











Association of Skin Dryness and Disease-related Parameters with Mechanical Allodynia in Atopic Dermatitis: A Cross-sectional and Prospective Cohort Study

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Mechanical allodynia, namely itch hypersensitivity evoked by normally innocuous mechanical stimuli, may exacerbate the itch-scratch cycle in atopic dermatitis. Although various molecular and neural pathways have been identified in animal models, the clinical mechanisms underlying mechanical allodynia remain unclear, particularly in relation to disease severity and biomarkers. We hypothesized that atopic dermatitis severity-related parameters are associated with mechanical allodynia. To investigate this, we performed a cross-sectional study comparing healthy controls and atopic dermatitis patients and a prospective cohort study evaluating atopic dermatitis patients receiving dupilumab. In the cross-sectional study, mechanical allodynia scores were significantly higher in lesional than in non-lesional or healthy skin. Skin dryness parameters (transepidermal water loss and stratum corneum hydration) showed no significant correlation with mechanical allodynia. Among serum biomarkers, only thymus and activation-regulated chemokine (TARC) levels showed a moderate positive correlation with mechanical allodynia but not with spontaneous itch. In the prospective study, dupilumab significantly reduced eosinophil counts, IgE, TARC, spontaneous itch and mechanical allodynia scores, although TARC remained correlated with mechanical allodynia after treatment. These findings suggest that TARC may be involved in the induction of mechanical allodynia and represent a potential biomarker or therapeutic target for mechanical allodynia in atopic dermatitis.

Key words: observational study; atopic dermatitis; pruritus; chemokine CCL17; dupilumab.

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SIGNIFICANCE

Atopic dermatitis patients often experience not only spontaneous itch but mechanical allodynia, namely itch triggered by normally innocuous mechanical stimuli. Mechanical allodynia, especially in lesional skin, may promote a vicious itch-scratch cycle that aggravates inflammatory skin pathology. Although many molecules and neural circuits involved in mechanical allodynia have been identified in animal models, the underlying factors in clinical settings remain unclear. In this study involving healthy controls and atopic dermatitis patients, serum TARC levels were found to be correlated with mechanical allodynia but not spontaneous itch, suggesting TARC may be at least partly involved in the mechanisms underlying mechanical allodynia in atopic dermatitis.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions (1, 2). Pruritus (itch) is one of the most burdensome and distressing symptoms in patients with AD (3). In addition to persistent spontaneous itch, patients with AD frequently exhibit “mechanical allodynia (MA),” a form of itch hypersensitivity elicited by normally innocuous mechanical stimuli (4, 5). MA, particularly in lesional skin, can occur as a result of scratching behaviour itself acting as a mechanical stimulus, and is thought to serve as a trigger for the vicious itch-scratch cycle, thereby exacerbating inflammatory conditions (6).

Animal studies have identified multiple molecular and neural pathways involved in MA, including mechanoreceptors, spinal neuronal circuits, and type 2 cytokine-mediated neuronal sensitization (7–13). However, the extent to which these experimental findings are relevant to AD in clinical practice remains unclear, as does the relationship between commonly used clinical parameters and MA.

We hypothesized that disease-related parameters used in routine clinical practice may be associated with the induction or modulation of MA in AD. To clarify the clinical characteristics and potential mechanisms of MA in AD, we performed a cross-sectional study comparing healthy controls and patients with AD, followed by a prospective cohort study of dupilumab-treated AD patients. Both studies examined the associations of MA with skin dryness parameters; transepidermal water loss (TEWL) and stratum corneum (SC) hydration; and disease-related parameters, including Eczema Area and Severity Index (EASI), eosinophil counts (Eos), immunoglobulin E (IgE), and thymus and activation-regulated chemokine (TARC).

MATERIALS AND METHODS

Study design and participants

This clinical study comprised a cross-sectional study (STEP 1 and STEP 2, shown in **Fig. 1**) and a prospective cohort study (STEP 3, shown in

Fig. 1). In STEP 1, spontaneous itch, mechanical alloknosis (MA), and skin dryness were compared between healthy controls ($n=30$) and patients with atopic dermatitis (AD) ($n=32$). In STEP 2, a cross-sectional sub-analysis was conducted in 24 AD patients to examine correlations between MA scores and disease-related parameters, including Eczema Area and Severity Index (EASI), eosinophil counts (Eos), IgE, and thymus and activation-regulated chemokine (TARC). In STEP 3, a prospective cohort analysis was conducted in AD patients who selected dupilumab treatment ($n=17$ at enrollment), of whom 10 patients who completed all scheduled visits were included in the final analysis. Recruitment was conducted continuously from April 2021 through March 2025. Detailed eligibility criteria and study procedures are provided in the Appendix S1.

