

Decreased Sudomotor Function is Involved in the Formation of Atopic Eczema in the Cubital Fossa

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ABSTRACT

Background: Eczema in the cubital fossa, which is susceptible to sweat, is frequently observed in atopic dermatitis (AD). However, there has been no direct evidence that sweating causes eczema in the cubital fossa.

Methods: To investigate this issue, axon reflex-mediated sweating volume (AXR) and skin barrier function in the cubital fossa were measured in subjects with AD and in healthy volunteers, and were applied to clinical feature of the cubital fossa.

Results: AXR in the cubital fossa decreased in AD subjects; it positively correlated only with water-holding capacity in healthy subjects but not in patients with in AD. Furthermore, AD subjects with lichenoid eczema and either prurigo or papules over the cubital fossa showed extremely decreased AXR.

Conclusions: These results suggest that decreased sweating is a major source of water in the stratum corneum, and decreased sudomotor function may be involved in both the cause and aggravation of representative atopic eczema in the cubital fossa.

KEY WORDS

atopic dermatitis, exacerbation, homeostasis, skin barrier function, sweating

INTRODUCTION

Ordinarily, several types of eczema, such as red papules, xerosis, xerotic eczema, miliaria, lichenoid change, and prurigo, are observed in daily clinical practice. Recent advances on the mechanisms of atopic dermatitis (AD) suggest that the causes of AD range widely from 'allergic' to 'non-allergic'.^{1,2} In such complicated situations, establishing a link between the site of eczema and the cause of AD would be informative for all physicians.

Several factors maintain skin homeostasis of skin and coordinately regulate the permeability and solidity of the skin barrier. In evaluating methods to assess skin barrier function in AD, many reports have examined trans-epidermal water loss (TEWL) and water-holding capacity (WHC).^{3,4} Abnormal skin

physiology, such as decreased sweating, has also been thought to be involved in the pathogenesis of AD.^{5,6} At present, we have reported that axon reflex-mediated sweating volume (AXR) might be decreased according to the levels of stress and anxiety in patients.⁷⁻⁹ However, it is not known whether skin barrier function and clinical features of AD are closely connected to sweating volume. In particular, eczema on the cubital fossa (elbow) or behind the knees is frequently observed in AD patients¹⁰⁻¹² and appears to be susceptible to excessive sweating followed by retention of allergic or irritating substances under anatomically low-hydration circumstances.

Thus, we analyzed the interactions of the skin barrier function, AXR, and clinical manifestations of the cubital fossa in subjects with AD.

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Conflict of interest: No potential conflict of interest was disclosed.
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Received 15 February 2013. Accepted for publication 29 May 2013.

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Table 1 Breakdown of the concrete data of both AD and healthy subjects

	AD	Healthy control
Age [years: mean $\pm$ SD]	32.7 $\pm$ 8.95	33.3 $\pm$ 10.02
Case number	<i>n</i> = 35	<i>n</i> = 38
Age range [years]	16-61	22-59
Gender	Male 18, female 17	Male 16, female 13
AXR [mg/5min: mean $\pm$ SD]	0.95 $\pm$ 0.75	1.71 $\pm$ 0.8582
TEWL [g/m ² h: mean $\pm$ SD]	16.31 $\pm$ 9.996	11.68 $\pm$ 10.14
WHC [μ S: mean $\pm$ SD]	118.1 $\pm$ 76.73	212.6 $\pm$ 128.1

METHODS

SUBJECTS

Skin Barrier Function

TEWL and WHC were measured to evaluate the skin barrier function. A 3.5-MHz Skicon-200 (I.B.S., Japan) was used to measure water-holding capacity, which estimates skin conductance. An MPA-5 system with a TM 300 probe (Courage and Khazaka Electronic, Cologne, Germany) was used to measure TEWL. Measurements were performed on the cubital fossa in a hospital outpatient clinic; the average temperature of the room was 21.4°C and the relative humidity was 57.8%. The number of subjects is presented in Table 1.

Quantitative Sudomotor Axon Reflex Test (QSART)

In this study, acetylcholine (ACh)-induced sweating volume was measured quantitatively by QSART as described previously.¹³ Briefly, the subjects were asked to remain quiet for 20 min before undergoing QSART in a hospital outpatient clinic at constant temperature (20°C) and relative humidity (60%). The multi-compartmental sweat capsule used in QSART consists of two independent compartments. ACh (100 mg/ml) was iontophoretically applied to the skin from the outer compartment, which stimulates the underlying sweat glands directly, whereas the glands of the skin in the central compartment of the capsule are activated indirectly via an axon reflex. The central compartment of the capsule serves as the site of AXR measurement during the 5 min of iontophoresis. The area under the sweating curve was calculated from 0-5 min for AXR. The measurement of QSART was performed on the cubital fossa.

