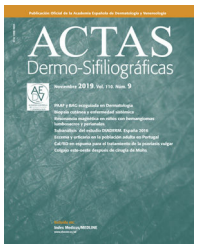
Actas Dermosifiliogr. 2020;111(6):481–486

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



CONTROVERSIES IN DERMATOLOGY

Comorbidities in Atopic Dermatitis: An Update and Review of Controversies☆

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Received 1 January 2020; accepted 21 April 2020
Available online 15 July 2020

KEYWORDS
Atopic dermatitis;
Comorbidity;
Cardiovascular system;
Malignancy;
Inflammation;
Obesity

Abstract Early onset of atopic dermatitis is considered a risk factor for any atopic disease, especially when the skin manifestations are persistent, and there is sensitization to multiple allergens and a family history. Atopic dermatitis is also thought to exert a synergistic effect with inflammation present in other organs and systems, as is the case in other immune-mediated inflammatory diseases. Most studies show a statistical relationship between obesity, various cardiometabolic comorbid conditions, and atopic dermatitis; this relationship is more marked when the disease is more severe or active over a longer period of time. However, other than epidemiological assessments, few studies provide in-depth evidence of functional mechanisms. Furthermore, various confounders, such as deterioration of quality of life and the psychological aspects of atopic dermatitis, could favor unhealthy habits, including a sedentary lifestyle and smoking, which could in turn increase the risk of morbidity and mortality. Chronic inflammation with differentiation toward a type 2 helper T cell pattern and the long-term use of immunosuppressants could be risk factors for some hematologic diseases, although they could exert a protective effect in some solid cancers. The presence of proinflammatory cytokines capable of crossing the blood-brain barrier could favor an increase in the frequency of psychological diseases (eg, depression, anxiety, and suicidal ideation) and attention disorders (eg, attention deficit or hyperactivity). However, other factors, such as chronic pruritus and sleep disorders, could also play roles.
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☆ Please cite this article as: Carrascosa JM, Morillas-Lahuerta V. Comorbilidades en dermatitis atópica: actualización y controversias. Actas Dermosifiliogr. 2020;111:481–486.

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PALABRAS CLAVE
Dermatitis atópica;
Comorbilidades;
Cardiovascular;
Neoplasia;
Inflamación;
Obesidad

Comorbilidades en dermatitis atópica: actualización y controversias

Resumen El desarrollo de dermatitis atópica (DA) precoz se considera un factor de riesgo para cualquier enfermedad atópica, especialmente cuando las manifestaciones cutáneas son persistentes y se acompañan de multisensibilización y de historia familiar. Se ha propuesto que la DA pueda tener también efectos sinérgicos con la inflamación presente en otros órganos y sistemas, tal y como ocurre en otras enfermedades inflamatorias inmunomediadas. La mayor parte de estudios permiten comprobar una relación estadística entre la obesidad, diversas comorbilidades cardiometabólicas y la DA, siendo mayor en aquellos pacientes con enfermedad más grave o activa durante un mayor periodo de tiempo. Existen, sin embargo, escasos estudios más allá de evaluaciones epidemiológicas que ahonden en evidencias funcionales. Por otro lado, existen numerosos factores de confusión, tales como el deterioro de la calidad de vida y la afectación psicológica asociadas a la DA que podrían favorecer hábitos poco saludables, incluyendo sedentarismo o tabaquismo, lo que a su vez incrementaría el riesgo de morbimortalidad. La inflamación crónica con una diferenciación hacia un patrón Th2 y el uso de fármacos inmunosupresores de forma prolongada pueden ser un factor de riesgo para el desarrollo de algunas enfermedades hematológicas, aunque puede representar un factor protector para algunos tumores sólidos. La presencia de citocinas proinflamatorias capaces de atravesar la barrera hematoencefálica podría facilitar un incremento de enfermedades psicológicas tales como la depresión, la ansiedad, la ideación suicida o los trastornos de la atención en forma de déficit de atención o hiperactividad. Sin embargo, pueden influir también otros factores como el prurito crónico o los trastornos del sueño.
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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects approximately 4% of the population in our setting.[1]

