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Adult Atopic Dermatitis and Metabolic Syndrome: A Case Controlled Study

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ABSTRACT

Background: Atopic dermatitis (AD) is the commonest inflammatory skin disorder globally. Metabolic syndrome (MetS) has become a worldwide problem. Cases that have severe AD might have undiagnosed components of MetS.

Objective: This study aimed to assess prevalence of MetS in adults with AD versus controls and its relationship to Atopic dermatitis Severity

Patients and methods: This case-control study included 30 atopic dermatitis cases and 30 age- and sex-matched controls to evaluate prevalence of metabolic syndrome. All of the studied groups (cases & control) were subjected to careful history taking and full dermatologic examination. Lipid profile was also done.

Results: A statistically significant higher prevalence of metabolic syndrome among atopic dermatitis cases than control group (40% & 16.7% respectively). A significant relationship was detected between presence of MetS and female sex. Atopic dermatitis score could be used as a good indictor in differentiating cases from control group (yielding sensitivity of 75% and specificity of 61.1%).

Conclusion: This study added important epidemiologic evidence about the correlation between AD and MetS and its components. A statistically significant higher prevalence of MetS among atopic dermatitis patients than among control group (40% & 16.7% respectively). A statistically significant relationship was detected between presence of MetS and female sex was reported.

Keywords: Atopic dermatitis, Metabolic syndrome, Lipid profile, Atopic dermatitis severity.

INTRODUCTION

AD is the commonest inflammatory skin disease globally. Patients present with generalized skin dryness, itching, and rashes. AD is due to interplay between environmental and genetic factors and its phenotype differs considerably, on the other hand it is characterized by remissions and relapses with acute flaring on a background of chronic dermatitis. It often starts in infancy, involving about 20% of children. About 80% of the children develop AD before 6 years of age. AD can affect any age. Its prevalence in young adults aged 26 years is 5–15%, with a lifetime prevalence >15% particularly in developed nations. AD often affects those with an 'atopic tendency' clustering with hay fever, bronchial asthma (BA), and food allergy [1].

Metabolic syndrome is characterized by at least 3 of the next: Central obesity, hypertriglyceridaemia, low HDL cholesterol, hypertension (HTN), and hyperglycemia [2]. It is estimated that about 25-35% of population has MetS worldwide [3]. The correlation between AD and MetS is not completely explained. A Korean study involving 5,007 adults found that abdominal obesity and hypertriglyceridaemia were positively associated with AD among females [4].

Furthermore, another major research revealed that the correlation of AD with MetS wasn't causal. Correlations between HTN, hyperglycaemia, cholesterol concentrations, and AD are still uncertain. Central obesity was the only criterion, which showed a positive correlation with AD [5]. Another case-control study and a systematic review revealed this result and obesity was correlated with high prevalence and severity of AD [3].

According to another cross-sectional study, severe AD might have an association with one or more undiagnosed MetS components [6]. Therefore, we aimed to assess prevalence of MetS in adults with AD versus control and its relationship to atopic dermatitis severity.

PATIENTS AND METHODS

This case-control study comprised 30 cases diagnosed as atopic dermatitis and age- and sex- 30 non-atopic dermatitis volunteers act as control who attended the dermatology outpatient clinic at Mansoura University Hospital.

Study Groups: Group (A) included patients with AD and group (B), which Included controls.

Inclusion criteria: 1. Patients aged 18-60 years (both males and females). 2. Presence of atopic criteria based on UK working party Clinical Criteria (itching, dryness, scaling, Lichenification) [7]. For Control only: no past history of inflammatory or allergic disorders.

Exclusion criteria: 1. Pregnancy and lactation. 2. Patients with other chronic dermatologic diseases known to be associated with MetS including psoriasis, acne, hirsutism, rosacea, androgenic alopecia, acanthosis nigricans and skin tags, lichen planus and skin cancers like malignant melanoma. 3. Patients with liver or kidney dysfunction. 4. Systemic inflammatory disorders such as rheumatoid arthritis, SLE and multiple sclerosis. 5. Drugs that change the lipid profile as (Statins, isotretinoin, acetritin). 6. Systemic corticosteroids and immunosuppressive treatment within the past month.

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All patients were subjected to: Detailed history taking was done including age, gender, occupation, residence, any special habit and marital status. Onset, course and duration of atopic symptoms were also assessed. History of current topical and systemic treatment, history of drug intake, history of other pathological conditions and family history of similar condition or allergies as BA, allergic rhinitis (AR) and allergic conjunctivitis were taken.