Study Design

This study was approved by the Institutional Review Board of Osaka University Hospital. All measurements were performed on all study subjects after they signed an informed consent form and provided written and oral information to the study physicians. Patients with AD fulfilled the diagnostic criteria by

Hanifin and Rajka,¹⁴ and the Japanese Dermatological Association¹⁵; patients consulted our clinic after complaining of resistance to standard therapy. The number of subjects is presented in Table 1.

Statistical Analysis

An unpaired *t* test or Pearson's correlation coefficient was used to compare differences in mean values or to assess the association between AXR and skin barrier function, respectively. These analyses were performed using Prism 5 software (GraphPad Software, La Jolla, CA, USA). The Pearson's chi square test was used to compare categorical variables using Statistical Package for the Social Sciences (SPSS) version 19.0 for Windows. In all analyses, a *p* value less than 0.05 was considered significant.

RESULTS

ACH-INDUCED SWEATING VOLUME IN HEALTHY AND AD SUBJECTS

ACh-induced AXR on the cubital fossa was measured in healthy and AD subjects. Comparison of AXR between healthy and AD subjects was performed (Fig. 1 A, B, Table 1). As for differences with respect to gender, AXR in females was lower than that in males, and AXR in female AD subjects was significantly lower than in other groups (Fig. 1A). The mean value of AXR of all AD patients was lower than that of healthy subjects with statistical significance (Fig. 1B).

RELATION BETWEEN SKIN BARRIER FUNCTION AND SUDOMOTOR FUNCTION IN BOTH AD AND HEALTHY SUBJECTS

Similar to previous reports, the measurement results of WHC of the cubital fossa in patients with AD were significantly lower than in healthy subjects (Fig. 1B, Table 1). On the one hand, the TEWL of the cubital fossa in AD patients tended to show higher measurement results than that in healthy subjects without statistical significance (Fig. 1C, unpaired *t* test, *p* = 0.0716). Next, we focused on the correlation between TEWL or WHC, and AXR in the cubital fossa of subjects with AD and in healthy volunteers (Fig. 2). In healthy subjects, AXR was positively correlated with WHC, but not with TEWL (Fig. 2A). On the other hand, in subjects with AD, AXR did not correlate with either WHC or TEWL (Fig. 2B).

ASSOCIATION BETWEEN THE CUTANEOUS MANIFESTATIONS OF THE CUBITAL FOSSA AND SUDOMOTOR FUNCTION

Subsequently, we took particular note of the existence of two distinct groups that were characterized by relatively less and sufficient sweating in subjects with AD and ascertained whether either group had distinct clinical features of AD in the cubital fossa. Therefore, subjects with AD were divided into two groups: below- or above-average AXR. As a result of

