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Atopic Dermatitis: Update on Pathogenesis and Comorbidities

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Abstract Atopic dermatitis (AD) is a significant cause of morbidity and healthcare costs in the United States and worldwide. The prevalence of AD in childhood is rising in the United States and other developed countries for reasons that are not well understood. Similarly, the prevalences of obesity and diabetes are on the rise, which might be contributing toward increased AD. This article reviews the association between AD and other atopic disorders with obesity and diabetes. Furthermore, recently recognized AD comorbidities, including fatty liver disease and erectile dysfunction, are reviewed. Potential mechanisms for the association between AD and metabolic disorders are discussed.

Keywords Atopic dermatitis · Hand dermatitis · Eczema · Asthma · Rhinoconjunctivitis · Food allergies · Atopy · IgE · Comorbidities · Obesity · Diabetes · Fatty liver · Erectile dysfunction · Filaggrin · Innate immune system · Cutaneous infections

Abbreviations

AD	Atopic dermatitis
BMI	Body mass index
FLG	Filaggrin
TLR	Toll-like receptor
IL	Interleukin
RAST	Radioallergosorbent test
IgE	Immunoglobulin E
NHANES	National Health and Nutrition Examination Survey
ISAAC	The International Study of Asthma and Allergies in Childhood

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Introduction

Atopic dermatitis (AD) is a significant cause of morbidity and healthcare costs in the United States. The annual direct healthcare cost of AD in the United States is estimated to be 900 million U.S. dollars per year [1]. The prevalence of AD in childhood was 2–3 % before 1960, 9–12 % after 1970, and is now as high as 20 % [2, 3]. The reasons for this increase are not well understood. There are new recent trends in the prevalence of AD and its comorbidities, which we review in this article (summarized in Table 1).

Pathogenesis of AD

The pathogenesis of AD is quite complex, involving an interaction between genetics and environmental factors. This is highlighted by a recent population-based study of U.S. children that found several socioeconomic risk factors for higher prevalence of AD in the United States, including black race, metropolitan living, and household education level greater than high school [4•].

The recent discovery of filaggrin gene (FLG) polymorphisms in the pathogenesis of AD was a significant breakthrough in our understanding of AD [5–12]. FLG mutations have thus far been found in up to 20 % of AD patients and may be associated with greater severity [9, 13]. SPINK5, a serine protease inhibitor involved in the regulation of stratum corneum thickness and function, is another gene of interest in AD. SPINK5 mutations are found in AD associated with Netherton's syndrome [14] and also have been found in some subsets of AD and are felt to confer risk of maternal transmission of AD [15, 16]. However, several observations suggest that genetic mutations resulting in barrier impairment are not the only pathogenic factor in AD. First, FLG and other skin-barrier gene mutations have been found in a minority of AD subjects. Second, genetic mutations alone would not

Table 1 Studies of the relationship between atopic dermatitis/eczema- and obesity-related comorbidities