The pathogenesis of AD is based on both an abnormal barrier function and a distorted immune response. The ability of drugs that act on key parts of the inflammatory process, i.e., the normalization not only of the process itself but also of structural elements, such as the skin barrier, lead us to propose that the underlying cause of AD is dysfunction of the immune system, with a tendency toward an exaggerated type 2 helper T (T_H2) response, which plays a key pathogenic role in this disease.[2] Furthermore, there is evidence that the immunological abnormalities of atopic disease reach far beyond the affected skin, with reports that the unaffected skin has up to 17% more inflammatory infiltrate than expected in healthy skin, as well as overexpression of cytokines of the T_H2 pattern (interleukin [IL] 13) or T_H22 pattern (IL-22).[3] Furthermore, activation of the circulating T cells $CD4^+$ and $CD8^+$ is more pronounced than observed in psoriasis, with serum levels of IL-4/IL-13 that correlate with the severity of the disease (according to SCORing Atopic Dermatitis tool).[4] In addition, several biomarkers that may be correlated with disease activity, e.g., alarmins (IL-33 or IL-25 or thymic stromal lymphopoietin), are present in peripheral blood.[5]

Therefore, we have a theoretical basis that could explain the impact of maintained systemic inflammation on other organs and systems in the form of comorbidities.[6] However, it remains to be seen whether there is firm evidence for this association and, in particular, what the clinical consequences might be.[7]

Atopic Comorbidities

AD is the atopic manifestation that precedes the development of other processes considered to be within the scope of atopic status, including food allergies, asthma, and allergic rhinoconjunctivitis, a sequence that has been termed the ''atopic march''.[8] Eosinophilic esophagitis is a T_H2-type comorbid condition that is increasingly diagnosed. It can present in both childhood and adulthood. The most common presentations in children are gastroesophageal reflux and vomiting, whereas in adults, dysphagia and abdominal pain are more common. Endoscopy reveals the presence of rings, exudate, and edema. The definitive diagnosis is based on histology, with the presence of eosinophil-rich inflammatory tissue.[9]

Early AD is considered a risk factor for any atopic disease, especially when the skin manifestations are persistent and are accompanied by multiple sensitization and a family history. Progression of AD to food allergy, particularly peanut allergy, is associated with multiple sensitization and development of bronchial asthma.[10] This association allows us to suggest that abnormal barrier function in patients with AD increases the risk of sensitization to food and inhaled allergens. The presence of mutations in the filaggrin gene increases the potential for sensitization via the skin and predisposes to the atopic march, a circumstance that reinforces impairment of the barrier function in this process.

In terms of pathogenesis, the appearance of the allergen favors activation of the immune system and development of atopic disease. In fact, improvement in barrier function resulting from early use of emollients in neonates could reduce by up to 50% the probability of developing AD and other atopic comorbid conditions from age 6 months onward.

However, in recent years, the validity of the atopic march as a paradigm capable of explaining the progress of the disease in most persons with AD has been criticized. Thus, only a small percentage of atopic children (3%) follow the complete sequence reported for the atopic march, especially those with more severe forms of skin disease.[11]

An alternative, or complementary, explanation for the atopic march would be justified by a predisposition to presenting more than 1 element within the constellation of atopic processes owing to, for example, the fact of sharing genetic loci or environmental exposure. Thus, the sequence of atopic processes observed in clinical practice could reflect more the peak of occurrence of the various processes—albeit with a different temporal progression—than a causal association. This new perspective would enable us to view atopic processes more as a cluster than as the outcome of disease progression.[12]

Nonatopic Comorbidities

An eventual association between AD and comorbid conditions could come about because of the presence of common genes that entail a risk of developing them. However, some meta-analyses performed in this area were unable to demonstrate a robust association between cardiovascular risk and the several variants of AD, although they were able to show an association for signaling in atherosclerosis. Alternatively, AD has been thought to be able to induce effects beyond the skin or to have synergistic effects with inflammation in other organs and systems, as proposed for the synergistic effects of inflammation on other immune-mediated inflammatory diseases. Below, we present a few—still controversial—examples of the association between AD and various comorbid conditions.[13]

Atopic Dermatitis and Obesity

While some results are contradictory, most studies reveal a statistically significant relationship between obesity and atopic dermatitis.[14]