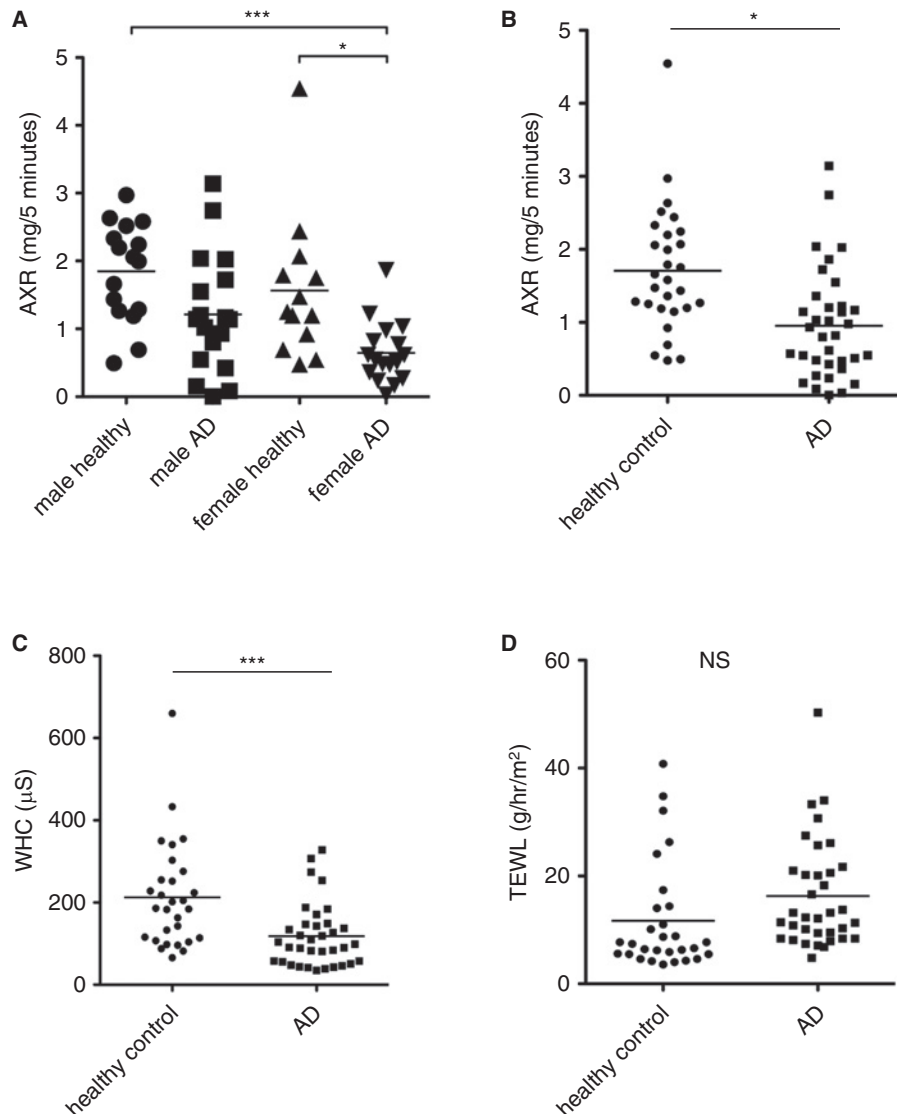


Fig. 1 **A.** Differences with regard to gender for AXR, measured by QSART in healthy and AD subjects. * $p < 0.05$, *** $p < 0.0005$, one-way analysis of variance, Bonferoni's multiple comparison test. **B.** Results for AXR, measured by QSART in healthy and AD subjects. * $p < 0.05$, unpaired t test. **C.** Results of WHC in healthy and AD subjects. *** $p < 0.0005$, unpaired t test. **D.** Results of TEWL in healthy and AD subjects. NS, no statistical significance in unpaired t test.

this grouping, we found that the below-average sweating group (<average AXR) had clinical characteristics different than the above-average sweating group (Table 2). Compared with the above-average sweating group (>average AXR), the below-average sweating group was associated with a much higher incidence of clinical manifestations, such as lichenoid eczema, prurigo, or papules (Table 2, Fig. 3). However, the above-average sweating group tended to have no eruptions (Table 2, Fig. 3).

DISCUSSION

Here we examined the relationship between AXR, and skin barrier function or clinical manifestations of the cubital fossa in AD. Our results indicate that atopic eczema in the cubital fossa might be related to both impaired sudomotor function and decreased WHC. With regard to the other clinical information, such as SCORAD score, disease duration, and serum concentrations of IgE, these parameters did not correlate with AXR (Supplementary Table 1).