Comorbidity	Study	Data source	Outcome measures	Findings
Obesity	Silverberg et al. [85••]	Retrospective pediatric practice-based study	Atopic dermatitis prevalence, severity and pediatrician visits	Association between obesity and atopic dermatitis prevalence, severity and healthcare utilization
	Silverberg et al. [86]	Retrospective adult allergy practice-based study	Atopic dermatitis prevalence (history of eczema, family history of atopic disease, positive skin-prick testing)	Association between obesity and atopic but not nonatopic dermatitis prevalence in adults
	Murray et al. [87••]	Prospective birth cohort study	Physician diagnosis of eczema in past 12 months	Association between obesity and physician diagnosed atopic dermatitis at age 5 and 8 years
	Suárez-Varela et al. [89••]	Spanish subset of ISAAC Phase 3	Itchy rash in the past 12 months and in the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes	Association between obesity and prevalence of atopic dermatitis
	Kusunoki et al. [88••]	Japanese questionnaire study	≥3/21 symptoms of atopic dermatitis	Association between obesity and prevalence and severity of atopic dermatitis
	Lee et al. [84]	Korean questionnaire study	Twelve-month prevalences of the symptoms of flexural eczema	Association between BMI and increased prevalence of flexural eczema
	Yao et al. [90]	Taiwanese questionnaire study	Ever- and current- history of eczema (using ISAAC questionnaire)	Association of obesity with ever- and current-atopic dermatitis
	Anveden Berglind et al. [97]	Swedish questionnaire study	Hand eczema in past 12 months	Association between obesity and hand eczema in men and women
	Mai et al. [59]	Swedish subset of ISAAC: Phase 2 study	Current wheeze, number of wheezing episodes in past 12 months, hypertonic saline provocation	Association between overweight/obesity and eczema in wheezing children
	Von Kries et al. [58]	Bavarian questionnaire study	Prevalence of doctor diagnosed eczema	No association between overweight/obesity and lifetime prevalence of eczema
	Vlaski et al. [83]	Republic of Macedonia subset of ISAAC: Phase 3 study	Self-report of eczema	No association between overweight/obesity and lifetime prevalence of eczema
	Violante et al. [82]	Mexico City subset of ISAAC Phase 3 study	Lifetime prevalence of eczema	Association between obesity and lower prevalence of eczema
Diabetes	Rosenbauer et al. [102]	German population-based study	New clinical diagnosis of type 1 diabetes and positive response to atopic dermatitis on questionnaire	Inverse association between type 1 diabetes and prevalence of AD in childhood
	Thomsen et al. [103]	Danish twin study	Hospital discharge diagnosis of type 1 diabetes and positive response to atopic dermatitis on questionnaire	Inverse association between type 1 diabetes and prevalence of AD
	Stene et al. [104]	Case-control study	Diagnosis of type 1 diabetes from the Norwegian childhood diabetes registry and positive response to physician-diagnosed eczema	Inverse association between type 1 diabetes and prevalence of AD in childhood
	Fsadni et al. [105]	Ecological study	Type 1 diabetes prevalence from the Mondiale Project Group and prevalence of AD from the ISAAC study	Positive association between type 1 diabetes and prevalence of AD in childhood
	Gazit et al. [106]	Case-control study	Clinical diagnoses of type 1 diabetes and atopic dermatitis	No association between type 1 diabetes and prevalence of AD in childhood
	Thomsen et al. [100]	Danish twin study	Hospital discharge diagnosis of type 2 diabetes and positive response to atopic dermatitis on questionnaire	Inverse association between type 2 diabetes and prevalence of AD in adults in univariate models; though, not significant in multivariate models
Erectile dysfunction	Chung et al. [128••]	Taiwanese population-based case-control study	Newly diagnosed erectile dysfunction and history of atopic dermatitis	Association between erectile dysfunction and history of AD in adults, even after controlling for obesity, hypertension, and diabetes
Fatty liver	Kimata [132]	Case-control study	Diagnosis of AD clinically and fatty liver by ultrasound	Association between AD and fatty liver in children
	Kimata [131]	Hospital-based incidence study	Diagnosis of AD clinically and fatty liver by ultrasound	Association between AD and fatty liver in children

account for the rapidly rising prevalence of AD in the United States and other developed countries.

It is well accepted that certain infectious exposures may decrease the risk of developing AD. This is referred to as the

"hygiene hypothesis," which states that certain infections and exposures can help guide the immature immune system away from a pro-atopic or inflammatory state [17]. We previously reported that exposure to varicella zoster virus in early childhood was associated with a lower odds of developing AD [18], asthma, and hay fever, as well as decreased serum immunoglobulin E (IgE), allergic sensitization, and persistent alterations of leukocyte subsets [19].

In contrast, some infections might play a pathogenic role in AD. A study of 451 human immunodeficiency virus (HIV)-infected children and 227 HIV-exposed but uninfected children and adolescents found that AD was significantly more common in HIV-infected children (20 % vs. 12 %) [20]. A cross-sectional study of 306 Ethiopian children age 1–5 years found that history of malaria, infection with the intestinal parasite Trichuris, and use of piped water as opposed to river water were all associated with increased risk of AD [21]. The authors also noted a lack of relationship of AD to family size, crowding in the home, or breast feeding [21].