Outcomes and statistical analysis

This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

STEP 1

Healthy Control (n=30)

- Spontaneous itch level
- MA scores for von Frey filaments with bending forces: 5.8/9.8/13.7/19.6 mN
- TEWL^a
- SC hydration^a

AD (n=32)

- Spontaneous itch level
- MA scores for 5.8/9.8/13.7/19.6 mN filaments
- TEWL^a
- SC hydration^a

STEP 2

Blood collection group (n=24)

- EASI^b
- Eosinophil counts (Eo)^b
- IgE^b
- TARC^b

STEP 3

Dupilumab group (n=10)

- Changes in NRS
- Eo, IgE and TARC after dupilumab^b

^a Skin dryness parameters
^b Disease-related parameters

Fig. 1. Outline and participants of this study. Healthy controls and atopic dermatitis (AD) patients aged 20–89 years participated in this study. In STEP 1, the levels of spontaneous itch, mechanical alloknosis (MA), and skin dryness were assessed in 30 controls and 32 AD patients. Itch intensity was evaluated using a numeric rating scale (NRS) from 0 to 10 under unstimulated conditions for spontaneous itch, and under stimulation with von Frey filaments (5.8, 9.8, 13.7 and 19.6 mN) for MA scores. Skin dryness was assessed by measuring transepidermal water loss (TEWL) and stratum corneum (SC) hydration. In STEP 2, 24 AD patients underwent blood sampling for the evaluation of disease-related parameters, including Eczema Area and Severity (EASI), eosinophil count (Eos), serum IgE and thymus- and activation-regulated chemokine (TARC) levels. Finally, in STEP 3, 17 AD patients with insufficient responses to standard treatments initiated dupilumab therapy; of these, 7 discontinued follow-up mainly due to scheduling difficulties and were excluded from the final analysis, while 10 patients completed nine consecutive administrations. Changes in spontaneous itch, MA scores, Eos, IgE and TARC levels were evaluated throughout the treatment period.

recommendations (14). The primary outcome was the MA score; secondary outcomes were spontaneous itch intensity, skin dryness and disease-related parameters. Spontaneous itch and MA were assessed by numerical rating scale, and skin dryness by transepidermal water loss and stratum corneum hydration. Group comparisons were analyzed using Student's t-test or one-way ANOVA followed by Tukey's or Dunnett's post hoc test, as appropriate. Correlations were assessed using Pearson's correlation coefficient, and categorical variables using Fisher's exact test. A *p*-value < 0.05 was considered statistically significant. Detailed methods are provided in the Appendix S1.

Ethics

This study was approved by the Juntendo University ethics committee (U20-0057), conducted in accordance with the Declaration of Helsinki, and based on written informed consent from all participants. The study was conducted as an observational study; although initially registered with UMIN (UMIN000059524) based on the original protocol, the intervention was not implemented due to a change in plan.

RESULTS

Study outline and participants

This study was an observational investigation comprising cross-sectional and prospective cohort components. The study outline is shown in Fig. 1. A total of 62 participants were enrolled (32 patients with AD and 30 healthy controls), and STEP 1 was performed on all participants. Among them, 24 and 17 patients proceeded to STEPS 2 and 3, respectively (Fig. 1 and Table I). In STEP 3, 17 patients initiated dupilumab treatment (Fig. 1); however, 7 discontinued due to failure to maintain regular visits. Table I presents data from the 10 patients who completed all scheduled visits.

