



Correlation between serum thymus and activation-regulated chemokine levels and stratum corneum barrier function in healthy individuals and patients with mild atopic dermatitis

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ABSTRACT

Background: Serum thymus and activation-regulated chemokine (TARC) levels closely reflect the disease activity of atopic dermatitis (AD). AD is characterized by impaired epidermal barrier function and atopic dry skin. However, dry skin is also a very common problem in healthy individuals.

Objective: To investigate the relationship between serum TARC levels and epidermal barrier function in healthy subjects and patients with mild AD.

Methods: This study included 2 groups, 121 healthy subjects (healthy group) and 66 patients with mild AD (mild AD group). Barrier function was assessed by transepidermal water loss (TEWL) and stratum corneum hydration (SCH).

Results: Significantly elevated serum TARC levels and TEWL values and significantly decreased SCH values were detected in the mild AD group compared to those in the healthy group. In the mild AD group, serum TARC levels were significantly correlated with TEWL values and were inversely correlated with SCH values. Importantly, serum TARC levels were also inversely correlated with SCH values in the healthy controls. TEWL values in the healthy group tended to be correlated with TARC levels but did not reach statistical significance.

Conclusion: Together with TEWL and SCH, serum TARC level is a useful biomarker, reflecting impairment of epidermal function in AD patients as well as healthy subjects.

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1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder of unknown cause. AD has characteristics commonly associated with atopy, including elevated serum IgE levels, IgE specific to environmental allergens such as mites, and tissue and peripheral blood eosinophilia, and is clinically characterized by pruritic and eczematous lesions [1]. In addition to its flexural distribution, dry skin is one of the most prominent features of AD [2]. Genetic abnormalities of skin barrier-related genes, such as filaggrin, immunological perturbation by a T helper 2 (Th2)-shifted microenvironment, and mechanical injury by scratching acting together in a complex manner may be responsible for the etiology of dry skin [1–4]. However, dry skin is a very common problem

affecting a substantial number of normal individuals, especially in the winter season [5,6]. People with dry skin often report, “I have sensitive or weak skin.” Self-reported sensitive or subclinical dry skin may be considered either within the normal range or as a very early sign of AD; however, it is a difficult task to discriminate these subtle differences.

Recently, thymus and activation-regulated chemokine (TARC), a chemokine involved in Th2 cell migration, was found to be associated with AD [7]. Serum TARC levels are significantly elevated in patients with AD, particularly in those severely affected by the disease, compared to the levels in patients with other inflammatory skin diseases and in healthy control subjects [7–11]. Therefore, serum TARC level is a good specific and objective indicator for AD disease severity. Another feature of serum TARC level that makes it useful as a clinical marker is its wide range of values; e.g., 100–40,000 pg/mL, as was demonstrated by Tamaki et al. [11]. However, in healthy adult individuals, serum TARC levels also vary widely, up to 450 pg/mL. This wide range of normal TARC levels prompted us to speculate that serum TARC level might

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reflect or correlate with dry skin or barrier dysfunction in healthy individuals.

Since increased transepidermal water loss (TEWL) and decreased stratum corneum hydration (SCH) are well-established physiological markers of barrier dysfunction that correlate with impaired stratum corneum function [12–15], we examined TEWL and SCH in healthy volunteers, using patients with mild AD as positive controls, in the winter season, and analyzed the correlation of TEWL and SCH values with serum TARC levels. We demonstrated for the first time that decreased SCH indeed correlated with increased TARC levels even in healthy individuals.

2. Materials and methods

2.1. Subjects and study design

This clinical study was conducted on a population of 121 healthy subjects (healthy group) and 66 patients with mild AD (mild AD group). Participants in the healthy group, which included 96 females and 25 males (mean age, 39.7 years; range, 20–60 years), had no past medical history related to AD or any other allergic and systemic diseases. Healthy subjects who had used oral or topical antihistamines or corticosteroids within the past 6 months were excluded. All AD patients [48 females and 18 males; mean age, 35.7 years; range, 20–57 years] were evaluated as mild according to the diagnostic criteria for AD developed by the Japanese Dermatological Association [16]. In addition, the serum TARC levels of AD patients did not exceed 700 pg/mL, because a TARC value of 700 pg/mL has been proposed as a cut-off for discriminating mild AD from moderate AD [11]. All mild AD patients were using topical treatment; however, those who used the strongest rank of topical corticosteroids, such as 0.05% clobetasol propionate and 0.05% diflorasone diacetate [16], or oral antihistamines or corticosteroids within the past one month were excluded. Prior to enrollment into the study, the protocol was explained in detail to each participant and written informed consent was obtained. The study was carried out from January to February 2010 in Japan with the cooperation of the Dermis Research Center as a clinical service organization center. The study protocol was approved by the Kenshokai Medical Center Ethical Review Board (Osaka, Japan), and was conducted in accordance with the principles of the amended Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research enacted by the Japanese Government in 2008.