A recent meta-analysis of 45 studies and 90 000 patients with AD showed that in most cases, obesity was positively associated with AD. Obese and/or overweight patients—both children and adults—also have higher rates of AD. In children, a greater prevalence of overweight, obesity, and dyslipidemia has been observed both in children aged 0-2 years and in adolescents aged 12-14 years.[15] However, some studies have shown how this association remained statistically significant in Asia and North America, but not in Europe. This observation allows us to suggest the implication of phenotypic differences and of differences associated with diet in both populations, beyond the role of the inflammatory process. While they vary widely depending on the study, in one meta-analysis, the OR for obesity in AD was calculated to be around 1.47 (1.21-1.79).[13]

The association between AD and obesity may already be evident in childhood. A Norwegian study found an association between AD and overweight for height at recruitment and after 2 years, but not at birth. Based on questionnaires from the American national health system for 13 275 children aged 0 to 17 years, Silberman[16] detected an OR (95% CI) of 1.61 (1.32-1.97) for having a body mass index (BMI) $\geq$ 50% and of 1.46 (1.15-1.86) for a BMI $\geq$ 95% in all patients with AD. This probability was even greater if the analysis was limited to those persons with moderate and severe forms of AD for a BMI $\geq$ 50% (2.46 [1.73-3.51]) and $\geq$ 95% (2.95 [1.73-3.51]). Using a Korean database of 53 769 adolescents (Korea Youth Risk Behavior Web-based Survey [KYRBWS]), Lim et al.[14] observed that individuals with AD were more frequently overweight, spent more time sitting for study or leisure, had a greater incidence of smoking, and slept less.

Atopic Dermatitis and Cardiovascular Comorbidity

Studies performed in the USA and Europe have shown a positive association between AD and cardiovascular comorbid conditions. This association is greater in patients with more severe AD and/or longer-term involvement.[17] In a study performed in Taiwan, Su et al.[18] compared 20 323 patients with DA with 20 323 controls and found an OR of 1.33 (95% CI, 1.12-1.59; $P = .001$) for ischemic stroke in the former. The adjusted probabilities for patients with mild, moderate, and severe forms were 1.20 (95% CI, 1.00-1.45; $P = .052$), 1.64 (95% CI, 1.23-2.19; $P = .001$), and 1.71 (95% CI, 1.15-2.56; $P = .008$), respectively. In contrast, in an open study of a cohort of 78 702 American nurses, of whom 10% were diagnosed with AD, no association was found between AD and acute myocardial infarction in the multivariate analysis adjusted for hypertension, hypercholesterolemia, and diabetes. In addition, the clinical implications may be unclear. In this sense, a study performed in Germany found that AD was associated with an increased risk of angina, hypertension, and peripheral arterial disease, but not with an increased risk of infarction or stroke.[19]

However, few studies other than epidemiological evaluations perform an in-depth analysis of functional evidence in AD and cardiovascular disease. One example can be found in the study by Hjuler et al.,[17] who showed that, in patients evaluated using computed tomography angiography, the prevalence of calcium in the coronary arteries was greater in patients with AD, even with respect to psoriasis and controls (45.2% vs. 29.8% in psoriasis and 15.2% in controls). In the same study, AD was more frequently associated with mild involvement of a vessel (40.7% vs. 9.1% controls; $P = .005$).

In any case, the low relevance of the results or even contradictory results make us think and lead us to rule out eventual confounders with respect to AD and cardiovascular disease.

In this sense, a Danish study whose objective was to evaluate the whole population (more than 5 million inhabitants) found that patients with severe atopic dermatitis had a greater risk of stroke and cardiovascular death. However, after adjusting for socioeconomic status, smoking, comorbidities, and use of medication, the association lost its statistical significance (increased risk of stroke in patients with severe AD in models adjusted for sex and age [1.51, 1.08-2.10], but not in models with all variables controlled for [1.19, 0.85-1.65]; increased risk of cardiovascular death in severe AD in models adjusted for sex and age [1.53, 1.23-1.91], but not in models with all the variables controlled for [1.17, 0.94-1.46]). In fact, and somewhat paradoxically,

the authors observed a reduction in the frequency of cardiovascular events in patients with mild AD, which they considered as being potentially associated with socioeconomic level and better adherence to therapy in this group.[20] In a population-based study of more than 250 000 inhabitants in Canada, Drucker et al.[21] found no association between AD and hypertension, type II diabetes mellitus, acute myocardial infarction, and stroke; in fact, even the OR was lower in these patients than in the healthy population (OR, 0.87 [95% CI, 0.83-0.90], 0.78 [95% CI, 0.71-0.84], 0.87 [95% CI, 0.75-1.00], and 0.79 [95% CI, 0.66-0.95], for hypertension, diabetes, myocardial infarction, and stroke, respectively).