Comorbidities of Atopic Dermatitis

Cutaneous Infection

Patients with AD have increased colonization with *Staphylococcus (S.) aureus* and have a higher risk of developing bacterial (*S. aureus*) and viral infections (e.g., eczema herpeticum, warts, molluscum) [22]. In an early study of bacterial colonization of flexural dermatitic skin, *S. aureus* was found to colonize 91 % of samples and occurred at much higher densities than normal skin [23]. Furthermore, increasing severity of dermatitis was found to have a linear increase in *S. aureus* colony and decreased diphtheroid counts [24]. Recently, more sophisticated bacterial gene sequencing studies revealed that AD flares were associated with increased *S. aureus* and *S. epidermidis* and decreased overall microbial diversity [25•]. AD treatment with emollients, topical corticosteroids, and bleach baths resulted in decreased *S. aureus* and increased microbial diversity, including *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species even before clinical improvement [25•].

Recent attention has been paid to the pathogenic role of defects of toll-like receptor 2 (TLR2) and other pathways of the innate immune system in AD and associated infections (reviewed in [26••]). TLR2 recognizes peptidoglycan and lipoteichoic acid, components of the cell wall of *S. aureus* and other gram-positive bacteria [27]. TLR2 also can recognize lipopolysaccharide on some gram-negative bacteria, as well as fungi and possibly even herpes viruses [28, 29]. In a study of 78 patients with mild to severe AD and 39 age-matched healthy controls, it was found that genetic polymorphisms of TLR2 occurred in 11.5 % of AD patients and only 2.5 % of controls, and TLR2 polymorphism was associated with more severe AD [30]. Thus, some patients with AD have impaired aberrancies of innate immunity that may predispose them to increased microbial colonization and infection, aside from skin barrier defects. It is interesting that obesity is associated with numerous effects on the innate immune system, including TLR2 expression (see below). Thus, it is possible that obesity predisposes AD patients to even higher risk of cutaneous infections.

Asthma

AD is associated with a number of comorbid health conditions. In particular, children with AD are more likely to develop asthma followed by hay fever as they grow older, termed the "atopic march" [31]. Ricci et al. (2006) performed a retrospective study of 252 Italian children with AD and a follow-up questionnaire 13–22 years later. They found that as the children grew older, the AD disappeared in 60 %, but asthma (34 %) and rhinoconjunctivitis (57 %) subsequently developed; the appearance of asthma occurred in children with severe AD [32]. The Multicenter Allergy Study, a German birth cohort, found that children with AD in the first 2 years of life were more likely to have wheeze at age 7 years if they had severe disease and atopic sensitization [33]. A systematic review of 13 prospective studies found that one out of three children with AD will develop asthma during later childhood [34]. The Tasmanian Longitudinal Health Study followed a cohort of 8,583 Australian 7-year-old children from 1968 until 2004 and found that childhood eczema was associated with significantly increased incidence of asthma in childhood, preadolescence, adolescence, and adult life [35]. A subsequent study from this cohort found that childhood eczema predicts atopic but not nonatopic asthma in adulthood [36].

Rhinoconjunctivitis

A cross-sectional study of 2,270 U.S. children with physician-diagnosed AD found that 38 % had the "atopic triad," including asthma and rhinitis [37]. A prospective study of 94 infants and toddlers with AD until age 7 years found that 45 % developed allergic rhinitis [38]. In a German Multicenter Atopy study, 1,314 newborns were recruited and analyzed, and of this group, 499 infants were at increased risk of atopic disease [33]. Their results showed that disease severity and atopic sensitization are major determinants of increased risk of subsequent wheeze or bronchial hyperreactivity; in contrast, early AD without these cofactors constituted no increased risk of subsequent wheeze.

Atopy

In a nested case-control study of 2,201 East German schoolchildren age 5–14 years, 75 % of children with AD had ≥1

positive radioallergosorbent test (RAST) compared with only 36 % of children without eczema [39]. Prevalence of allergic sensitization also was associated with AD severity [39]. A study of 116 adults with AD and 93 nonatopic controls found that serum IgE concentrations were higher in subjects with AD, particularly severe disease with more flares [40].

