Egyptian Pediatric Association Gazette

RESEARCH Open Access

Metabolic and inflammatory biomarkers in children with atopic dermatitis (AD): a case-control study

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Abstract

Background: Atopic dermatitis is characterized by impaired skin barrier and altered cutaneous innate immunity. The estimated prevalence among Egyptian children was 10–12%. Several studies suggest that it may be associated with systemic comorbidities other than the spectrum of atopy, such as metabolic syndrome and other inflammatory conditions. The aim of this study is to compare the profile of systemic conditions of diabetes, dyslipidemia, and multiple inflammatory markers in children with and without diagnosed atopic dermatitis.

Methods: One hundred atopic dermatitis patients and 101 normal controls were collected from outpatient clinic based on their clinical condition, both had measurement of body mass index, blood sugar, serum insulin, lipid profile, C reactive protein, and gamma-glutamyl transferase.

Results: Children diagnosed with atopic dermatitis had significantly higher levels of body mass index (34.7 ± 5.7 vs 26.1 ± 4.9), fasting glucose (143.2 ± 30.3 vs 100.8 ± 16.0), serum insulin (11.3 ± 4.4 vs. 4.6 ± 3.0), serum triglycerides (194.1 ± 38.1 vs 156.2 ± 31.6), total cholesterol (198.4 ± 27.7 vs 163.7 ± 27.7), alkaline phosphatase (229.4 ± 89.8 vs. 189.4 ± 46.8), and gamma-glutamyl transferase (54.7 ± 19.9 vs 34.3 ± 9.5), C-reactive protein level was approximately four times higher (19.9 ± 13.2 vs 5.1 ± 3.4) and the immunoglobulin E level was approximately 10 times higher (2050.3 ± 843.8 vs 252.7 ± 103.1) than in controls

Conclusion: We found a positive relationship of atopic dermatitis with both diabetes and hyperlipidemia among children, and positive dose-response relationship of several non-traditional biomarkers of C-reactive protein, gamma-glutamyl transferase, and alkaline phosphatase with the presence and severity of atopic dermatitis.

Keywords: Atopic dermatitis, Diabetes, Dyslipidemia, C reactive protein, IgE, Glutamyl gamma transferase, Alkaline phosphatase, Alkaline phosphatase

Background

Atopic dermatitis (AD), a chronic relapsing skin disease, is characterized by impaired skin barrier and altered cutaneous innate immunity [1] that affects children more than adults [2]. The estimated AD prevalence among Egyptian children was 10–12% [3–6] with different severity levels and complications. Evidence documenting association between AD and systemic comorbidities other than the spectrum of atopy is still controversial, such as metabolic syndrome [7–9] and other inflammatory conditions [10]. However, inconsistent findings have been reported around the associations of AD with diabetes and dyslipidemia [11–14]. The aim of this study is to compare the profile of systemic conditions of diabetes,

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dyslipidemia, and multiple inflammatory markers in children with and without diagnosed AD.

Methods

We conducted a case-control study of children (ages 5–18) who sought outpatient care in the Dermatology Department. Study participants were enrolled between June 2018 and May 2019. One hundred cases were ascertained by a licensed dermatologist and recruited for the study. We used the standard AD diagnostic criteria by Hanifin and Rajika [15] to identify cases. Using the scoring atopic dermatitis (SCORAD) index, we classified the severity of AD in all cases into three levels—mild (SCORAD index < 25), moderate (SCORAD index 25–40), and severe (SCORAD index > 40). From the same outpatient care facility, we also recruited one hundred and one children without AD as controls. Children who reported prior diagnosis of systemic diseases other than bronchial asthma or diabetes, those who received systemic treatment for AD or other concomitant dermatologic diseases (psoriasis, vitiligo, ichthyosis, and current skin infections) were excluded. From the same source population where patients have shared socioeconomic circumstances, we identified and recruited 101 children as controls who fulfilled the criteria of having no AD or any other dermatological disease and were between aged 1 to 14 at the time of recruitment. Informed verbal consent was obtained from the parents of all children who participated in the study. This study was approved by the NHTMRI research ethical committee.

Measurement of biomarkers

Diabetes was diagnosed by measuring blood glucose levels in blood samples withdrawn from the participants after 8 h of no caloric intake. Fasting blood glucose level of 126 mg/dl or higher was diagnostic of diabetes.