2.2. Measurement of serum TARC levels

Serum samples were obtained from clotted blood following centrifugation at 4 °C for 10 min, and then stored at –60 °C until analysis. The serum concentration of TARC was measured using a commercially available enzyme-linked immunosorbent assay kit (Allerport[®]; Shionogi & Co., Ltd., Osaka, Japan) according to the manufacturer's instructions. The detection sensitivity of the kit for TARC was 125 pg/mL, and all undetectable values were estimated as 62.5 pg/mL.

2.3. Measurement of stratum corneum functions

Before the measurement was done, participants were instructed to wash their faces and were acclimatized for more than 20 min in an air-conditioned room adjusted to a temperature of 20 ± 1 °C and relative humidity of 50 ± 5%. The 2 barrier function parameters, TEWL and SCH, were measured on clinically normal-appearing skin of the left cheek using non-invasive biophysical methods. TEWL, a measure of the water barrier function of the stratum corneum, was determined using a Tewameter TM 210

Table 1

Thymus and activation-regulated chemokine, transepidermal water loss, and stratum corneum hydration levels in mild atopic dermatitis patients and healthy volunteers.

	Mild AD patients (n = 66)	Healthy volunteers (n = 121)	P value
TARC levels (pg/mL)	214.5 (186–250) ^a	177 (165–198)	0.032
TEWL (g/m ² h)	21.9 (19.2–26.4)	16.9 (15.5–18.1)	<0.001
SCH (μS)	64.5 (48.7–81.9)	106.4 (94.0–122.7)	<0.001

TARC, thymus and activation-regulated chemokine; TEWL, transepidermal water loss; SCH, stratum corneum hydration.

^a Values are expressed as the median (95% confidence interval).

(Courage & Khazaka, Köln, Germany). It measures the water evaporation gradient in an open loop system chamber. Measured values were expressed in grams per square meters per hour. SCH was evaluated using a skin surface hydrometer (Skicon-200EX; IBS Co., Ltd., Hamamatsu, Japan) that measures the high-frequency conductance of the skin as a reflection of skin surface moisture [17]. The Skicon-200EX values were expressed in digital terms of micro-Siemens (μS).

2.4. Statistical analyses

The Mann–Whitney *U*-test was used to analyze numerical variables and the chi-square test was used to compare proportions. The correlation between TARC and each of the 2 barrier function parameters, TEWL and SCH, were analyzed by Spearman rank correlation test. All comparisons were two-tailed, and a *P* value <0.05 was considered statistically significant.

3. Results

3.1. TARC, TEWL, and SCH levels in patients with mild AD and healthy volunteers

As shown in Table 1, the median serum TARC level in the healthy group was significantly lower than the level in the mild AD group (*P* = 0.032). Regarding the barrier function parameters, the median TEWL value was significantly lower and the median SCH value was significantly higher in the healthy group than in the mild AD group (*P* < 0.001 for each). These results demonstrated that TEWL, SCH, and TARC were good parameters reflecting cutaneous and serological abnormalities of AD even in mild cases.

3.2. Correlation between serum TARC levels and barrier function parameters

The relationship between serum TARC level and barrier functions (TEWL and SCH) was assessed in mild AD patients and healthy volunteers. Serum TARC levels were significantly correlated with TEWL values in the mild AD group (correlation coefficient (*r*) = 0.395, *P* < 0.001); however, this correlation did not reach a significant level in the healthy volunteers (*r* = 0.268, *P* = 0.102) (Fig. 1). In contrast, significant inverse correlations were observed between serum TARC levels and SCH values in both the mild AD patients (*r* = –0.265, *P* = 0.032) and the healthy volunteers (*r* = –0.222, *P* = 0.014) (Fig. 2). Further statistical analysis did not show any significant correlation among TARC levels, age and sex.

4. Discussion

In this study, we determined serum TARC levels and the 2 barrier function parameters of the stratum corneum, i.e., TEWL and SCH, in healthy individuals and patients with mild AD. In patients with AD, serum TARC levels are well correlated with the clinical