General examination was done, which included blood pressure (hypertension is diagnosed as systolic blood pressure (SBP) > 130 mmHg or diastolic (DBP) above 85 mmHg. Waist circumference (WC) was measured (using a measuring tape at the level of the uppermost part of the hip bone horizontally around the abdomen) . Assessment of body mass index through: BMI= kg/m^2. **Full dermatological examination** was done. Each patient was examined to assess the affected areas of the skin regarding distribution and nature of lesion.

Criteria for clinical diagnosis of AD: [7] Included itchy skin and presence of three of the following; Visible flexural eczema, history of dermatitis, history of skin dryness over the previous 12 months, history of BA or AR and onset of clinical manifestations before the age of 24 months (Such criteria are not to be utilized in children below 4 years).

Lipid profile sampling: 2 cm venous blood were taken from fasting patient for at least 6 hours in a plain tube, serum was separated from sample by End Point Chemistry method.

Severity Scoring of Atopic Dermatitis (SCORAD) [8]:

SCORAD is a composite scoring index consisting of objective signs (Extent and severity of involvement) and subjective manifestations (Itchy skin and trouble sleeping) (Severity Scoring of Atopic Dermatitis 1993). The score is calculated as follows:
A. Extent of affection; exclude nine is used in adult patients but modified in pediatric population. Scores of all areas are added together, to give a total area referred to as "A" (maximum score = 100). Eczema intensity is scored as none (zero), mild (I), moderate (II), or severe (III) depending on Erythema, oedema/population, Oozing/crusting, lichenification and dry skin. Intensity scores are added together to give "B" (maximum score = 18). Subjective manifestations in the previous three days or nights include pruritus (VAS 0-10) and trouble sleeping (VAS 0-10).
Both scores were got "C" (maximum score= 20).
SCORAD underwent calculation based on the following formula: A/5+7B/2+C.
According to SCORAD, Patients were classified according to AD severity into mild (< 25), moderate (25-50) and severe (>50).

Assessment of metabolic syndrome: Presence of at least three of the National Cholesterol Education Program Adult Treatment Panel III criteria are essential for diagnosis of MetS **[9]**, which includes WC ≥ 102 cm (males) or ≥ 88 cm (females), hypertriglyceridaemia ≥ 150 mg/dl), HDL-C < 40 mg/dl (males) or < 50 mg/dl (women), hypertension blood pressure ≥ 130 ⁄85 mmHg and hyperglycemia ≥ 100 mg/dl.

Ethical considerations: Our study obtained its approval from The Institutional Review Board, Faculty of Medicine, Mansoura University at 09/01/2022 and its approval code MS.21.12.1786 and followed the Declaration of Helsinki. Confidentiality and privacy were maintained throughout our study. Any patient was free to withdraw at any time without consequences. Patients' data weren't utilized for any other purpose. Informed written consents were obtained from all participants.

Statistical analysis

Data underwent analysis by SPSS software, V 25 (PASW statistics for windows, Chicago, SPSS Inc.). Qualitative data were represented in numbers and percentages. Quantitative data were expressed as means ± SDs for normally distributed data after testing normality using Kolmogorov-Smirnov test. The significance level was set at ≤ 0.05 level. Chi-Square, Fisher exact test and Monte Carlo tests were utilized for comparing qualitative data among the groups. Student-t test was utilized to compare 2 independent groups for normally distributed data. The Spearman's rank-order correlation determined the strength and direction of a linear connection among two non-normally distributed continuous variables. ROC curve was used to measure the validity of continuous variables and the best cut-off point was calculated.

RESULTS

The present study was case-control study that was carried out on 30 atopic dermatitis cases versus 30 age- & sex-matched control group to evaluate prevalence of MetS in adults with AD and its relationship to disease severity. Cases that following inclusion criteria aged 18 - 60 years. All of the studied groups (cases & control) were subjected to careful history taking, general and full dermatologic examination. Mean age of the studied cases is 35.7 ± 12.69 years versus 33.43 ± 10.79 years for control group without significant difference between them (p=0.459). No significant difference was detected between cases & control regarding sex with 80% of cases versus 73.3% of control were females and males were 20% of cases versus 26% of control as shown in table (1).