Statistical analysis

This study was approved by the research ethical committee in june 2018. serial 12-2018

body mass index (BMI) calculated for each participant as body (weight kg)/height^2 (m^2)

Five milliliters of blood was withdrawn from each participant allowed to clot, and then centrifuged at 3000 rpm for 15 min and serum separated for quantitative determination of the following tests fasting glucose (mg/dL), alkaline phosphatase (U/L), serum triglycerides (mg/dL), cholesterol (mg/L), and GGT (IU/L) which assessed by wet chemistry Bachman machine while CRP (mg/L), IgE were measured by ELISA according to manufacture instructions. We presented the population characteristics of demographic, clinical, and laboratory variables in mean± standard deviation (SD) and tested

Table 1 Baseline demographic, clinical, and laboratory characteristics of cases and controls

	Controls $N = 101$	Cases $N = 100$	*P* value
Gender			< 0.001
Males	63 (62.4%)	39 (39.0%)	
Females	38 (37.6%)	61 (61.0%)	
Age (years)	9.2 ± 3.3	11.0 ± 2.7	< 0.001
Age categories			< 0.001
Children	78 (77.2%)	53 (53.0%)	
Adolescents	23 (22.8%)	47 (47.0%)	
BMI	26.1 ± 4.9	34.7 ± 5.7	< 0.001
BMI for age and gender			< 0.001
Normal	14 (13.9%)	0 (0.0%)	
Overweight	52 (51.5%)	19 (19.0%)	
Obese	35 (34.7%)	81 (81.0%)	
Fasting glucose (mg/dL)	100.8 ± 16.0	143.2 ± 30.3	< 0.001
Diabetes			< 0.001
Normal	63 (62.4%)	6 (6.0%)	
Prediabetes	32 (31.7%)	25 (25.0%)	
Diabetes	6 (5.9%)	69 (69.0%)	
Insulin (mIU/L)	4.6 ± 3.0	11.3 ± 4.4	< 0.001
CRP (mg/L)	5.1 ± 3.4	19.9 ± 13.2	< 0.001
CRP categories			< 0.001
Normal	95 (94.1%)	18 (18.0%)	
Elevated	6 (5.9%)	82 (82.0%)	
IgE	252.7 ± 103.1	2050.3 ± 843.8	< 0.001
IgE categories			< 0.001
Normal	93 (92.1%)	5 (5.0%)	
Elevated	8 (7.9%)	95 (95.0%)	
Serum triglycerides (mg/dL)	156.2 ± 31.6	194.1 ± 38.1	< 0.001
Triglycerides categories			< 0.001
Normal	51 (50.5%)	5 (5.0%)	
Borderline high	32 (31.7%)	58 (58.0%)	
High	18 (17.8%)	37 (37.0%)	
Cholesterol (mg/L)	163.7 ± 27.7	198.4 ± 27.7	< 0.001
Cholesterol categories			< 0.001
Normal	96 (95.0%)	66 (66.0%)	
Borderline high	2 (2.0%)	21 (21.0%)	
High	3 (3.0%)	13 (13.0%)	
Alkaline phosphatase (U/L)	189.4 ± 46.8	229.4 ± 89.8	< 0.001
Alkaline phosphatase categories			0.67
Normal	87 (86.1%)	84 (84.0%)	
Elevated	14 (13.9%)	16 (16.0%)	
GGT (IU/L)	34.3 ± 9.5	54.7 ± 19.9	< 0.001
GGT categories			< 0.001
Normal	54 (53.5%)	17 (17.0%)	
Elevated	47 (46.5%)	83 (83.0%)	

the distribution difference using Student's *t* test for continuous variables; and presented categorical variables in frequency (proportions) and examined the differences using χ^2 test. We calculated the coefficient of variation (CV) for all continuous markers, as group mean/standard deviation, by the three levels of AD (mild, moderate, and severe) and the control group. We graphically display the distributions of all the continuous markers by AD severity using box and whiskers plots. We considered 2-sided p value < 0.05 statistically significant. The data were analyzed using Stata Software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp. LLC).