Patterns of spontaneous itch and mechanical allodynia in atopic dermatitis patients

In STEP 1, a cross-sectional study was performed in 32 AD patients and 30 healthy individuals (Fig. 1). Their demographic characteristics are shown in Table I. While AD patients were younger, there was no statistically significant sex difference between groups. The sites of healthy skin in controls and non-lesional skin in AD patients were confirmed to have an NRS score of 0 for spontaneous itch, and the AD lesional skin group showed significantly higher NRS scores compared to the other groups (Fig. 2a). MA scores were recorded as itch elicited by each mechanical stimulus itself,

Table I. Demographic characteristics of study participants in STEPS 1–3

| | Healthy controls (n=30) | AD (n=32) | <i>p</i> -value |
|---|----------------------------|-----------------|-----------------|
| STEP 1 | | | |
| Number of subjects | 30 | 32 | - |
| Age (years, mean±SD) | 45.3±12.2 | 33.3±11.1 | 0.0002** |
| Male:Female | 22:8 | 22:10 | 0.783 |
| STEP 2 | | | |
| Number of subjects | - | 24 | - |
| Age (years, mean±SD) | - | 31.5±10.4 | - |
| Male:Female | - | 17:7 | - |
| EASI (mean±SD) | - | 26.4±8.6 | - |
| Eos (×10 ⁹ cells/L, mean±SD) | - | 782.9±838.1 | - |
| IgE (IU/ml, mean±SD) | - | 11973.2±15856.9 | - |
| TARC (pg/ml, mean±SD) | - | 5265.8±5934.4 | - |
| STEP 3 | | | |
| Number of subjects | - | 10 | - |
| Age (years, mean±SD) | - | 29.1±11.2 | - |
| Male:Female | - | 6:4 | - |
| EASI (mean±SD) | - | 29.0±6.2 | - |
| Eos (×10 ⁹ cells/L, mean±SD) | - | 605±333.2 | - |
| IgE (IU/ml, mean±SD) | - | 11219±13024.2 | - |
| TARC (pg/ml, mean±SD) | - | 4223.4±4038.1 | - |

Demographic characteristics of study participants in STEP 1, STEP 2, and STEP 3. In STEP 1, the age of AD patients was significantly lower than that of healthy controls, while no significant difference was observed in the sex ratio between the two groups. Age was compared using a two-tailed Student's t-test, and sex ratio was analyzed by Fisher's exact test. STEP 2 involved 24 AD patients who underwent blood sampling for evaluation of disease-related parameters, including EASI, Eos, serum IgE and TARC levels. STEP 3 included 10 AD patients who received dupilumab therapy according to the standard regimen (a 600 mg loading dose followed by 300 mg every 2 weeks). Disease-related parameters (EASI, Eos, IgE and TARC) were obtained prior to treatment initiation. Data are expressed as the mean±SD. ***p*<0.01. AD:atopic dermatitis; EASI:Eczema Area and Severity Index; Eos:eosinophil count; IgE:immunoglobulin E; SD:standard deviation; TARC:thymus and activation-regulated chemokine.

rather than as a change from ongoing spontaneous itch. MA scores were significantly higher in lesional AD skin than in healthy control skin or non-lesional AD skin at all filament forces (Fig. 2b). In contrast, healthy control skin and non-lesional AD skin showed a force-dependent increase in MA, with higher scores at stronger filament forces, whereas this trend was not evident in lesional AD skin. Detailed summary statistics are provided in Tables S2–S4.

Correlation between itch level and skin dryness in atopic dermatitis patients

To evaluate skin dryness, TEWL and SC hydration were compared among healthy control skin, non-lesional AD skin and lesional AD skin (Fig. 2c, d). TEWL values in the lesional skin of AD patients were significantly higher than those in the non-lesional skin area, but no significant difference was observed compared with TEWL values in healthy skin (Fig. 2c, *p*=0.472). SC hydration values were significantly lower in both non-lesional and lesional AD skin than in healthy controls (Fig. 2d). Detailed values are shown in Tables S5 and S6. Pearson correlation analysis in the AD group