First, although there was a positive correlation be-

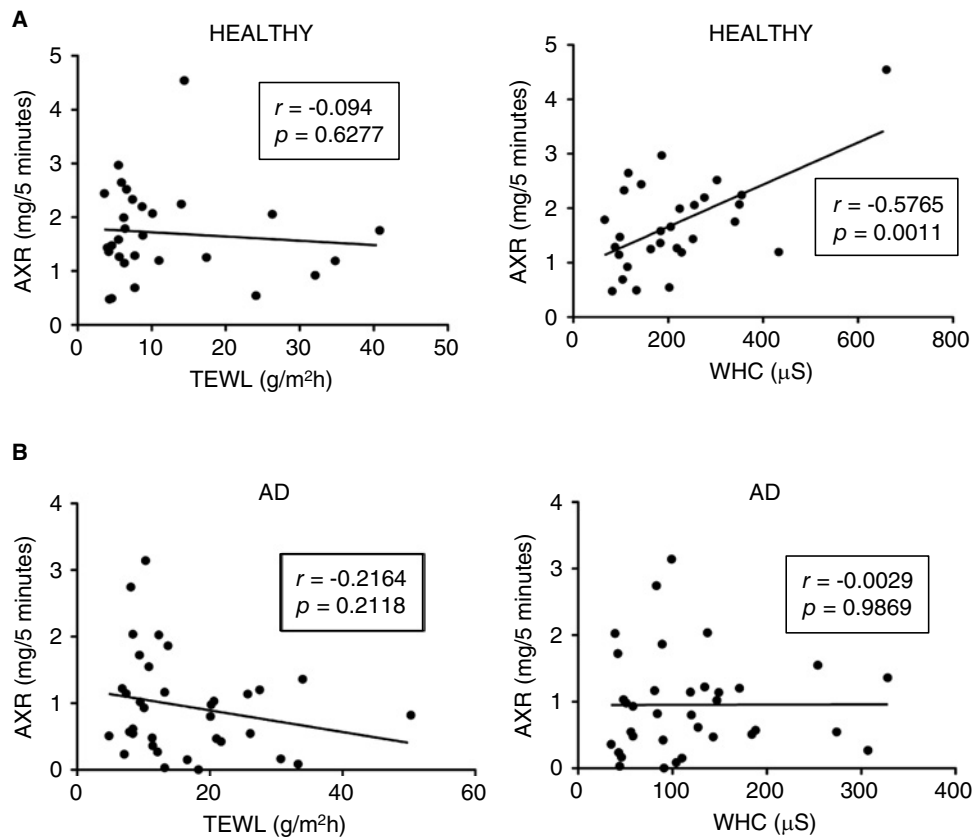


Fig. 2 Correlation between AXR and skin barrier function. **A.** Correlation between AXR, and TEWL or WHC in healthy subjects. **B.** Correlation between AXR, and TEWL or WHC in AD patients. TEWL, trans-epidermal water loss; WHC, water-holding capacity. Figures in the squares in the graphs represent the results of Pearson's correlation coefficient.

Table 2 Cross tabulation presenting the frequency of characteristic clinical manifestation in less or above-average sweating subject with AD

	Lichenoid eczema	Papules, prurigo	No eczematous change	Total
Above-average sweating	6 (23.1%)	5 (23.8%)	10 (83.8%)	21 (35.6%)
Less-average sweating	20 (76.9%)	16 (76.2%)	2 (16.7%)	38 (64.4%)
Total	26 (100%)	21 (100%)	12 (100%)	59 (100%)

Pearson's Chi-square test for independence, $p = 0.0001$.

tween AXR and WHC in healthy subjects, there was no correlation between AXR and WHC in AD. These results suggest that sweat might be a major source of water in the stratum corneum, and functional abnormalities of the stratum corneum in AD might impair the evaluation of WHC, even if patients have a sufficient sweating volume. From this point of view, maintenance of damaged stratum corneum in AD patients might be important to maintain water retention capacity.

Additionally, our study revealed decreased AXR in AD subjects with eczema in the cubital fossa. In this evaluation, AD patients were divided into two groups:

'above-average sweating' and 'below-average sweating.' We found the clinical manifestations of xerosis, xerotic eczema, papules, lichenoid changes, and prurigo to be associated with inadequate sweating. It is easy to assume that xerosis might be caused by a lack of sweat, as the water source for the stratum corneum. Lichenified skin lesions in AD patients are characterized by epidermal hyperplasia and are thought to develop by certain scratching-derived inflammatory mediators.^{16,17} The involvement of sweat in the pathogenesis of lichenoid dermatitis has been suggested by the histopathological abnormalities of sweat glands in lesional skin.¹⁸ However, little is

