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ORIGINAL RESEARCH ARTICLE

Atopic Dermatitis and Celiac Disease: A Cross-Sectional Study of 116,816 Patients

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Abstract

Background Both atopic dermatitis and celiac disease are often accompanied by other immune-mediated disorders.

Objective The objective of this study was to evaluate the potential association between atopic dermatitis and celiac disease in a broad community-based population.

Methods A cross-sectional observational design was used. Demographic and clinical data were collected for patients enrolled in a large health management organization who were diagnosed with atopic dermatitis by a dermatologist in 2002–17. The presence of celiac disease/celiac disease-related morbidities was recorded for the whole group, for adults (age > 18 years), and for adults with moderate-to-severe atopic dermatitis. Findings were compared with a matched control group without atopic dermatitis.

Results The study group included 116,816 patients of whom 45,157 were adults; 1909 adult patients had moderate-to-severe atopic dermatitis. Compared to the respective control subjects, the prevalence rate of celiac disease in the whole group was 0.6% vs. 0.4%; in the adults, 0.6% vs. 0.3%; and in the adults with moderate-to-severe atopic dermatitis, 0.8% vs. 0.3% ($p < 0.001$ for all). On multivariate analysis, atopic dermatitis was associated with a significantly higher prevalence of celiac disease (odds ratio = 1.609, 95% confidence interval 1.42–1.82, $p < 0.001$) in the entire study population and each subgroup.

Conclusions We observed a significant association between atopic dermatitis and celiac disease. This association emphasizes the need for timely screening of gastrointestinal morbidities in individuals with atopic dermatitis to prevent long-term complications.

Key Points

This large-scale cross-sectional study revealed an over-representation of celiac disease (CD) in patients with atopic dermatitis (AD).

The awareness of CD may be of benefit to physicians managing patients with AD, and clinicians could consider lowering the threshold for the appropriate screening tests for CD in patients with AD.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatosis that poses a significant burden on healthcare resources and patient quality of life. Atopic dermatitis affects 15–20% of children and 1–3% of adults worldwide, and its prevalence is

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increasing [1, 2]. The onset of AD is usually in early childhood [3, 4]. It may be followed by symptoms of other allergies, including food allergies, in 50% of patients in the first year of life, and in 85% before age 5 years [5, 6]. Cumulative evidence suggests that autoimmunity may play a role in AD. Atopic dermatitis has been found to be associated with a variety of other immune-mediated diseases, including those with an autoimmune basis [7–9].

Celiac disease (CD) is a chronic immune-mediated gluten-induced enteropathy that affects genetically predisposed individuals of all ages. Histological evidence of inflammatory changes on an intestinal biopsy study is the gold standard for CD diagnosis, even in the absence of gastrointestinal symptoms and suggestive findings on serological analyses [10]. A life-long gluten-free diet is mandatory to achieve clinical and histological recovery in most patients. Compared with the general population, patients with CD are more frequently affected by other immune-mediated disorders, including inflammatory skin diseases [10, 11]. While dermatitis herpetiformis is the best characterized cutaneous manifestation of CD, it may coexist with a variety of other dermatoses, including AD [10].

Although the co-occurrence of AD and CD had been reported in some cases, there is a paucity of well-designed controlled studies investigating the potential association between the two conditions [11–14]. The little knowledge available so far is derived mainly from case series and cohort studies of up to 1044 participants that tracked patients with CD, but not AD. Further large-scale epidemiological studies are highly warranted.

The aim of the present study was to investigate the relationship between AD and CD in a real-life setting using a broad population database.

2 Patients and Methods

Clalit Health Services (CHS) is the largest health maintenance organization (HMO) in Israel, serving a population of about 4,500,000. Besides the in-hospital and outpatient settings, members of CHS may consult a non-hospital-affiliated board-certified dermatologist in one of its primary care (community) clinics. For the present study, we focused on the community setting, where patients with AD are usually evaluated and treated. The medical, pharmaceutical, and administrative data of each CHS enrollee are entered into a comprehensive computerized database in real time. A continuous validation system automatically assesses and consolidates diagnoses made by CHS physicians, registered prescriptions, pharmacy claims, laboratory tests, and auxiliary tests for each patient. Inconsistencies are resolved after authentication by the registry manager. Well-diagnosed and fullly validated chronic diseases such as CD are recorded in the CHS Chronic Disease Register. A previous study of the CHS Chronic Disease Register found it to be highly accurate [15].

We designed a cross-sectional observational study to investigate the relationship between AD and CD using the CHS database. The study group included all patients who received at least one documented diagnosis of AD between 2002 and 2017 by CHS dermatologists working in primary care, outpatient or inpatient clinics, and dermatology hospital wards. The control group consisted of age- and sex-matched subjects without AD randomly selected from the general population of CHS enrollees during the same period.