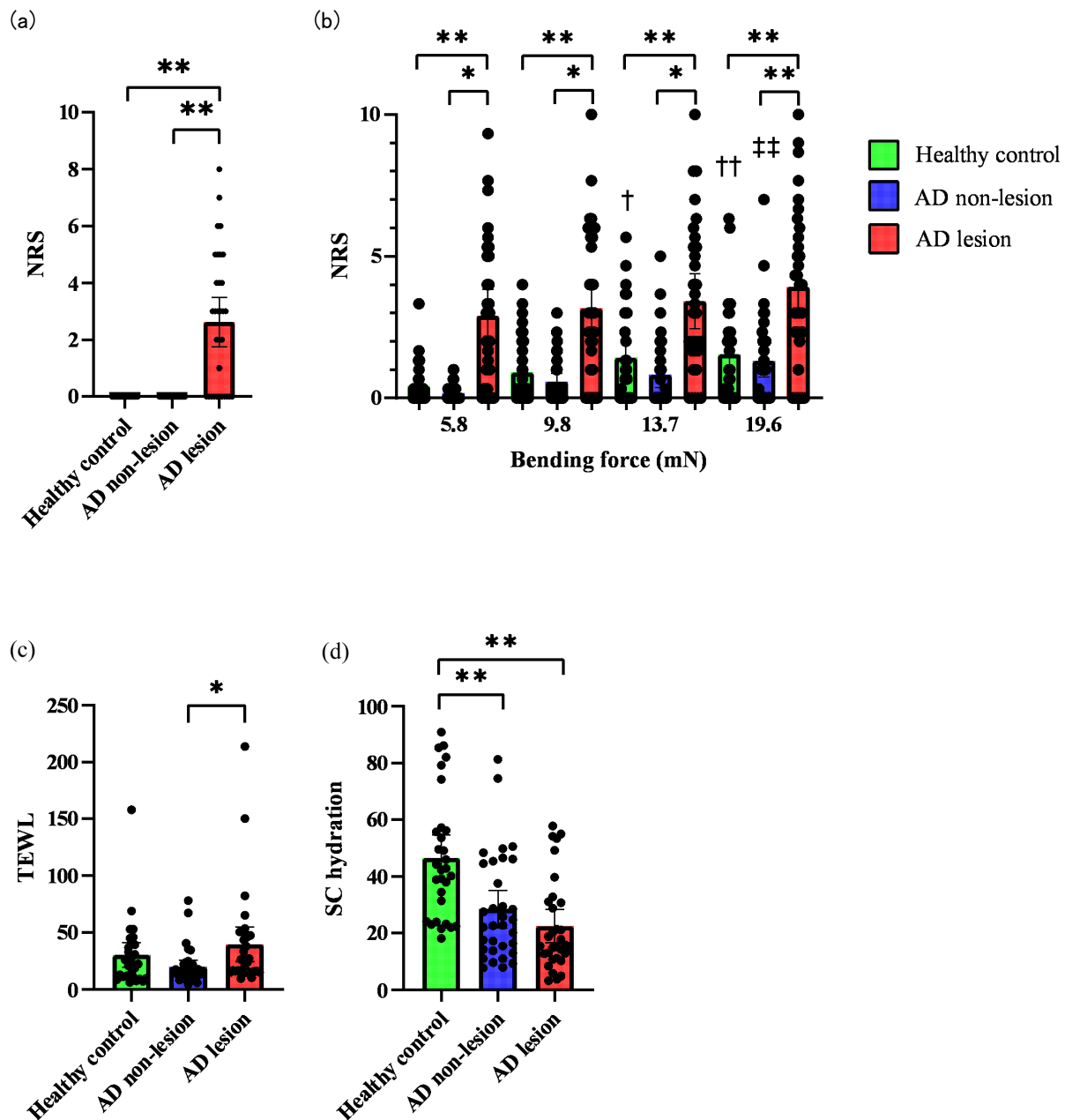


Fig. 2. Comparison of spontaneous itch, mechanical allodynia (MA) scores and skin dryness in healthy controls and atopic dermatitis (AD) patients in STEP 1. Levels of (A) spontaneous itch, (B) MA (numeric rating scale scores) at bending forces of 5.8, 9.8, 13.7 and 19.6 mN, (C) transepidermal water loss, and (D) stratum corneum hydration were compared among healthy control, non-lesional and lesional skin sites in patients with AD. Statistical analyses were performed using one-way ANOVA followed by Tukey's multiple-comparison test (*) to evaluate differences among groups (control, non-lesional and lesional skin), and Dunnett's multiple-comparison test (†) to examine force-dependent changes in MA scores within each skin condition. * $p < 0.05$, ** $p < 0.01$, † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.01$.

revealed no significant correlation between spontaneous itch or MA scores and either TEWL or SC hydration in either lesional or non-lesional skin (Table S7).