A paucity of studies have examined the prevalence of food allergies in AD. Silverberg and Simpson recently analyzed a U.S. population-based parental questionnaire study found a much higher prevalence of food allergies in children with AD compared with no AD (15.1 % vs. 3.6 %) [41]. Similarly, a randomized, double-blind, U.S. multicentered study of 1,087 infants with AD treated with pimecrolimus found a 15.7 % prevalence of food allergies in children with AD [42]. Some studies using food challenges ("gold standard" for diagnosing food allergies) found even higher prevalence of type I mediated food allergies (37–56 %); however, those studies were not population-based and suffered from selection bias of more severe cases of AD [43–45]. On the other hand, a study of 8,206 children and adults in the National Health and Nutrition Examination Survey (NHANES) 2005–2006 study examined allergen-specific serum IgE levels and found positive specific-IgE to food allergens in 17.8 % of participants, and only 1.9 % with high specific-IgE levels indicating likely food allergy [46]. However, the study included more adults than children, age-related differences of food allergies were not explored in AD, and history of diagnosed food allergy was not explored [46].

Obesity and Diabetes

Epidemiology of Obesity and Diabetes

The prevalence of obesity in the United States and other developed countries has steadily increased during the past 30 years. Obesity affected 10 % of U.S. adults in 1980 but has now more than tripled to 35 % in 2010 [47, 48]. Similarly, obesity in children increased from 5–7 % in 1980 to 16.9 % in 2010 [49]. It is estimated that 50–51 % of adult men and 45–52 % of women in the United States will be obese by the year 2030 [50]. Similarly, the prevalence of obesity in the United Kingdom has more than doubled from 8 % of women and 6 % of men in 1980 to 21 % of women and 17 % of men in 1998 [51] and is estimated to further increase to 41–48 % in men and 35–43 % in women [50]. The number of obese people worldwide by the year 2030 is estimated to be 1.12 billion [52].

The prevalence of diabetes in U.S. adults aged ≥20 years is estimated to be 11.3 %, and 26.9 % in aged ≥65 years [53]. Based on data from the NHANES III (1988–1994) and 2010 study, the prevalence of diagnosed diabetes (type 1 or 2) in U.S. children aged 12–19 years was estimated to be 0.4 % and 0.26 %, respectively [53, 54]. Children with type 2 diabetes are most commonly aged 10–19 years, obese, insulin-resistant, with a family history of type 2 diabetes and elevated glycosylated hemoglobin levels (10–12 %) [54].

Obesity and diabetes are associated with increased cardiovascular disease, cancer, and many other chronic health conditions. The increasing prevalence of obesity and to a lesser extent diabetes during the past 30 years coincides with the rising prevalence of AD, suggesting that there may be a relationship between them.

Obesity and Asthma

Multiple large-scale epidemiological studies demonstrated that obesity is a risk factor for atopic disorders, including asthma and atopy. A cross-sectional study of 7,367 children aged 4–17 years from the NHANES III (1988–1994) survey found a significantly higher prevalence of asthma and atopy with increased body mass index (BMI) [55]. Similarly, studies from the United Kingdom, Australia, Bavaria, and Sweden have all shown elevated BMI, overweight, and/or obesity in children with asthma [56–59]. Most of these studies observed the association between obesity and asthma in both boys and girls [56, 57, 59], whereas only one found it to be female gender-specific [58].

Similarly, obesity in adulthood is associated with increased asthma [60–67] and airway hyperactivity [64], poorer asthma control, asthma-specific quality of life, and having more asthma-related healthcare utilization [60–63]. Fitzpatrick et al. conducted a clinical study of 246 adult allergy patients in New York City and found that obesity was associated with significantly higher odds of developing atopic asthma, more severe asthma, and markers of poorer lung function (decreased peak flow, forced expiratory volume in 1 second (FEV1), and forced vital capacity (FVC)), increased asthma exacerbations requiring oral corticosteroids, poorer long-term asthma control requiring inhaled corticosteroids, and increased serum IgE compared with atopic nonasthmatic controls [68].