The following data were collected for each patient: age, sex, socioeconomic status, ethnicity, smoking status, body mass index, Charlson comorbidity index (a validated method for classifying comorbid conditions that are associated with mortality risk) [16], and severity of AD. Socioeconomic status (low, intermediate, high) was defined according to the average socioeconomic status of the catchment area of the clinics in which the enrollee was registered. A patient was considered a smoker if he/she had an active smoking diagnosis in the CHS Chronic Disease Register. Severity of AD was evaluated according to the prescribed treatments and healthcare utilization: moderate-to-severe AD was defined as at least one hospitalization due to an exacerbation of AD or at least one course of a systemic AD-related medication (methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil) prescribed at or near the time of AD diagnosis with more than two succeeding prescriptions over a period of more than 4 weeks or a prescription for phototherapy for the indication of AD.

The CHS Chronic Disease Register was then searched for all patients in the study and control groups with regard to the presence of a CD diagnosis. In CHS, the diagnosis of CD is based on clinical symptoms suggestive of the disease and concomitant positive serologic screening tests for anti-transglutaminase or anti-endomysial antibodies (immunoglobulin A and/or immunoglobulin G). In the presence of suggestive symptoms and a negative serologic test, an endoscopic biopsy is performed by a gastroenterologist. If biopsy findings are unequivocal, the diagnosis is confirmed when symptoms improve after the patient is placed on a gluten-free diet under the supervision of a gastroenterologist.

The study was approved by the Institutional Review Board of the Soroka Medical Center, Ben Gurion University of the Negev, Beer Sheva, Israel, which waived the need for signed informed consent.

2.1 Statistical Analysis

Analyses were performed for the study group as a whole, for adults only (age > 18 years), and for adults with

moderate-to-severe AD, with comparison to the respective control group/subgroups. Continuous variables were compared between patient and control groups/subgroups with *t* tests, and dichotomous variables were compared with Pearson's chi-squared test. The proportion of each comorbidity was calculated in each group and subgroup, and univariate comparative analyses were performed accordingly. The data were then entered into a multivariate logistic regression model. The vast study sample (which prevented considering it as sparse data) as well as the exact age matching both permitted the use of unconditional logistic regression. The selection of this type of logistic regression was determined relying on the features of the study regardless of the results. Effect modification was identified using the Breslow–Day test, and interaction terms for statistically significant effect modifiers were added to the model when appropriate. All statistical analyses were performed using SPSS software, version 23 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

3 Results

The study group included 116,816 patients with AD who accounted for 2.7% of all CHS enrollees during the study period. There were 45,157 patients with AD aged older than 18 years of whom 1909 (4.2%) had moderate-to-severe disease. The control group consisted of 116,812 subjects matched for age and sex to the AD group. The demographic and clinical characteristics of the study population are presented in Table 1. Patients with AD were more likely than controls to have a high or intermediate socioeconomic status. There were no significant differences in the mean body mass index between the patients and controls, either the whole groups or by subgroup.

The results of the univariate analysis of the association between AD and CD and other CD-related comorbidities (adults only) are presented in Table 2. Celiac disease was diagnosed in 677 patients with AD (0.6%) and 412 control subjects (0.4%). This difference was statistically significant ($p<0.001$). Compared with their respective controls, the prevalence of CD was significantly higher ($p<0.001$) in the subgroup of adult patients with AD (0.6% vs. 0.3%) and in the subgroup of adult patients with moderate-to-severe AD (0.8 vs. 0.3%). The prevalence of CD was directly related to the severity of AD. These results were consistent on a multivariate comparative analysis adjusting for age, sex, smoking status, and annual primary care visits (Table 3). A significant association was found between AD and CD in the entire study population, the subgroup of adult patients with AD, and the subgroup of adult patients with moderate-to-severe AD.

4 Discussion

We investigated the concomitant occurrence of AD and CD using a large population-based HMO database. The study yielded strong statistical evidence of an association between AD and CD. Patients with AD had a 60% higher odds of