Table (1): Demographics characteristics of the two groups

	Cases group (n=30)	Control group (n=30)	test of significance	p value
Age in years Mean ± SD	35.70±12.69	33.43±10.79	t=0.745	0.459
Sex Male Female	N (%) 6(20.0) 24(80.0)	N (%) 8(26.7) 22(73.3)	χ^2=0.373	0.542

t: Student t test, χ^2=Chi-Square test.

A significant higher mean SBP (P value = 0.01) & DBS (P = 0.039) among cases than among control group. Mean levels of fasting blood glucose (mg/dl) (P = 0.01), TG (mg/dl) (P = 0.001), cholesterol (mg/dl) (P value = 0.017) and LDL-cholesterol (mg/dl) (P = 0.019) were higher among cases than among control group with significant difference between them. No significant difference was found between both groups regarding weight, height, BMI, WC and HDL-cholesterol as shown in table (2).

Table (2): Parameters for metS among studied groups

Assessment of Metabolic Syndrome	Cases group (n=30)	Control group (n=30)	test of significance	p value
Weight (Kg)	83.3 7±20.81	77.67±19.24	t=1.10	0.275
Height(m)	1.64±0.06	1.64±0.09	t=0.255	0.800
BMI (kg/m^2)	30.43±7.32	27.90±5.51	t=1.51	0.135
Waist Circ.(cm)	100.57±14.67	99.43±16.47	t=0.281	0.779
SBP	118.83±20.20	106.17±17.20	t=2.62	0.01*
DBP	77.50±12.23	70.83±12.18	t=2.12	0.039*
Fasting blood glucose (mg/dl)	110.33±3.41	86.07±9.55	t=4.17	0.001*
Triglyceride (mg/dl)	119.43±3.74	85.33±8.94	t=4.20	0.001*
Total cholesterol (mg/dl)	193.53±5.68	169.53±27.70	t=2.46	0.017*
LDL-Cholesterol(mg/dl)	125.35±6.62	105.89±24.78	t=2.41	0.019*
HDL-Cholesterol (mg/dl)	47.70±5.99	46.27±5.42	t=0.971	0.335

t: Student t test, *statistically significant.

A statistically significant higher prevalence of metabolic syndrome among atopic dermatitis cases than among control group (40% & 16.7%, respectively) was shown in table (3).

Table (3): Comparison of metabolic syndrome prevalence in the two groups

MetS	Cases group (n=30)	Control group (n=30)	test of significance	p value
Not MetS	18(60.0) 12(40.0)	25(83.3) 5(16.7)	χ^2=4.02	0.04*

χ^2=Chi-Square test *statistically significant

Among 30 cases of atopic dermatitis, 80% chronic stage, 10% acute and 10% subacute stage as demonstrated in table (4).

Table (4): Stage of atopic dermatitis among studied cases

Stage of Lesion	n=30	%
Subacute Acute 3 Chronic 24	3	10.0 10.0 80.0

Among studied cases, 33.3% had positive family history of BA, 16.7%, AR and 3.3% AD as shown in table (5).

Table (5): Atopic dermatitis score of the studied cases

score	n=30	%
Value median (min-max)	39(9-68)	
Description Mild Moderate Severe	 4 21 5	 13.3 70.0 16.7

A significant negative association was found between atopic dermatitis score and weight of the studied cases (r=-0.396) (P = 0.03). Also, statistically significant negative association between AD score and BMI of the studied cases (r=-0.433) (P = 0.02). There was a significant negative correlation between atopic dermatitis score and waist circumference of the studied cases (r=-0.528) (P = 0.003). No significant association existed between disease score and height, SBP, DBP, fasting blood sugar, TG, cholesterol, HDL and LDL as shown in table (6).

Table (6): correlation between atopic dermatitis score and metabolic syndrome items of assessment among studied cases

	Score	
	r	*p value*
Weight (Kg)	**-0.396**	**0.03***
Height(m)	0.122	0.521
BMI (kg/m^2)	**-0.433**	**0.02***
Waist Circ.(cm)	**-0.528**	**0.003***
SBP	-0.182	0.335
DBP	-0.101	0.597
FBG (mg/dl)	-0.288	0.123
TG (mg/dl)	0.08	0.675
TC (mg/dl)	-0.269	0.150
LDL-C(mg/dl)	-0.342	0.064
HDL-C(mg/dl)	-0.108	0.569

r: Spearman correlation coefficient, *statistically significant

Area under curve for atopic dermatitis score was good in differentiating cases from control group with the best cut-off value was 39.5 yielding sensitivity of 75% and specificity of 61.1% as demonstrated in table (7) and figure (1).