Obesity and Atopy

A study of 4,111 U.S. children aged 2–19 years from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 study found that serum IgE levels and atopy were higher among obese children, with a predominance of food allergy sensitization [69•]. Elevated CRP levels are associated with total IgE levels, atopy, and food sensitization [69•].

There are conflicting data regarding the role of obesity in adult atopy. Some studies found an association between

atopy and central and/or general obesity in adults [70–72], whereas others did not [73–76].

Obesity and Rhinoconjunctivitis

Multiple studies found no association between obesity and rhinoconjunctivitis in either children [58, 59, 77–79] or adults [80]. One study of 10,667 Finnish university students aged 18–25 years found that obesity was significantly associated with rhinoconjunctivitis in women but not men [81].

Obesity and Atopic Dermatitis

Secondary Outcomes Data

Several studies of AD as a secondary outcome found conflicting results regarding about an association with BMI, with asthma or atopy as the primary study outcomes (Table 1) [58, 59, 82, 83]. A questionnaire-based study to 38,955 Korean children age 6–15 years found a significant association between increasing BMI and eczema [84]. Another questionnaire-based case-control study of 457 Swedish adolescents (12 years) found an association between overweight with history of wheezing and eczema in wheezing children [59].

In contrast, a questionnaire-based study of parents of 9,357 children aged 5–6 years in rural areas in Bavaria found an association between obesity and ever-asthma in girls, but not eczema in boys or girls [58]. A questionnaire-based study of 2,926 adolescents aged 13–14 years in the Republic of Macedonia found no association between being overweight and eczema [83]. Last, a questionnaire-based study of 8,624 children aged 6–7 years and 13–14 years in Mexico City as part of The International Study of Asthma and Allergies in Childhood (ISAAC) Phase III study found that obesity in 6- to 7-year-old girls and 13- 14-year-old boys was associated with less eczema [82]. (Note: ISAAC Phase I study enrolled 721,601 children aged 6–7 years and 13–14 years in 156 collaborating centers in 56 countries between 1993–1995. ISAAC Phase II enrolled 53,383 children aged 10–12 years in 30 centers in 22 selected countries starting in 1998. ISAAC Phase III was a repeat of Phase I to examine time trends of allergic disease and enrolled 1,187,496 children from 237 collaborating centers in 98 countries between 2001–2003.) From these conflicting data, it is difficult to make definitive conclusions about the association between obesity and AD.

Primary Outcomes Data

During the past 2 years, a number of studies were published that were primarily designed to examine the role of obesity in AD. Silverberg et al. (2011) conducted a retrospective, pediatric practice-based, case-control study that randomly sampled 414 children and adolescents aged 1–21 years with physician-diagnosed AD and 828 age-matched healthy control subjects [85••]. We found that obesity in childhood was associated with a twofold higher odds of subsequently developing AD. The increased odds of developing AD occurred particularly in children who had prolonged duration (>2.5 years) and early onset (ages 0–2 or 2–5 years) of obesity. Obese children with AD had more severe disease and frequent pediatrician visits devoted to AD [85••]. Although the study was retrospective, the data were longitudinal and showed that obesity preceded the diagnosis of AD.

Another study conducted by Silverberg was a prospective, allergy practice-based study using patient questionnaires, height and weight measurements, and skin-prick testing in 2,090 adults [86]. AD was defined using a composite of answering yes to eczema and yes to family history of atopic disorders on questionnaire and having at least one positive skin-prick test. We found that obesity in adults is associated with increased odds of AD, but not eczema or atopy alone [86]. However, obesity conferred a smaller risk of AD in adults (odds ratio (OR)=1.43) than in the abovementioned pediatric cohort (OR=2.15 for obesity at any age, OR=15.1 for onset of obesity in the first 2 years of life).

The Manchester Allergy and Asthma Study prospectively followed 731 children from a birth-cohort at age 3, 5, and 8 years using parental questionnaires and height and weight measurements [87••]. They found that increasing BMI z-score was significantly associated with increased odds of physician-diagnosed eczema at age 5 and 8 years [87••].