Table 1 Demographic and clinical characteristics of the study population

Characteristics	Comparison group without AD $n = 116,812$	Patients with AD $n = 116,816$	Adult patients with AD $n = 45,157$	Adult patients with moderate-to-severe AD $n = 1909$
Age, years, mean (SD)	21.4 (20.1)	21.4 (20.1)	41.7 (18.5)	50.2 (19.8)
Female sex, *n* (%)	61,889 (53)	61,892 (53)	28,582 (63.3)	1114 (58.4)
Socioeconomic status, *n* (%)				
Low	55,692 (47.7)	**41,405 (35.4)**	**14,555 (32.2)**	**566 (29.6)**
Intermediate	34,693 (29.7)	**41,790 (35.8)**	**17,165 (38.0)**	**742 (38.9)**
High	19,539 (16.7)	**27,243 (23.3)**	**11,415 (25.3)**	**522 (27.3)**
Arab ethnicity	36,133 (30.9)	**21,207 (18.2)**	**5090 (11.3)**	**157 (8.2)**
Currently smoking, *n* (%)	14,355 (12.3)	14,383 (12.3)	13,992 (31.0)	**694 (36.4)**
Obesity	15,150 (13.0)	15,338 (13.1)	**7573 (16.8)**	**423 (22.2)**
BMI, mean (SD)	22.1 (9.6)	22.4 (6.0)	25.9 (8.0)	26.1 (5.4)
Charlson comorbidity index mean (SD)	0.7 (1.6)	0.6 (1.6)	1.4 (2.3)	**2.7 (2.9)**
Moderate-to-severe disease, based on healthcare utilization, *n* (%)	NA	2193 (1.9)	1909 (4.2)	1909 (100)

AD atopic dermatitis, *BMI* body mass index, *NA* not applicable, *SD* standard deviation

Note: statistically significant differences between patients with AD (whole group, adults, adults with moderate-to-severe AD) and age- and sex-matched subjects without AD are indicated in bold (two-tailed test with Bonferroni correction for multiple comparisons)

Table 2 Association between atopic dermatitis (AD) and celiac disease (CD) and CD-associated morbidities in adults: univariate analysis

	Comparison pediatric subjects without AD $n=71,655$	Pediatric patients with AD $n=71,659$	*P* value	Comparison adult subjects without AD $n=45,157$	Adult patients with AD $n=45,157$	*P* value	Adults with moderate-to-severe AD $n=1909$	*P* value
CD, *n* (%)	419 (0.6)	263 (0.4)	**< 0.001**	149 (0.3)	258 (0.6)	**< 0.001**	149 (0.8)	**0.001**
Addison disease, *n* (%)	6 (0)	2 (0)	0.157	12 (0)	17 (0)	0.361	2 (0.1)	0.108
Cushing disease, *n* (%)	2 (0)	1 (0)	1	9 (0)	18 (0)	0.123	3 (0.2)	**0.011**
Diabetes insipidus, *n* (%)	8 (0)	12 (0)	0.502	16 (0)	22 (0)	0.417	0	1
Hyperprolactinemia, *n* (%)	1 (0)	1 (0)	1	90 (0.2)	100 (0.2)	0.513	5 (0.3)	0.440
Hypophyseal adenoma, *n* (%)	1 (0)	1 (0)	1	56 (0.1)	62 (0.1)	0.645	5 (0.3)	0.101
Pernicious anemia, *n* (%)	2 (0)	0 (0)	1	37 (0.1)	50 (0.1)	0.165	3 (0.2)	0.220

Statistically significant differences between patients with AD and subjects without AD are indicated in bold

being diagnosed with CD than control subjects without AD. The association was more prominent in adult patients with moderate-to-severe AD.

4.1 Comparison of Our Findings to the Literature

The co-occurrence of AD and CD has been explored to date in only a handful of well-designed controlled observational studies. Two studies, both hospital based, evaluated the rate of CD in patients diagnosed with AD [12, 17]. Ress et al. [12] reported an estimated CD prevalence of 1.4% among 351 pediatric patients from Estonia with AD. This rate was four-fold higher than the rate of CD in the general pediatric population from the same region (odds ratio 4.18; 95% confidence interval 1.1–15.7). Accordingly, in the second hospital-based study that included 401 Italian patients with atopic diseases, Zauli et al. [17] found a significantly higher prevalence of CD (1.0%) relative to the general Italian population. The slightly higher rates in both these studies compared to ours may be explained by ascertainment bias, as individuals in a tertiary care setting may be more likely to be diagnosed with CD in the context of a concurrent disease or to undergo evaluation for a minor manifestation of an associated or asymptomatic disease once they are diagnosed with AD. In addition, the selection bias characteristic of hospital-based studies can lead to an overestimation of underlying diseases. The large sample size in our study provided sufficient power to exclude chance findings and minimized the likelihood of selection and ascertainment biases.

More studies have explored the frequency of AD in cohorts of patients with CD. In a case-control study, Ciacci et al. [13] followed 1044 Italian adult patients with CD and found a 3.8% prevalence rate of AD, which was three times higher than the rate in their spouses (odds ratio 3.17; 95% confidence interval 1.02–9.82). A 1-year gluten-free diet had no effect on the prevalence of AD. Verkasalo et al. [14] found that the prevalence of AD in a Finnish pediatric cohort of 42 patients with CD was as high as 45%, compared with 25% in a corresponding general pediatric population. In large cohort studies (more than 100 patients), the prevalence rates of AD among patients with CD ranged between 1.3% in Italy [11] and 5.4% in the UK [18].