Table (7): Validity of topic dermatitis score in differentiating cases with metabolic syndrome from case without metabolic syndrome

	AUC (95% CI)	P – value	Cut-off point	Sensitivity %	Specificity %
SCORE	0.671 (0.477-0.866	0.117	39.5	75.0	61.1

AUC: Area under curve, CI: Confidence interval

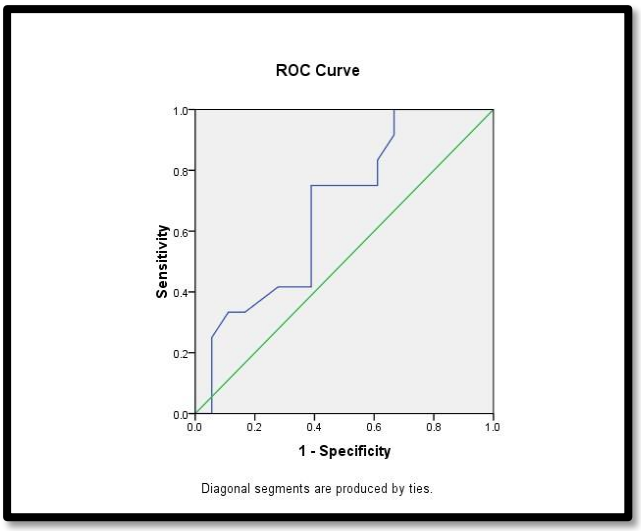

Figure (1): ROC curve for atopic dermatitis score in differentiating cases with metabolic from no metabolic syndrome.

DISCUSSION

AD is an inflammatory skin disease of a high prevalence globally. AD is characterized by itching and trouble sleeping that significantly decreases quality of life [10]. In recent years, the interest towards considering AD as a systemic disorder has increased after recognizing evidence about its correlation with several comorbid conditions [11]. Metabolic diseases (as obesity) co-existent with chronic skin diseases, like AD, have attracted significant attention and warranted more research. MetS is associated with DM and CAD [12]. It is diagnosed by the presence of at least 3 of the following criteria: increased WC, increased TG, low HDL, hyperglycemia and hypertension (2). Though the pathophysiology of MetS remains not fully understood, an interaction between genetic and environmental factors may have a role (3). Correlation between MetS and BA has been also suggested [13]. So far, the relationship between AD and MetS remains unclear [14]. Though some previous studies suggested a correlation between AD and lipid profile and obesity, or insulin resistance (IR), the results are inconsistent [15, 16].

Our study was a case-control study that involved 30 atopic dermatitis cases versus 30 age- and sex-matched control group to evaluate prevalence of MetS in AD adults and its relationship to disease severity.

In our study, mean age of cases was 35.7 ± 12.69 years versus 33.43 ± 10.79 years for control group without significant difference between them (p=0.459). No significant difference existed among cases & controls as regards sex with 80% of cases versus 73.3% of control were females and males were 20% of cases versus 26% of control. Similarly, **Ivert *et al.*** [17] found that most of AD cases were females (66·1%) with a mean age of 34·9 years. AD has long been considered as a primarily pediatric condition. But, there is evidence for an increased rate of adult-onset AD [18]. Similarly, **Talamonti *et al.*** [19] found that the mean age of AD cases and control group was 38.1±14 years and

39.9±13.1 years, respectively. **Salava *et al.*** [20] did not report significant sex difference, however the number of female cases was higher among all age groups. This was clarified by the increased number of female cases in primary care.

In our study, the commonest site of involvement was limbs (86.7%) followed by head & neck and trunk (26.7% each) and the least is in genitalia (3.3%). Among 30 cases of atopic dermatitis: 80% chronic stage, 10% acute and 10% subacute stage. **Wang *et al.*** [21] reported that the top 5 sites affected in AD were fossa cubitalis (44.1%), knees (37.4%), front of neck (33.6%), upper extremity (30.9%), and face (30.6%). The reason for such difference remains not clear, likely because of thickness of cut-in as well as friction frequency, as they have thinner stratum corneum and are susceptible to friction [22]**.** On the other hand, body areas with thick SC such as hands and feet are not susceptible for AD. AD shows more diverse skin lesions compared to other dermatitis forms, particularly in xerosis, scratches, and scales. This highlights the significance of utilizing emollients in AD cases to restore or replace skin abnormalities [23]. These differences of AD and other dermatitis forms, to some extent, help their clinical diagnoses [24].