Correlation between itch level and disease-related parameters in atopic dermatitis patients

STEP 2 was conducted as a cross-sectional sub-analysis among the AD patients included in

STEP 1. Among the AD patients in STEP 1, 24 who underwent blood sampling during routine medical examinations were included. The demographic characteristics and measured values of disease-related parameters (EASI, Eos, IgE and TARC) are shown in Table I. Pearson correlation analysis was performed to examine the relationships between these parameters and each itch measure (Table II; Fig. S1). No significant correlations were

Table II. Correlation between itch NRS scores and disease-related parameters in STEP 2 AD patients

| | | EASI | | Eos | | IgE | | TARC | |
|-----|------------------|----------|-----------------|----------|-----------------|----------|-----------------|--------------|-----------------|
| | | <i>r</i> | <i>p</i> -value | <i>r</i> | <i>p</i> -value | <i>r</i> | <i>p</i> -value | <i>r</i> | <i>p</i> -value |
| NRS | Spontaneous itch | -0.145 | 0.521 | 0.255 | 0.230 | 0.143 | 0.506 | 0.342 | 0.102 |
| | 5.8 mN | -0.006 | 0.977 | 0.353 | 0.090 | 0.238 | 0.264 | 0.446 | 0.029* |
| | 9.8 mN | -0.012 | 0.959 | 0.342 | 0.101 | 0.187 | 0.381 | 0.440 | 0.031* |
| | 13.7 mN | -0.063 | 0.781 | 0.362 | 0.083 | 0.151 | 0.483 | 0.454 | 0.026* |
| | 19.6 mN | -0.147 | 0.514 | 0.316 | 0.132 | 0.153 | 0.475 | 0.362 | 0.082 |

Correlation coefficients (*r*) and *p*-values are shown for relationships between itch NRS scores (spontaneous itch and MA) and disease-related parameters, including EASI, Eos, serum IgE and TARC levels, in AD patients. Correlation coefficients were calculated using Pearson's correlation test. **p*<0.05.

AD:atopic dermatitis; EASI:Eczema Area and Severity Index; Eos:eosinophil count; IgE:immunoglobulin E; MA:mechanical allodynia; NRS:numeric rating scale; TARC:thymus and activation-regulated chemokine.

found between spontaneous itch or MA and EASI, blood Eos or serum IgE levels. Among the disease-related parameters, however, only serum TARC levels showed a significant moderate correlation with MA scores at bending forces of 5.8 mN, 9.8 mN and 13.7 mN, while no significant correlations were found for spontaneous itch scores or for MA at 19.6 mN ($r=0.362$, $p=0.082$). These findings suggest that TARC was the disease-related parameter most consistently associated with MA in STEP 2. Scatterplots for each of the data in Table II are shown in Fig. S1.

Time-dependent effects of dupilumab on mechanical allodynia scores and spontaneous itch

In STEP 3, longitudinal changes were evaluated in 10 AD patients who completed follow-up during dupilumab treatment (Table I). Both spontaneous itch and MA scores showed a clear decreasing trend during the early phase of treatment, from baseline to the 5th administration (Fig. 3a–e). The reduction was statistically significant for spontaneous itch and MA at all filament forces (5.8–19.6 mN, Tables S8–S12). Additional analysis showed a significant negative correlation between dose number and itch scores