4.2 Interpretation of the Findings

Celiac disease is considered a T-cell-mediated immune disease in which gliadin-derived peptides activate lamina propria effector CD4+ T cells [13]. This leads to the release of cytokines compatible with a T helper-1-like pattern [19]. By contrast, in immunoglobulin E-mediated allergic diseases such as AD, T helper-2 lymphocytes predominate. Although the co-existence of T helper-1 and T helper-2 disease has been reported in distinct patient populations, the subject remains controversial [13, 20].

The biologic mechanism that might underlie an association of AD and CD has not been established, but several hypotheses have been proposed to account for the findings. Some authors suggested that in CD, the damage to the intestinal barrier enhances its permeability and exposes the lymphoid tissue to a larger amount of macromolecules, triggering allergic reactions in distant sites [21]. The pathogenesis of atopic diseases has been linked to mucosal damage [17], as the increased mucosal permeability may allow for the passage of autoantigens through the intestinal wall thereby inducing hyperactivation of the immune system [12]. Additionally, a polymorphism of the cytotoxic

Table 3 Logistic regression results for the association between atopic dermatitis (AD) and celiac disease, fully adjusted (cross-sectional study design)

	Patients with AD vs. subjects without AD			Pediatric patients with AD vs. pediatric subjects without AD			Adult patients with AD vs. adults subjects without AD			Adult patients with moderate-to-severe AD vs. adult subjects without AD		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Celiac disease[a]	1.609	1.42–1.82	**< 0.001**	1.565	1.34–1.87	**< 0.001**	1.652	1.35–2.02	**< 0.001**	2.132	1.25–3.64	**0.006**
Age	0.99	0.98–0.99	**< 0.001**	1.096	1.08–1.12	**< 0.001**	0.986	0.98–0.99	**< 0.001**	0.993	0.98–0.99	**0.028**
Sex	1.595	1.41–1.81	**< 0.001**	1.568	1.35–1.83	**< 0.001**	1.583	1.26–1.98	**< 0.001**	1.617	1.32–1.98	**< 0.001**
Smoking	0.868	0.70–1.07	0.187	0.806	0.30–2.17	0.669	0.922	0.74–1.15	0.922	0.755	0.53–1.07	0.112
Primary care visits	1.008	1.005–1.008	**< 0.001**	1.008	1.005–1.008	**< 0.001**	1.008	1.006–1.01	**< 0.001**	1.007	1.003–1.01	**< 0.001**

Statistically significant differences are indicated in bold

CI confidence interval

[a] Adjusted for age, sex, smoking status, and primary care visits

T-lymphocyte-associated protein 4 gene has been associated with AD and several autoimmune diseases, including CD, and is suspected of playing a vital role in regulation of the immune response in these conditions [12, 22–24].

The cause of the stronger association among adult patients with moderate-to-severe AD could not be determined on the basis of our data. Nevertheless, our hypothesis is that the correlation between AD severity and the strength of association to CD strengthen our observation as CD cannot be acquired from exposure to systemic AD-related medication or phototherapy, which were the markers for moderate-to-severe AD in our study.

4.3 Strengths and Limitations

We conducted a large, registry-based real-life study of patients diagnosed with AD by dermatologists both in primary care and community as well as in tertiary care settings. Thus, the main strength of the study is the inclusion of patients from different healthcare settings, thereby avoiding the potential selection bias inherent to observational studies conducted in tertiary centers. This is the setting where the vast majority of patients with AD are encountered. However, the study was limited by the possibility of incidence prevalence and temporal biases owing to the cross-sectional design, and a potential detection bias because of the possibly increased frequency of primary care physician visits by patients with disturbing medical conditions such as AD. Furthermore, as the case definition was based on digitally transmitted data, we may have missed some undiagnosed patients with AD. Diagnosis by a dermatologist is likely to bias the data towards patients with more severe conditions, particularly in the pediatric population.

5 Conclusions

Our study provides important epidemiological evidence regarding the association between AD and CD, particularly among adult patients with moderate-to-severe AD. Clinicians should consider lowering the threshold for the appropriate screening tests for CD in patients with AD. This would allow for a more timely diagnosis of CD to prevent long-term complications.

Compliance with Ethical Standards

Funding No funding was received for the conduct of this study or the preparation of this article.

Conflict of interest Guy Shalom, Khalaf Kridin, Keren-Or Raviv, Tamar Freud, Doron Comaneshter, Rivka Friedland, Arnon D. Cohen, and Dan Ben-Amitai have no conflicts of interest that are directly relevant to the content of this article.

Ethical approval The present study was conducted in accordance with the Declaration of Helsinki and all appropriate amendments. The study was approved by the Ethics Review Committee of Clalit Health Services.

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