis, TCS – topical corticosteroids, TCI – topical calcineurin inhibitors, MMF – mycophenolate mofetil

**Table 2. Comorbidities**

	Psoriasis	Atopic dermatitis
<b>Well-established comorbidities</b>	Psoriatic arthritis Cardiovascular disease Metabolic syndrome Hypertension Obesity Anxiety/depression Diabetes Dyslipidemia Smoking Alcoholism Inflammatory bowel disease	Allergic rhinitis Bronchial asthma Allergic conjunctivitis Food allergy ADHD Depression/anxiety Autism Infection: <ul style="list-style-type: none"> <li>• Eczema herpeticum</li> <li>• Bacterial (most commonly <i>S. aureus</i>)</li> <li>• Viral warts</li> <li>• Eczema vaccinatum</li> <li>• Eczema coxsackium</li> <li>• Molluscum contagiosum</li> </ul>
<b>Emerging comorbidities</b>	Coeliac disease <sup>37</sup> Erectile dysfunction <sup>37</sup> Parkinson's disease <sup>37</sup> Osteoporosis <sup>37</sup> COPD <sup>38</sup> MS <sup>39</sup> Uveitis <sup>40</sup> Migraine <sup>41</sup> AAA <sup>42</sup>	Obesity <sup>75</sup> Alopecia areata <sup>78</sup> Vitiligo <sup>78</sup> Rheumatoid arthritis <sup>77</sup> Inflammatory bowel disease <sup>77</sup>

COPD – chronic obstructive pulmonary disease, MS – multiple sclerosis, AAA – abdominal aortic aneurysm, ADHD – attention deficit hyperactivity disorder

Parkinson's disease, osteoporosis, and chronic obstructive pulmonary disease (COPD). A meta-analysis has shown that patients with psoriasis are at a greater risk of developing COPD than the general population (OR, 1.90; 95% CI, 1.36-2.65) and this risk is stronger among patients with severe psoriasis (OR, 2.15; 95% CI 1.26-3.67).<sup>38</sup> It has also been demonstrated that psoriasis may confer a disease-severity-dependent risk of multiple sclerosis,<sup>39</sup> uveitis,<sup>40</sup> migraine,<sup>41</sup> and abdominal aortic aneurysms.<sup>42</sup>

Available data on psoriasis comorbidities need to be interpreted with some caution. A variety of sources has been used to collect these data. Several approaches have been adopted to assess psoriasis severity, which may have resulted in patients being incorrectly classified. The use of surrogate parameters as opposed to clinical data can lead to substantial bias, and patient-level validation studies on the large databases used for psoriasis comorbidity research have not yet been published.

### Atopic dermatitis comorbidities

Professor Eric Simpson, Oregon Health and Science University, Portland, Oregon, United States, highlighted the high rate of sensitization and clinical allergy in pediatric and adult AD. Approximately 80% of patients with AD at various ages are sensitized by IgE. Of interest, IgE sensitization is not unique to atopic diseases – one study examining sensitization in psoriasis showed 44% of psoriasis patients exhibiting sensitivity to IgE.<sup>43</sup> A large collaborative analysis of European birth cohorts found IgE sensitization explained only 38% of allergic comorbidity, adding further evidence that IgE is not the causal link between atopic diseases but likely is a marker of type 2 immune dysfunction.

Population-based studies reveal 15.9% of children are reported to have clinically relevant food allergy by the age of 4.<sup>44</sup> Limited data are available on food allergy in adults, with one small, single-center study reporting clinically relevant food allergy in 51.8% of adults with mild to moderate AD, and in 58.6% of adults with severe AD.<sup>45</sup>

Significant atopic comorbidity has been observed in adult patients with AD recruited for clinical trials, with one trial reporting asthma in 40.3% of patients, allergic rhinitis in 51.3%, and allergic conjunctivitis in 24.2%.<sup>46</sup> The prevalence of comorbidity in AD is known to correlate with skin severity, and clinical trial data likely reflect a cohort of patients with more severe disease.