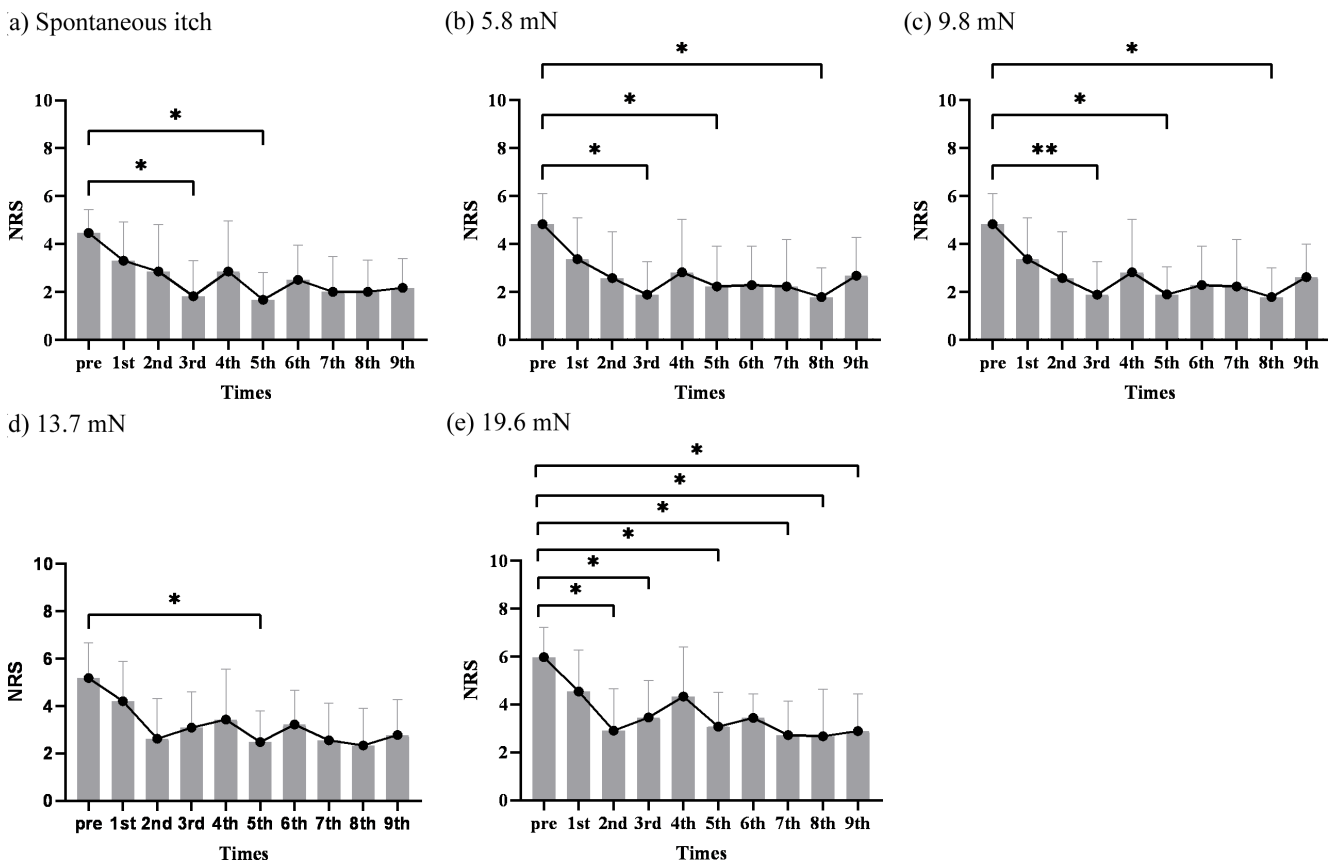


Fig. 3. Time-dependent changes in spontaneous itch and mechanical allodynia (MA) scores in atopic dermatitis (AD) patients treated with dupilumab in STEP 3. (a–e) Itch numeric rating scale (NRS) scores for (A) spontaneous itch and MA at bending forces of (B) 5.8, (C) 9.8, (D) 13.7 and (E) 19.6 mN were evaluated from pre-treatment (pre, baseline) to the 9th dupilumab administration at each consecutive visit in AD patients. Statistical analyses were performed using one-way ANOVA followed by Dunnett's multiple-comparison test to examine time-dependent differences in NRS scores across visits (from pre to 9th dose). **p*<0.05, ***p*<0.01.

up to the 5th administration, but not thereafter, suggesting that symptom improvement plateaued after approximately 5 doses (Table S13; see also Fig. S2).

Correlation between disease-related parameters and itch scores after continuous dupilumab administration in STEP 3

At the visit for the 9th administration of dupilumab, blood samples were collected and Eos, IgE and TARC levels were measured in the 10 patients in STEP 3. Serum IgE and TARC levels at the 9th administration (Post) showed a significant decrease from baseline levels (Pre) (Fig. S3b, c, Tables S15 and S16). Eos also showed a decreasing trend (Fig. 3a, Table S14). At the 9th dupilumab administration, neither Eos nor IgE levels showed significant correlations with spontaneous itch or MA, whereas TARC levels displayed significant positive correlations with MA scores at 5.8 mN, 9.8 mN and 13.7 mN. No significant correlations were observed for spontaneous itch scores or MA at 19.6 mN. TARC remained the parameter most consistently associated with MA (Table III; see also Fig. S4).