As possible confounders, impaired quality of life and psychological involvement associated with AD could favor unhealthy habits, including sedentary lifestyle and smoking, which would in turn increase the risk of morbidity and mortality.[22] Andersen et al.[23] concluded that it was unlikely that AD itself was an independent factor for cardiometabolic disease and considered that the differences between the studies could be due to difficulties and limitations in the classification of AD, as well as to interference of the disease in physical activity, body weight, and the use of corticosteroids and ciclosporin in treatment.

The relationship between AD and diabetes is also controversial.[24] A Danish study revealed that patients with type 2 diabetes mellitus had higher rates of mutations in the filaggrin gene, which is a common finding in patients with AD.[25]

Multivariate studies found an association between type 2 diabetes and AD, although they also frequently identified confounders such as age, smoking, alcohol consumption, and corticosteroids (both systemic and topical). Thus, an increased frequency of adult-onset diabetes mellitus has been reported (OR, 1.41 [1.18-1.68]), although this is attenuated after adjustment for sociodemographic factors (1.41 [1.18-1.68]).[26]

Atopic Dermatitis and Cancer

In their systematic review and meta-analysis, Legendre et al.[27] reported a slight increase in the risk of lymphoma, with a relative risk (RR) of 1.43 (95% CI, 1.12-1.81). This risk was very similar to that reported by Rafig et al.[28] in a case-control study in which a previous history of allergic disease or eczema was associated with an increased risk (OR) of Hodgkin lymphoma of 1.4, which reached 6.18 (95% CI, 3.04-12.57) in the case of an association with immunosuppression. It is generally considered that disease severity, chronic inflammation with differentiation toward a T_H2 pattern, and long-term immunosuppressive therapy could be risk factors for developing cancer.

In contrast, no association has been found, or the association found has been an inverse one in the case of solid tumors such as pancreatic or brain cancer. The incidence of IgE-mediated allergic diseases, especially rhinitis, has been found in women with breast cancer.[29] Here, excessive immunological surveillance and overexpression of IgE, which could favor cross-presentation of neoplastic antigens to dendritic cells, may act as protective factors.[24]

Jensen et al.[30] found a reduced risk of melanoma in patients with AD, although their results were only significant in patients who had had AD with more than 5 years of follow-up. In contrast, an increased incidence of nonmelanoma skin cancer was observed, although the results were statistically significant only in the case of basal cell carcinoma. A recent meta-analysis was unable to show statistically significant differences between patients with or without AD for the risk of developing melanoma or cutaneous squamous cell carcinoma. However, it did reveal an increased risk of basal cell carcinoma in patients with AD, although many of the studies included did not adjust their findings for phenotypic characteristics and/or sun exposure.

Atopic Dermatitis and Neuropsychiatric Comorbidities

AD is epidemiologically related to an increase in the frequency of psychological conditions such as depression, anxiety, suicidal ideation, and attention disorders in the form of attention deficit or hyperactivity. In the literature, increased ORs in patients with AD have been reported for depression (3.27 [1.61-6.62]), anxiety (2.01 [1.10-3.68]), and suicidal ideation (2.03 [1.20-3.45]) in nonadjusted models. This effect is attenuated in adjusted models (1.32 [0.75-2.33]).

The presence of AD or other atopic diseases before age 3 years increases the possibility of attention deficit or hyperactivity disorders (adjusted OR, 1.3 [1.1-1.6]) or autism (OR, 3.04 [2.13-4.34]), which is greater in severe forms.[21]

While the presence of proinflammatory cytokines able to cross the blood-brain barrier may play a role in these processes, there may also be numerous confounders, such as harmful effects on quality of life, chronic pruritus, and sleep disorders.[31]

Atopic Dermatitis and Ocular Comorbidities

The eventual impact of dupilumab, an anti–IL-4/13 agent, and other interleukin inhibitors (e.g., tralokinumab) on keratoconjunctivitis in some patients has brought to the forefront the well-known association between AD and various ocular manifestations.[32] A recent review found a significant association between AD and a greater risk of conjunctivitis, keratitis, and keratoconus, with respect to the general population. The risk was also associated with the severity of the skin condition.