Results

Our study recruited 100 AD cases and 101 controls. Among the cases, the numbers of mild, moderate and severe AD were 16 (16%), 34 (34%), and 50 (50%), respectively. Compared to controls, children diagnosed with AD were more likely to be females (61.0% vs 37.6%), older in age (11.0 ± 2.7 vs 9.2 ± 3.3) and had significantly higher levels of body mass index (BMI) (34.7 ± 5.7 vs 26.1 ± 4.9), fasting glucose (143.2 ± 30.3 vs 100.8 ± 16.0), serum insulin (11.3 ± 4.4 vs. 4.6 ± 3.0), serum triglycerides (194.1 ± 38.1 vs 156.2 ± 31.6), total cholesterol (198.4 ± 27.7 vs 163.7 ± 27.7), alkaline phosphatase (229.4 ± 89.8 vs. 189.4 ± 46.8), and gamma-glutamyl transferase (GGT) (54.7 ± 19.9 vs 34.3 ± 9.5) (Table 1). Specifically, the serum C-reactive protein (CRP) level was approximately four times higher (19.9 ± 13.2 vs 5.1 ± 3.4) and the immunoglobulin E (IgE) level was approximately 10 times higher (2050.3 ± 843.8 vs 252.7 ± 103.1) in AD cases than in controls, respectively. The distributions of the continuous diabetes, lipids, and inflammatory markers displayed in the box and whiskers plots (Fig. 1) show consistent positive dose-response relationship between AD severity and level of the markers. Markers of serum insulin, CRP, IgE, alkaline phosphatase, and GGT have shown high variability (CV > 30%) across AD severity.

Discussion

In the current case-control study of children, 5–18 years of age, we observed that AD cases have significantly higher prevalence of diabetes and dyslipidemia compared to children without AD. We found that biomarkers of diabetes, lipids, inflammation (CRP and IgE), alkaline phosphatase, and GGT have a positive dose-response relationship with the presence and severity of AD.

Several studies have reported findings of positive association between diabetes and atopy that are consistent