*Staphylococcus aureus* is a common cause of infection in AD. Colonization with *S. aureus* also appears to be

increased in psoriasis, although the clinical relevance of this is unknown.<sup>47</sup> Skin barrier dysfunction, Th2-mediated inhibition of antimicrobial peptides, and immunological dysfunction are thought to explain the infection susceptibility.

Finally, an important question in the field is whether comorbidities can be prevented in patients with AD. It is not known whether aggressive treatment modifies the risk for developing it. In infants with severe AD, food allergy guidelines from the National Institute of Allergy and Infectious Diseases (NIAID) recommend early introduction of peanuts at 4-6 months of age to prevent the development of peanut allergy.<sup>48</sup> Results from the Learning Early About Peanut Allergy (LEAP) study found marked decreases in peanut allergy at 5 years of age in children fed peanut protein early in life compared to delayed introduction.<sup>49</sup> There are no generally accepted strategies for the prevention of asthma or allergic rhinitis in children with AD.

### Pediatrics: diagnosis, phenotypes, and translating from adults

A special section dedicated to pediatric psoriasis and pediatric AD was presented by Professor Amy S. Paller, Northwestern University, Chicago, Illinois, United States. Children generally present with typical features of psoriasis, but may also exhibit atypical clinical features, especially including some signs of dermatitis (Table 3). Hence, psoriasis can pose a diagnostic challenge in children. Presentation of AD in children is more straightforward, although there are differences in distribution between children and adults.

### Epidemiology

In the pediatric population, psoriasis is primarily a disorder of adolescents with 0.1-0.5% affected before puberty and 0.6-1.3% after puberty.<sup>50</sup> In AD, onset is primarily in infants and young children, with 10-20% of children affected with AD, and 90% developing disease under age 5. Both AD and psoriasis have increased in incidence in children by 2- to 3-fold in the past 30 years, with a parallel increase in asthma, allergic rhinitis, and food allergies.<sup>6,51</sup> Environmental triggers may include reduced exposure to organisms for AD (especially in industrialized countries), but potential drivers for both diseases are increases in psychosocial stress, obesity, and, perhaps, infections.<sup>52,53</sup>

### Pathomechanism

Although all studies have been performed in adult psoriatic skin, it is presumed that pediatric psoriasis is similarly

**Table 3. Pediatric psoriasis and atopic dermatitis**

	Psoriasis	Atopic dermatitis
<b>Clinical features</b>	Thinner scale, indistinct borders, more facial involvement, diaper area involvement; guttate more common following streptococci infection	Young children: cheek, chin, trunk involvement, significant exudation; older children: exhibit periorbital, perioral, neck, flexural, hand and foot involvement, and more lichenification associated with chronicity
<b>Epidemiology and natural history</b>	Disorder of adolescents, with 0.1-0.5% affected before puberty and 0.6-1.3% after puberty	Primarily onset in infancy and young children, with 10-20% of children overall affected and 90% developing disease under the age of 5
<b>Environmental triggers</b>	Psychosocial stress, obesity, and infections	Reduced exposure to organisms especially in industrialized countries; psychosocial stress, obesity, and infections
<b>Disease severity</b>	Majority of children with psoriasis have mild disease	Percentage of children with moderate to severe AD increases with age
<b>Pathomechanism</b>	Pediatric psoriasis is driven by the Th17/IL-23 pathway based on responses to therapy	Th2 and Th22 pathways; children, in contrast with adults, show significantly higher induction of Th17-related cytokines, antimicrobial peptides, and innate markers than adults with AD; only Th2 CLA+ CD4+ T cells are increased in early pediatric AD blood
<b>Comorbidities</b>	Arthritis, obesity, Crohn's disease, and early signs of cardiovascular comorbidities	Food allergy, asthma, allergic rhinoconjunctivitis, ADHD, including <i>S. aureus</i> infections, herpes virus, and molluscum; also, an increase in infections of non-cutaneous sites
<b>Quality of life</b>	Risk of depression, anxiety, and bipolar disorder	Risk of depression and anxiety, conduct disorder and autism, ADHD

driven by the Th17/IL-23 pathway, based on responses to therapy. A recent study aimed to identify differences between early onset AD in children and the chronic version of the disease in adults. It showed comparable Th2 activation in both pediatric and adult AD in blood.<sup>54</sup> However, in pediatric AD, the Th2 imbalance was confined to skin homing/CLA+ T cells and did not extend to CD8+ T cells, whereas, in adults, Th2 activation extended into systemic/CLA- T cells and CD8+ T cells. Th1, Th22, Th17, or Th9 subset expansion was not identified in the blood of children with AD.<sup>34</sup>