DISCUSSION

In the present study, we evaluated MA in AD using cross-sectional and prospective cohort analyses. The principal findings were as follows: (i) MA was markedly enhanced in lesional AD skin compared with healthy control skin and non-lesional AD skin; (ii) skin dryness parameters were not significantly correlated with spontaneous itch or MA; (iii) among disease-related parameters, only serum TARC showed significant positive correlations with MA at 5.8–13.7 mN, whereas no significant correlation was observed with spontaneous itch; and (iv) dupilumab reduced spontaneous itch and MA, especially up to the 5th administration, but TARC remained correlated with MA after treatment. The association between TARC

and MA suggests that TARC may contribute to MA in AD through mechanisms beyond systemic Th2 immune activation, potentially including the promotion of neuronal sensitization.

Whereas spontaneous itch is considered ongoing itch present at baseline, MA is defined as itch evoked by normally innocuous mechanical stimuli, indicating that the two are conceptually distinct. However, in areas where itch is nearly constant, such as the lesional skin of AD patients in the present study, complete separation of the two may be challenging. Nevertheless, we evaluated them separately using questions designed to distinguish them as clearly as possible. Moreover, serum TARC was associated with MA but not with spontaneous itch, both at baseline and after dupilumab treatment, supporting the view that MA in the present study was not merely a reflection of baseline spontaneous itch. This interpretation is also consistent with previous reports suggesting that mechanically evoked itch and ongoing spontaneous itch are mediated, at least in part, by distinct neural mechanisms (10, 15, 16).

The finding that MA was highest in lesional AD skin is consistent with previous clinical reports showing enhanced mechanically evoked itch in AD (4), particularly in lesional areas. In contrast to that report (4), we did not detect a significant difference between healthy skin and non-lesional AD skin. One possible explanation is the difference in demographic background between our cohort and previous studies, as our participants were older overall and the healthy control group was older than the AD group. Since ageing has been reported to increase mechanical itch sensitivity in animal studies (15, 17), age-related effects may have increased baseline mechanical itch sensitivity in healthy controls.

Nonetheless, within-group comparisons still showed that healthy skin and non-lesional AD skin exhibited a force-dependent increase in MA, similar to a previous report (18), whereas lesional AD skin did not. This plateau-like pattern in lesional skin may reflect a ceiling effect caused by peripheral and/or central sensitization (19).

With respect to skin barrier parameters, lesional AD skin showed higher TEWL than non-lesional skin, and SC hydration was lower in lesional AD skin than in non-lesional skin and healthy skin, supporting impaired barrier function in AD, consistent with previous reports (20–22). However, neither TEWL nor SC hydration was significantly correlated with spontaneous itch or MA. Although skin dryness parameters are influenced by environmental conditions and interindividual variability, which may have attenuated detectable associations, these findings suggest that barrier dysfunction alone does not fully explain itch severity.

In STEP 2, we analysed correlations between disease-related parameters and itch scores in AD

Table III. Correlation between itch NRS scores and disease-related parameters (Eos, IgE, TARC) at the 9th dupilumab administration in STEP 3 AD patients

| | Eos | | IgE | | TARC | |
|----------------------|----------|-----------------|----------|-----------------|--------------|-----------------|
| | <i>r</i> | <i>p</i> -value | <i>r</i> | <i>p</i> -value | <i>r</i> | <i>p</i> -value |
| NRS Spontaneous itch | -0.203 | 0.574 | 0.299 | 0.401 | 0.412 | 0.237 |
| 5.8 mN | -0.017 | 0.962 | 0.060 | 0.869 | 0.665 | 0.036* |
| 9.8 mN | 0.289 | 0.418 | 0.129 | 0.722 | 0.836 | 0.003** |
| 13.7 mN | 0.188 | 0.603 | 0.116 | 0.750 | 0.667 | 0.035* |
| 19.6 mN | 0.237 | 0.509 | 0.105 | 0.774 | 0.583 | 0.077 |

Correlation coefficients (*r*) and *p*-values are shown for relationships between itch NRS scores (spontaneous itch and MA) and disease-related parameters (Eos, IgE, and TARC) after 9 or more dupilumab doses. Correlation coefficients were calculated using Pearson correlation test. **p*<0.05, ***p*<0.01.