In a parental-questionnaire study of 45,520 Japanese schoolchildren age 7–15 years, increasing BMI was associated with AD [88••]. Furthermore, obesity was associated with more severe, but not higher, AD prevalence [88••].

A study of 13,153 Spanish children from a subset of the ISAAC Phase 3 questionnaire-study also found that obesity was associated with increased odds of AD [89••]. A cross-sectional study of 5,351 Taiwanese children age 4–18 years who participated in the ISAAC study also found that obesity was associated with ever- and current-eczema [90].

All of these studies used BMI to determine obesity, rather than measurements of abdominal/truncal obesity. It is theoretically possible that the association of obesity with AD is even stronger with abdominal obesity, given the strong associations with numerous medical disorders and health outcomes [91–96]. Nevertheless, these studies demonstrate a strong association between childhood obesity and AD both in the United States and internationally.

Obesity and Hand Dermatitis

A recent questionnaire-based study 27,793 Swedish adults aged 18–64 years found a significant association between

obesity and the prevalence of hand dermatitis in both men and women [97]. It is likely that a significant subset of respondents had atopic hand dermatitis. However, there are other phenotypes of hand dermatitis, such as chronic fissured, allergic, and irritant hand dermatitis, which occur in absence of atopic phenotype and have distinct FLG mutations [98, 99].

Diabetes and Asthma

A study of 34,782 Danish adult twins aged 20–71 years found that diagnosis of type 2 diabetes was associated with history of asthma in both men and women, even after adjusting for BMI and other confounding variables [100]. A retrospective, longitudinal cohort study using the electronic records from Kaiser-Permanente in northern California found that the incidence of asthma was higher in diabetics than nondiabetics (0.48 vs. 0.22 per 1,000 person-years) [101].

Diabetes and Atopic Dermatitis

There are conflicting studies about an association between AD and type 1 diabetes. A German population-based study of 760 children newly diagnosed with type 1 diabetes and 1,871 age-, sex-, and residence-matched controls found an inverse association with AD but not with asthma or rhinoconjunctivitis [102]. In a study of 54,530 Danish twins aged 3–71 years found that diagnosis of type 1 diabetes was associated with decreased AD [103], Similarly, a case-control study of 339 children with type 1 diabetes and 985 controls an inverse association between AD and type 1 diabetes, independent of mutations in the *HLA-DQ*, *CTLA4*, and *PTPN22* genes [104].

In contrast, an ecologic study design using merged data from the ISAAC and Diabetes Mondiale Project Group found that type 1 diabetes was associated with AD and wheeze in adolescents aged 13–14 years [105]. Finally, a case-control study of 65 Israeli children with type 1 diabetes and 74 nondiabetic controls found no association with eczema, other atopic diseases or total and specific serum IgE levels [106].

Little is known about the relationship between type 2 diabetes and AD. The abovementioned Danish twins study found that type 2 diabetes was associated with a lower prevalence of AD compared with nondiabetics (3.2 % vs. 6.1 %), although the association was not significant after adjusting for confounders [100].

Mechanism of Association between AD and Metabolic Factors

The mechanism(s) behind the association of metabolic factors and AD is unknown. Although the association of AD and FLG mutations is now well established, it is not clear how obesity interacts with such genetic predisposition. One possibility is that FLG and other genetic mutations involved in AD result in both an AD phenotype and increased risk for obesity and its sequel. Alternatively, obesity may be independent of FLG mutations and acts as a trigger in an already genetically predisposed person. It is therefore possible that obesity may act as a trigger in other disorders associated with FLG mutations. In fact, most of the cross-sectional studies are not able to distinguish between these two options. The pediatric-practice based study of Silverberg et al. [85••] and Manchester Allergy and Asthma Study [87••] both followed children over an extended period of time. Thus, they were able to show that the obesity clinically preceded the AD well in advance, suggesting that obesity is a trigger or exacerbating for AD, and not merely an epiphenomenon. There is growing use of the term "overweight hypothesis" [83], which states that being overweight or obese early in childhood may guide the immature immune system toward a pro-atopic or inflammatory state.