Lesional skin in children showed comparable or greater epidermal hyperplasia and cellular infiltration than adults with AD.<sup>55</sup> Similar to adults, strong activation of the Th2 and Th22 axes occurred. There was a higher level of Th1 activation in adult AD. Children demonstrated stronger induction of Th17-related cytokines and antimicrobials, Th9/IL9, IL-33, and innate markers than adults ( $p < 0.02$ ). Nonlesional skin in pediatric patients showed higher levels of inflammation and epidermal proliferation markers when compared to adults ( $p < 0.001$ ). IL-9 and IL-33 increased in pediatric but not in adult AD. These cytokines are also associated with peanut and mite sensitization and food allergy in healthy children and pediatric AD. Surprisingly,

flaggrin gene and protein expression was similar in children with AD and healthy children.

### Comorbidities

In the US population, 10% of children with psoriasis have arthritis, with a lower prevalence in Europe. Other comorbidities observed in children include obesity, Crohn's disease, and early signs of cardiovascular comorbidities (Table 3).<sup>51</sup> One study showed that the risk of obesity was proportional to disease severity and that children with mild disease also have an increased odds ratio of being obese,<sup>56</sup> although in general the extent of excess adiposity is related to disease severity.<sup>57</sup> Another study showed that excess adiposity precedes the onset of psoriasis by at least 2 years in 93% of children with psoriasis.<sup>58</sup> Children with moderate to severe psoriasis have a high waist circumference percentile and waist-to-height ratio, which is one of the important criteria for metabolic disease.<sup>56</sup> In addition, despite comparable traditional lipid values, children with pediatric psoriasis had lipid functional abnormalities, with higher apolipoprotein B concentrations, decreased large high-density lipoprotein particles, and reduced cholesterol efflux capacity in comparison to controls and consistent with a more atherogenic cardiometabolic risk profile.<sup>59</sup> However, the

overall cardiovascular risk profile of children with psoriasis remains to be fully characterized.

Not only are children with psoriasis at increased risk of developing Crohn's disease, but children with established Crohn's disease receiving TNF- $\alpha$  inhibitors often develop a psoriasiform dermatitis. In one prospective study of 64 children undergoing infliximab therapy, 55% developed psoriatic reactions, half of which were considered severe.<sup>60</sup> Interestingly, this risk of developing psoriasiform disease tends to correlate with good control of the underlying bowel disease.

### Quality of life/mental health

Children with psoriasis and children with atopic dermatitis have poorer quality of life than patients with epilepsy, enuresis, or diabetes.<sup>61</sup> A number of studies have shown an increased risk of depression in pediatric psoriasis,<sup>62</sup> anxiety, and bipolar disease.<sup>63</sup> In AD, pediatric patients exhibit similarly increased risks of depression and anxiety, but also of conduct disorder and autism, with a severity-dependent relationship observed between the prevalence of a mental health disorder and the reported severity of skin disease.<sup>64</sup> There is now an established association between AD and attention deficit hyperactivity disorder (ADHD), with the strongest association observed in patients with severe AD.<sup>65-68</sup>

### Treatment

Both psoriasis and AD are primarily treated with topical corticosteroids, although more potent topical steroids are required to achieve disease suppression in psoriasis than in AD.<sup>69</sup> In Europe, cyclosporin (43%), steroids (31%) and azathioprine (22%) are the most commonly used first-line agents for AD.<sup>70</sup> In the United States and Canada, the most commonly used first-line agents include cyclosporin (45%), methotrexate (30%) and mycophenolate mofetil (13%).<sup>71</sup> In an international retrospective chart review investigating the use of systemic agents in treating pediatric psoriasis, methotrexate was the most commonly used systemic agent (69%) and etanercept the most commonly used biologic agent (19%).<sup>72</sup> There are few controlled trials in the pediatric population; however, growing evidence has demonstrated safe and effective treatment with adalimumab<sup>73</sup> and ustekinumab of children and adolescents with moderate to severe psoriasis.<sup>74</sup>