Our study revealed that the median score of atopic dermatitis is 39 ranging from 9 to 68. For atopic dermatitis score, 70% moderate, 16.7% severe and 13.3% mild. Also **Silverberg *et al.*** [25] found that SCORAD was 32.0 ± 17.5. Our study showed that 33.3%of cases have positive family history of BA, 16.7% AR and 3.3% AD. Similarly, **Liu *et al.*** [26] conducted their study on 16 (10 men and 6 women, mean age was 45.63 years) moderate-to-severe AD patients showed that 25 % of cases had positive family history of BA, 12.5 % AR and 18.8% AD.

Our study revealed a statistically significant higher mean SBP (P = 0.01) & DBP (P = 0.039) among cases than among control group. Mean fasting blood glucose (P = 0.01), TG (P = 0.001) and cholesterol (P = 0.017), LDL-c (P = 0.019) were higher among cases compared to controls with significant difference between them. No significant difference existed among both groups regarding weight, height, BMI, WC and HDL-cholesterol. In the same line, **Yousaf *et al.*** [27] reported an association AD with higher odds of high blood pressure when compared to control group. Therefore, it was postulated that negative lifestyle factors could enhance the risk for cardio-metabolic consequences among AD cases [28]. In **Lee *et al.*** [4] study, they reported that female cases with AD were more likely to have hypertriglyceridemia compared to non-AD female cases. Also, **Seino *et al.*** [29] reported that TG accumulation was increased in mice with AD. They proposed that stress caused by AD may affect lipid and carbohydrate metabolism, resulting in MetS. Of note, there was a synergism between central obesity and hypertriglyceridemia in AD. IR has been recommended as a risk factor for allergic disorders [30].

Furthermore, **Singh *et al.*** [31] revealed a correlation between BA and MetS by demonstrating that IR is a potent, independent risk factor for BA. However, there was no evidence of a correlation between AD and hyperglycaemia in our study. Moreover, we found that BMI, WC, BF, and TG levels were more elevated among AD cases with coexistent AR or BA compared to cases with AD only. **Takeuchi and co-workers** [32] found that HDL concentrations were lower among AD cases with allergic conditions compared to cases with AD only. Many genome-wide association studies demonstrated that AD and BA share sone genes [33]**. Lee *et al.*** [4] found a significant correlation between MetS and AD in females only. Estrogen enhances the activity of eosinophils and inhibits cortisol synthesis [34]**.** Thus, women have more susceptibility to develop more severe allergy. This mechanism may have a role in the sex difference in that study.

We found a significantly higher prevalence of metabolic syndrome among atopic dermatitis cases than control group (40% & 16.7% respectively). A significant relationship was detected between presence of metabolic syndrome and female sex. Also, a significant relationship between presence of metabolic syndrome and absence of BA (P= 0.018), no significant difference existed among metabolic and non-metabolic cases as regards age, site of involvement, stage of lesion, score value and description of disease. In consistence with our results, **Shalom *et al.*** [16] found that moderate and severe AD were correlated, respectively, with greater prevalence rates of MetS (17.0% versus 9.4%), its components [(obesity: 22.2% versus 18.6%; DM: 15.9% versus 9.2%; hypertension 27.9% versus 15.3%; dyslipidemia 47.1% vs. 28.5%, and cardiovascular morbidity (P < 0.001)]. They stated that cases with severe AD might have one or more unidentified MetS components. Similarly, **Lee *et al.*** [4] found that AD was accompanied by the MetS and some of its components in females (P = 0.02). **Silverberg *et al.*** [35] evaluated 132 children having moderate-to-severe AD, a correlation with central obesity and high SBP was found. In a more refined analysis, the cardiovascular risk factors were similar between AD cases group and control group [28].

RECOMMENDATION

So, we recommend screening for metabolic abnormalities, including dyslipidemia, obesity, and HTN at the time of AD diagnosis and in follow up visits. Appropriate control of metabolic comorbidities among pediatric population is important to decrease the risk of MetS and cardiovascular complications in adults.

CONCLUSION

Our study added epidemiologic evidence about the correlation between AD and the MetS and its components. A statistically significant higher prevalence of metabolic syndrome among atopic dermatitis cases compared to control group (40% &

16.7% respectively). A significant relationship was detected between presence of MetS and female sex.

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