There is a strong relationship between adiposity and the innate immune system. Multiple TLRs (TLR1–5, 7, and 9) are expressed on adipocytes, at least some of which appear to be functionally active [107–110]. High levels of free fatty acids from obesity and glucose from diabetes activate the innate immune system, with upregulated TLR expression that correlates with insulin resistance and increased inflammatory cytokine release in macrophages [111–113].

Obesity also impacts a number of inflammatory cytokines, cellular pathways. Tumor necrosis factor (TNF) alpha and interleukin (IL)-6 are expressed by macrophages [114] and cytotoxic T cells [115] in adipose tissue [114]. TNF-α, IL-6 [116], interferon (IFN)-γ, and IL-2 [117, 118] are all upregulated by the adipokine leptin. Leptin also polarizes T cells toward a T-helper 1 (Th1) cytokine profile [117]. Leptin also induces proliferation and activation of circulating monocytes [119] and CD4+ and CD8+ T cells [118] and promotes neutrophil chemotaxis [120, 121].

Adipokines may play an important role in allergic inflammation. Nagel et al. found a disease-specific association between low adiponectin levels and AD [122]. Adiponectin levels tend to be lower in obesity [123]. Leptin is an adipokine that is upregulated in obesity. Leptin has been shown to induce eosinophils *in vitro* to upregulate expression of adhesion molecule ICAM-1 and CD18, stimulate chemokinesis, and induce the release of IL-1β, IL-6, IL-8, growth-related oncogene-α, and MCP-1 [124]. Leptin may play a role in the pathogenesis of allergic asthma [125]. A study of 25 children with AD and 25 age-matched nonatopic controls found increased serum leptin levels in AD [126]. However, another study of 20 children aged 1–8 years with AD and 20 age-matched controls found no differences of leptin levels in AD [127]. It is likely that the mechanism of association between obesity and AD is multifactorial and may include any and all of the above pathways.

Erectile Dysfunction and Atopic Dermatitis

A recent population-based study of 23,982 subjects from the Taiwan National Health Insurance program found that erectile dysfunction (ED) was associated with a higher prevalence of AD than non-ED controls (10.6 % vs. 6.7 %) [128••]. AD was associated with higher odds of ED even after controlling for obesity, hypertension, and diabetes [128••]. This novel association is likely related to a combination of factors, including obesity and diabetes, stress, and lifestyle factors. A study of 36 adult AD patients with ED found that viewing humorous films improved their ED, increased serum testosterone, and decreased serum estradiol 4 days later [129]. This study suggests that there is a psychogenic component of ED in AD. However, ED in AD patients may have a neuropathic or vascular occlusive component secondary to comorbidities (e.g., obesity and/or diabetes).

Fatty Liver and AD

Several studies by Kimata showed an association between fatty liver and AD. Children with AD were found to have increased fatty liver [130–132]. Children with AD had increased serum leptin levels and even higher leptin levels in AD with fatty liver [126]. Fatty liver also was associated with increased skin-prick test positivity [133]. However, these associations have yet to be verified in humans by other authors. In NC/Nga mice (animal model of AD [134]) , development of AD-like skin lesions was associated with reduced glucose levels and altered transcription of lipid catabolism genes that might lead to cholesterol accumulation in liver [135]. It is possible that the association between fatty liver and AD is secondary to circulating free fatty acids in chronic obesity.

Conclusions

The associations between AD, obesity, and other metabolic factors have important clinical ramifications. These associations highlight the importance of maintaining ideal BMI, especially during early childhood, and suggest that weight loss may actually improve AD in some children. To date, no studies have examined the role of weight loss in either high-risk children for prevention of AD or the treatment of children with AD. Previous studies found a significant improvement of allergic asthma with weight loss [136, 137]. Future studies are needed to elucidate whether weight loss and dietary modification can impact incidence and severity of AD. Finally, they underscore the profound impact that AD has on overall health. It is important to recognize these comorbidities and diagnose them early to prevent the long-term harmful sequelae.

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- •• Of major importance

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