### Conclusion

In summary, psoriasis and AD are systemic diseases characterized by large infiltrates of T cells and dendritic cells, with associated upregulation of cytokines. However,

the pattern of cytokine upregulation is different. Unlike psoriasis, the AD phenotype cannot be explained by a single cytokine pathway. The targeting of specific pathways by small molecules and biologics have advanced management for both psoriasis and AD.

Dermatologists should screen patients for disease-modifying factors and comorbidities in an effort to detect concomitant diseases at an early stage and to allow initiation of treatment where necessary. With the development of targeted therapies, the long-term safe control of psoriasis has been improved. In particular for pediatric disease, a prospective registry is needed, which would allow collection of safety and efficacy data across a wide variety of systemic medications for both diseases. Ultimately, treatment of these inflammatory disorders is best achieved through a personalized approach, in which patients are endotyped, allowing prediction of course, relevant disease-modifying factors, and optimal individualized management.

The questions as to where similarities end and differences begin require comparative studies in both psoriasis and AD. The present overview indicates similarities, but, at the same time, we realize that the information is fragmentary and study designs have been entirely different. Comparative studies between the two diseases will yield important new information.

Epidemiological studies in psoriasis and AD revealed that disease expressions during life vary considerably. For both diseases, prevalence varies among different countries. In AD, epidemiological research has been focused on disease-modifying factors, whereas this information still is sparse in psoriasis.

In both psoriasis and AD, IL-17 and IL-22 are increased. These cytokines seem to represent common pathways in the pathogenesis of both diseases. However, IL-4 and IL-13 signaling are highly relevant to AD, whereas activation of myeloid dendritic cells appear to drive T-cell activation in psoriasis. Comparative studies on pathogenesis of these two diseases will provide further insights in common trunks and disease-specific factors. Both are immune-mediated conditions driven by specific T-cell subsets and cytokines.

From the therapeutic point of view, several treatments are effective in both diseases: corticosteroids, coal tar, phototherapy, cyclosporin, methotrexate, apremilast, and janus kinase inhibitors. Psoriasis-selective treatments are dithranol, retinoids, dimethylfumarate, and anti-TNF agents.

An AD selective treatment is duplidumab. Anti-IL-23 and

anti-IL-17 treatments have been approved for treating psoriasis. At present, it is remotely possible that these approaches have value in the treatment of AD.

Studies so far show that comorbidities in psoriasis and AD are highly different. In psoriasis, arthritis, metabolic syndrome, cardiovascular disease, depression and sleep disorders, and inflammatory bowel disease are well established. In AD, these comorbidities have not been reported, but comorbidities of atopic syndrome are well established. A striking difference is bacterial infection of the skin – frequent in AD and sparse in psoriasis.

In pediatric dermatology, the increased frequency over the last 30 years of both psoriasis and AD suggests common disease-modifying factors in childhood. Pathogenetic principles in children show differences when compared to adult AD, and the same may be true for psoriasis. Therefore, comparative studies in childhood AD vs psoriasis are worthwhile. Studies in pediatric psoriasis indicate that the above-mentioned comorbidities are already relevant in childhood. Evidence is accumulating that metabolic syndrome may even develop before psoriasis is overt. In both diseases, quality of life is impaired, although the diseases may differ with respect to psychiatric comorbidities. In both psoriasis and AD, most treatments are off label. However, etanercept, adalimumab, and ustekinumab have a label for pediatric psoriasis. In both conditions, active intervention at childhood is needed and innovative treatments need to be investigated in children with these inflammatory skin diseases.

The International Eczema Council and the International Psoriasis Council state that comparative investigations between psoriasis and atopic dermatitis will be relevant for insights into pathogenesis, morbidity, comorbidities, and therapeutic approaches. ■

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