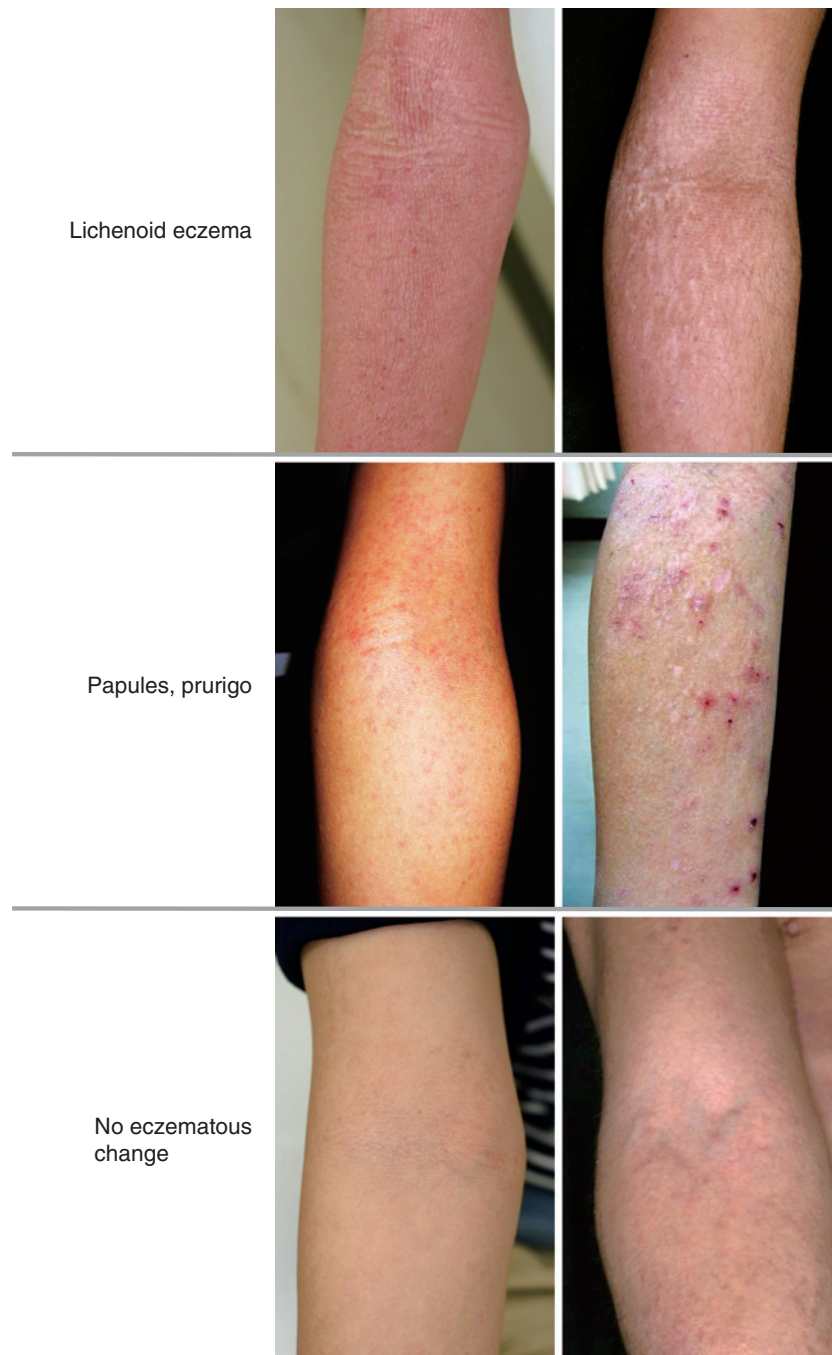


Fig. 3 Clinical manifestations of the cubital fossa.

known about the relationship between sweating and lichenoid changes. Our findings support the possible involvement of abnormally impaired sweating in the pathogenesis of lichenoid dermatitis. As for prurigo, some reports have mentioned the possible involvement of sweat abnormalities in its pathogenesis.¹⁹⁻²¹ Our report is the first to evaluate the relationship between symptoms of prurigo and sweating volume. In the past, pathological alterations of eccrine sweat ducts were thought to cause anhidrosis and prurigo

nodularis.¹⁹ The present study does not explore the mechanisms of anhidrosis in AD, and further studies, including histopathological analyses, will be required to explore this possible connection.

From the perspective of educating patients with AD, the present report indicates that clinicians can predict abnormal sweating from the patient's clinical manifestations. At present, we have no data regarding the involvement of sweating dysfunction on AD onset but have confirmed the existence of sweating dys-

function in the lesioned skin of patients. Thus, if the patient exhibits below-average sweating, heat retention due to anhidrosis might be an exacerbating factor of AD.^{22,23} In such cases, we suggest cooling the skin to reduce itching.²⁴ Moreover, exercise-induced sweating along with recommended therapies may yield good results for below-average sweating subjects. Validating the effects of this advice is our task and requires further investigation.

ACKNOWLEDGEMENTS

This study is supported by the Ministry of Health, Labor, and Welfare, Japan.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 is available online.

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