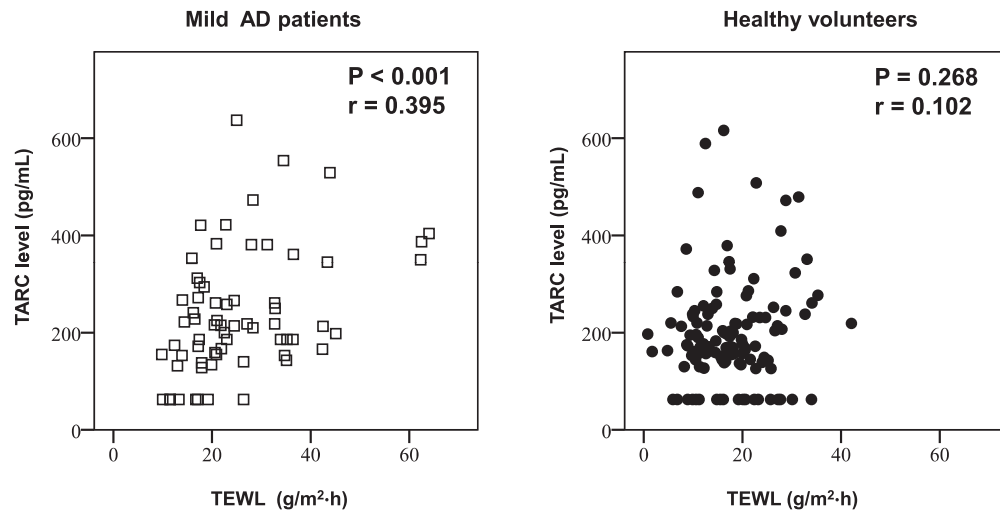


Fig. 1. Correlation between serum thymus and activation-regulated chemokine (TARC) levels and transepidermal water loss (TEWL) values in the mild atopic dermatitis (AD) ($n = 66$) and healthy groups ($n = 121$).

severity of the disease assessed by the scoring AD (SCORAD) system [7,9,11,18]. However, a direct relationship between TARC and epidermal barrier function parameters in AD has not been reported previously. Here, we showed for the first time that the serum TARC levels were significantly correlated with barrier function even in mild AD. Furthermore, it is interesting to note that a similar correlation was also observed in the healthy group.

Several papers have reported that the extent of barrier function impairment corresponds to the severity of AD [19–21]; therefore, it is quite conceivable that barrier impairment positively correlates with the serum TARC levels. The fact that the barrier dysfunction also correlated with TARC level in healthy controls, albeit to a lesser extent than in AD, further stresses the important close relationship between these physiological and immunological parameters. Although the mechanisms underlying the elevated TARC levels in barrier-impaired individuals remain unclear, we speculate that defects in barrier function resulting in skin dryness may nonspecifically influence the expression or secretion of TARC by dendritic cells, particularly those related to skin tissues [22–25] and/or epidermal keratinocytes [26]. In keeping with this notion, Morita et al. recently demonstrated that stratum corneum TARC

levels were significantly correlated with local disease activity [27]. In AD patients, impaired barrier function was detected even in non-eczematous skin with normal appearance, often called atopic dry skin or atopic xerosis [12–15,28,29]. Increased secretion of TARC from barrier-disturbed dry skin over the entire body is likely to explain the significantly higher serum TARC levels found in patients with mild AD compared to normal controls.

We recruited healthy individuals without any history of AD and other allergic diseases. However, the possibility still exists that some volunteers had subclinical or very early-stage AD. Another limitation of this study is that we measured the epidermal function only on the cheek, but not on the entire surface of the subjects. Therefore, it may over- or under-estimate the real dryness of the entire skin of the individuals. Based on the practicability and applicability, we selected the clinically normal-appearing skin of the left cheek as the representative area for the subject's general epidermal condition. Our previous report has revealed that the epidermal function of the cheek correlates with the individual skin aging in the 11-year longitudinal study [30], therefore, we assume that the epidermal function of the cheek may represent, at least in part, the individual general epidermal condition. Despite such

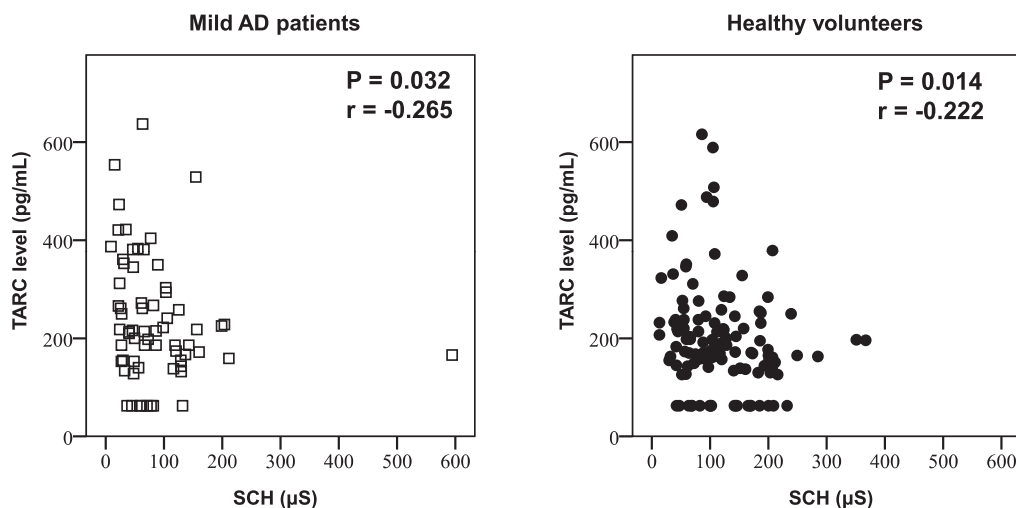


Fig. 2. Correlation between serum thymus and activation-regulated chemokine (TARC) levels and stratum corneum hydration (SCH) values in the mild atopic dermatitis (AD) ($n = 66$) and healthy groups ($n = 121$).

limitations, serum TARC level is a useful biomarker, together with TEWL and SCH, reflecting impairment of epidermal function in AD patients as well as in healthy subjects.

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