Furthermore, an association was found between the risk of cataracts in individuals aged less than 50 years, although no greater risk of glaucoma was detected.[33]

Atopic Dermatitis and Autoimmune Diseases

AD has been associated with various autoimmune diseases, such as alopecia areata, vitiligo, lupus erythematosus, chronic urticaria, and inflammatory bowel disease. In contrast, the T_H1/T_H2 dichotomy might explain the inverse association with processes such as multiple sclerosis or type 1 diabetes, although some recent meta-analyses were unable to establish an association between both processes.[21]

Conclusions

There is evidence to consider that the chronic inflammation underlying AD could justify the occurrence of numerous atopic and nonatopic comorbid conditions. However, most evidence is based on epidemiological and not mechanistic data. Furthermore, the results can be affected by numerous confounders. In many of these comorbid conditions, aspects associated with the magnitude of the inflammation or even with diverse phenotypes may have to be taken into account and clarified in future studies.

Conflicts of Interest

Jose-Manuel Carrascosa has acted as a consultant and speaker, participated in clinical trials, and attended meetings and conferences with financial support from Sanofi-Aventis, AbbVie, Leo-pharma, Lilly, and Pfizer.

Victor Morillas declares that he has no conflicts of interest.

References

1. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015;66:8–16, http://dx.doi.org/10.1159/000370220.
2. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139:S65–76, http://dx.doi.org/10.1016/j.jaci.2017.01.011.
3. Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nogra-les K, Cardinale I, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalites. Allergy Clin Immunol. 2011;127:954–64, http://dx.doi.org/10.1016/j.jaci.2010.12.1124, e644.
4. Czarnowicki T, Gonzalez J, Bonifacio KM, Shemer A, Xiangyu P, Kunjravia N, et al. Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. J Allergy Clin Immunol. 2016;137:118–29, http://dx.doi.org/10.1016/j.jaci.2015.08.027.
5. Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Why-not J, Novitskaya I, Cardinale I, et al. Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis. J Allergy Clin Immunol. 2007;119:1210–7, http://dx.doi.org/10.1016/j.jaci.2007.03.006.
6. Andersen YMF, Egeberg A, Skov L, Thyssen JP. Comorbidities of atopic dermatitis: beyond rhinitis and asthma. Curr Dermatol Rep. 2017;6:35–41, http://dx.doi.org/10.1007/s13671-017-0168-7.
7. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. J Invest Dermatol. 2017;137:18–25, http://dx.doi.org/10.1016/j.jid.2016.08.022.
8. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol. 2018;121:604–12, http://dx.doi.org/10.1016/j.anai.2018.07.042.
9. Surdea-Blaga T, Popovici E, Fadgyas Stănculete M, Dumitrascu DL. Scarpignato C. Eosinophilic esophagitis: diagnosis and current management. J Gastrointest Liver Dis. 2020;29:85–97, http://dx.doi.org/10.15403/jgld-768.
10. Graham F, Eigenmann PA. Atopic dermatitis and its relation to food allergy. Curr Opin Allergy Clin Immunol. 2020;20:305–10, http://dx.doi.org/10.1097/ACI.0000000000000638.
11. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. J Allergy Clin Immunol. 2019;143:46–55, http://dx.doi.org/10.1016/j.jaci.2018.11.006.
12. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med. 2014;11(10):e1001748, http://dx.doi.org/10.1371/journal.pmed.1001748.
13. Ali Z, Suppli Ulrik C, Agner T, Thomsen SF. Is atopic dermatitis associated with obesity? A systematic review of observational studies. J Eur Acad Dermatol Venereol. 2018;32:1246–55, http://dx.doi.org/10.1111/jdv.14879.
14. Lim M-S, Lee CH, Sim S, Hong SK, Choi HG. Physical activity, sedentary habits, sleep, and obesity are associated with asthma, allergic rhinitis, and atopic dermatitis in Korean adolescents. Yonsei Med J. 2017;58:1040–6, http://dx.doi.org/10.3349/ymj.2017.58.5.1040.
15. Agón-Banzo PJ, Sanmartin R, García-Malinis AJ, Hernández-Martín A, Puzo J, Doste D, et al. Body mass index and serum lipid profile: association with atopic dermatitis in a paediatric population. Australas J Dermatol. 2020;61:e60–4, http://dx.doi.org/10.1111/ajd.13154.
16. Silverberg JI. Atopic disease and cardiovascular risk factors in US children. J Allergy Clin Immunol. 2016;137:938–40, http://dx.doi.org/10.1016/j.jaci.2015.09.012.
17. Hjuler KF, Böttcher M, Vestergaard C, Deleuran M, Raaby L, Bøtker HE, et al. Increased prevalence of coronary artery disease in severe psoriasis and severe atopic dermatitis. Am J Med. 2015;128:1325–34, http://dx.doi.org/10.1016/j.amjmed.2015.05.041.
18. Su VY, Chen T-J, Yeh C-M, Chou KT, Hung MH, Chu SY, et al. Atopic dermatitis and risk of ischemic stroke: a nationwide population-based study. Ann Med. 2014;46:84–9, http://dx.doi.org/10.3109/07853890.2013.870018.
19. Drucker AM, Li W-Q, Cho E, Li T, Sun Q, Camargo CA, et al. Atopic dermatitis is not independently associated with nonfatal myocardial infarction or stroke among US women. Allergy. 2016;71:1496–500, http://dx.doi.org/10.1111/all.12957.
20. Egeberg A, Andersen YMF, Gislason GH, Skov L, Thyssen JP. Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. Eur J Allergy Clin Immunol. 2017;72:783–91, http://dx.doi.org/10.1111/all.13085.
21. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. J Invest Dermatol. 2017;137:26–30, http://dx.doi.org/10.1016/j.jid.2016.07.012.
22. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol. 2015;135:721–8, http://dx.doi.org/10.1016/j.jaci.2014.11.023.
23. Andersen YMF, Egeberg A, Gislason GH, Hansen PR, Skov L, Thyssen JP. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138:310–2, e3, http://dx.doi.org/10.1016/j.jaci.2016.01.015.
24. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. Allergy Eur J Allergy Clin Immunol. 2014;69:37–45, http://dx.doi.org/10.1111/all.12246.
25. Thyssen JP, Linneberg A, Carlsen BC, Johansen JD, Engkilde K, Hansen T, et al. A possible association between