AD: atopic dermatitis; Eos: eosinophil count; IgE: immunoglobulin E; MA: mechanical allodynia; NRS: numeric rating scale; TARC: thymus and activation-regulated chemokine.

patients. EASI, Eos, serum IgE, and TARC are established indices of AD severity and disease activity (2, 23). Among these parameters, only serum TARC was correlated with MA at 5.8, 9.8, and 13.7 mN, but not with spontaneous itch or MA at 19.6 mN.

In STEP 3, we prospectively evaluated AD patients treated with dupilumab. Both spontaneous itch and MA were reduced by the 5th administration, consistent with a previous report showing early improvement in touch-evoked itch after dupilumab treatment (24). At the 9th administration, serum IgE and TARC had decreased and Eos showed a decreasing trend, supporting the anti-inflammatory effect of dupilumab. Further improvement after the 5th administration was limited, suggesting that the antipruritic effect of dupilumab largely plateaued thereafter.

After 9 doses, the correlation pattern remained similar to baseline: TARC was again associated only with MA at 5.8, 9.8, and 13.7 mN, and these correlations were numerically stronger despite the small sample size. This differs from previous studies, including our own, in which spontaneous itch correlated with Eos, serum IgE or TARC (23, 25, 26). One possible explanation is differences in disease severity and population heterogeneity, as the present cohort included a broader range of AD severity than our previous dupilumab-eligible cohort (23).

These findings suggest that the role of TARC may vary with the inflammatory milieu. TARC is induced by Th2 cytokines and promotes Th2 inflammation (27–30), but may also contribute to sensory hypersensitivity through peripheral neurons and CCR4-related pathways (31–33). In less inflammatory settings, this neural-sensitization component may become more apparent, potentially explaining why TARC was more closely associated with MA than with spontaneous itch.

Conversely, in milder AD, the inflammatory contribution of TARC may be limited while its role in neuronal hypersensitivity may become more evident, making its association with MA stronger than with spontaneous itch. The persistence of TARC–MA correlations after dupilumab treatment suggests a partly Th2-independent pathway. Because Th2 cytokines enhance mechanical allodynia via neuronal sensitization (6, 12, 13), baseline MA was also likely influenced by Th2 cytokine activity, and its blockade by dupilumab may explain the stronger post-treatment TARC–MA correlation.

This interpretation is consistent with our previous experimental finding that weaker pruritogenic input may induce MA alone, whereas stronger input can evoke both MA and spontaneous itch, suggesting a continuum of peripheral neuronal sensitization (34).

Finally, the absence of correlation at 19.6 mN may reflect recruitment of different peripheral sensory

neuron populations by stronger mechanical stimuli, including high-threshold mechanoreceptors, resulting in a more TARC-independent response (35).

Limitations of this study include the modest sample size, demographic imbalance, possible interference of spontaneous itch with MA assessment in AD lesions, variability in TEWL and SC hydration, and the observational design, which precludes causal inference between TARC and MA. Although serum TARC levels have been reported to correlate with local TARC levels and disease activity in AD (2, 23, 26, 36), demonstrating the role of TARC in MA in AD requires multifaceted experiments, including analysis of local expression levels of TARC and CCR4 in human skin, as well as animal behavioural experiments.

In conclusion, serum TARC was selectively associated with MA but not spontaneous itch, both before and after dupilumab treatment, suggesting a contribution of TARC to mechanically evoked itch that is at least partly independent of Th2-mediated inflammation. TARC may therefore reflect not only systemic inflammation but also peripheral neuronal sensitization in AD. Clinically, assessment of MA may complement conventional disease severity indices, particularly for evaluating residual itch sensitivity during biologic therapy. Although validation in larger multicentre cohorts is needed, these findings support incorporating MA and TARC assessment into a more comprehensive evaluation of itch in AD.

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Data availability statement: Data are available from the corresponding author upon reasonable request.

Ethics declaration & trial registry information: This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Juntendo University (U20-0057). Written informed consent was obtained from all participants. The study was originally registered in UMIN (UMIN000059524), but no intervention was performed after protocol amendment; only the observational component is reported.

The authors have no conflicts of interest to declare.

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