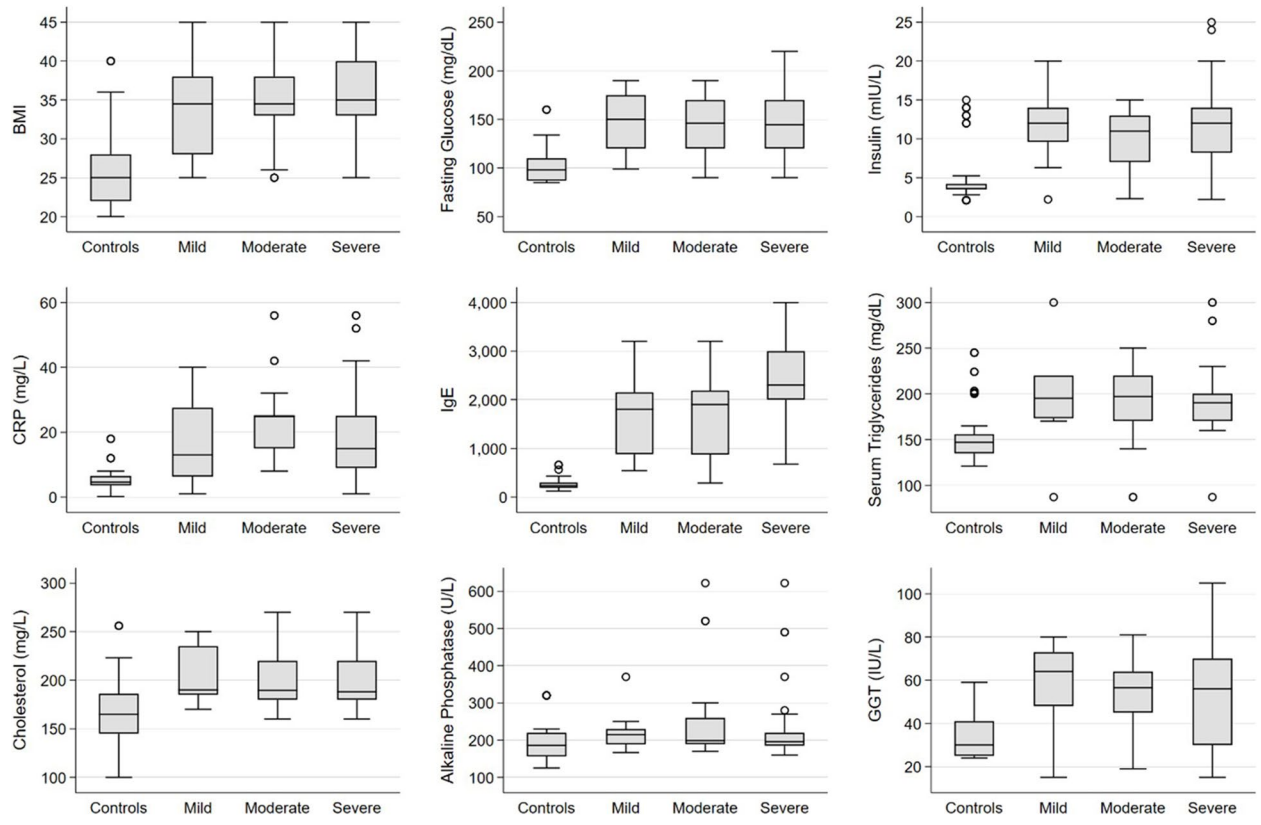

Fig. 1 Box and whiskers plot of several biomarkers by the severity of atopic dermatitis and control. Kruskal-Wallis test $p < 0.001$ for all biomarkers

with our study [11, 16–18]. However, the association between AD and diabetes was not conclusive in the literature. A large cohort of total 178,507 adults had showed no positive or negative association between diabetes and AD [12]. On the other hand, three European case-control studies, including both children and adults, had found that the two conditions were inversely associated [19–21]. The most adopted hypothesis for this inverse association is the T-helper1/2 (TH1/TH2) paradigm, which proposed that AD protects patients from developing diabetes [22, 23]. However, findings by other studies argued against the oversimplicity of this hypothesis, as the pathogenesis of both conditions involves autoimmunity components other than T cells, such as TH17, Tregs, and NK T cells [24, 25]. Genetic predisposition supports the positive association between AD and diabetes, as five chromosomal loci were found to be shared by both conditions (1q21, 2q33, 5q31.1-q33.1, 6p21, and 11q13) [26].

We observed that inflammatory markers (CRP and IgE) were significantly elevated in children with AD compared to controls. Other pediatric studies had found that early elevation of CRP is associated with lower risks of AD [10, 27] and decreases allergic sensitization in children [28]. However, multiple studies of adults with AD reported similar findings as ours, and the overall evidence supports the systemic involvement of AD in immune response [29, 30], even in the early stage of life, as shown in our results.

Limitation of this study included the use of observational case-control study design and a small sample size. However, given the relatively low prevalence of AD among children (approximately 10%) and the challenge of recruiting and following-up cases, a case-control study is the most cost-efficient design for examining this topic with our restricted resources.

Conclusion

We found a positive relationship of AD with both diabetes and hyperlipidemia among children, and positive dose-response relationship of several non-traditional biomarkers of CRP, GGT, and alkaline phosphatase with the presence and severity of AD. Our findings provide insights to hypothesis generation and risk factor identification for future research to protect children with AD.

Acknowledgements
To the patients and their guardians, no funding was received.

Authors' contributions
All authors put the study design. Drs. Amal Ahmed Mohamed, Dina M Bassiuny, and Naglaa Fawzy were responsible of sample assessments and lab measurements. Drs. Eman M. Salah, Aliaa E.M. Daifullah, and Nermeen Ibrahim Bedair were responsible of dermatological examination and determination of AD and severity. Drs. Ola Gamil Behairy and Mohamed F. Alsoda were responsible of pediatric exam and BMI. Dr. Youssef Farag was responsible for statistical analysis. Drs. Nermeen Ibrahim Bedair and Youssef Farag were responsible for literature review and preparing the draft for this manuscript. All authors approved the manuscript for publishing.

Funding
No funding was received for this work.

Availability of data and materials
Dr. Amal Ahmed. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data and materials are available upon request.

Declarations

Ethics approval and consent to participate
Ethical committee of the National Research Institute of Hepatic Disease and Tropical Medicine, approval serial 12/2018 was granted prior to the study and consent was obtained the guardians of all participants. All participants approved publication of the studies based on their data.

Consent for publication
Not applicable. All participants approved publication of studies based on their data, this manuscript contains no individual details, images, or videos that may require a special consent from any of the participants/guardians and this is not a case report. All authors approved the manuscript for publishing.

Competing interests
All authors declare that they have no competing interests.

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Received: 21 September 2021 Accepted: 25 October 2021
Published online: 03 November 2021

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