a dysfunctional skin barrier (filaggrin null-mutation status) and diabetes: a cross-sectional study. BMJ Open. 2011;1, http://dx.doi.org/10.1136/bmjopen-2011-000062.
26. Thyssen JP, Halling-Overgaard AS, Andersen YMF, Gislason G, Skov L, Egeberg A. The association with cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol. 2018;178:1272–9, http://dx.doi.org/10.1111/bjd.16215.
27. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. J Am Acad Dermatol. 2015;72:992–1002, http://dx.doi.org/10.1016/j.jaad.2015.02.1116.
28. Rafiq M, Hayward A, Warren-Gash C, Denaxas S, Gonzalez-IzquierdoF A, Lyratzopoulos G, et al. Allergic disease, corticosteroid use and risk of Hodgkin's lymphoma: a United Kingdom Nationwide case-control study. J Allergy Clin Immunol. 2020;145:868–76, http://dx.doi.org/10.1016/j.jaci.2019.10.033.
29. Bożekid A, Jarzab J, Mielnik M, Bogacz A, Kozlowska R, Mangold D. Can atopy have a protective effect against cancer? PLoS One. 2020;15, http://dx.doi.org/10.1371/journal.pone.0226950.
30. Jensen AO, Svaerke C, Körmendiné Farkas D, Olesen AB, Kragballe K, Sørensen HT. Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977-2006). Am J Clin Dermatol. 2012;13:29–36, http://dx.doi.org/10.2165/11593280-000000000-00000.
31. Yarlagadda A, Alfson E, Clayton AH. The blood brain barrier and the role of cytokines in neuropsychiatry. Psychiatry. 2009;6:18–22.
32. Ivert LU, Wahlgren CF, Ivert LU, Lundqvist M, Bradley M. Eye complications during dupilumab treatment for severe atopic dermatitis. Acta Derm Venereol. 2019;99:375–8, http://dx.doi.org/10.2340/00015555-3121.
33. Thyssen JP, Toft PB, Halling-Overgaard A-S, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Dermatology. 2017;77:280–6, http://dx.doi.org/10.1016/j.jaad.2017.03.003, e1.