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Original Article

Squamous cell carcinoma antigens are sensitive biomarkers for atopic dermatitis in children and adolescents: a cross-sectional study

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ABSTRACT

Background: We recently reported that squamous cell carcinoma antigen 2 (SCCA2) is a reliable biomarker for atopic dermatitis (AD).
Objective: To further clarify its utility, we investigated for effects of comorbid allergies and AD treatment on serum SCCA levels.
Methods: Volunteers <18 years old were recruited through our website. Their allergic status was elucidated using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. We also recruited pediatric patients who were hospitalized because of severe AD. The serum levels of SCCA1 and SCCA2 were measured by enzyme-linked immunosorbent assays. In the severe AD patients, the levels of thymus and activation-regulated chemokine (TARC), SCCA1, and SCCA2 were measured before and after hospitalization. The severity of AD was assessed using the severity scoring of atopic dermatitis (SCORAD).
Results: A total of 576 participants (547 volunteers and 29 patients) were enrolled in the study. The levels of SCCA1 and SCCA2 were significantly higher in volunteers with mild AD and patients with severe AD than in healthy volunteers without allergic diseases. The levels were not elevated in those who had mild bronchial asthma or allergic rhinitis without AD. TARC, SCCA1, and SCCA2 were decreased during the treatment in severe AD patients, reflecting clinical improvement in response to treatment. Linear regression analysis for predicting a decrease in the SCORAD index showed R^2 values of 0.16, 0.38, and 0.48 for TARC, SCCA1, and SCCA2, respectively.
Conclusion: SCCAs, especially SCCA2, are sensitive biomarkers for detecting AD in children and adolescents and for assessing the severity and response to treatment of severe AD.

Keywords: Atopic dermatitis; Biomarkers; Child; Squamous cell carcinoma-related antigen; chemokine CCL17

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Conflict of Interest
TF received lecture fees from Thermo Fisher Scientific and Sino-test Corporation. MN received lecture fees from Thermo Fisher Scientific and Sino-test Corporation. KI is a scientific advisor of Sino-test Corporation. YA and JO are employees of Shino-Test Corporation. All other authors declare that they have no conflicts of interest.

Author Contributions
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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder, and its increasing prevalence is a major public health concern. The goal of treatment of AD is to control skin eruptions and bothersome symptoms, such as itching, so that patients can lead an uninterrupted social life with the best possible quality of life [1]. To achieve that goal, full control of skin inflammation is essential. However, accurate assessment of skin inflammation is sometimes difficult since a physician's visual examination may not always identify subclinical inflammation [2]. To date, many biomarkers for monitoring skin inflammation in AD have been proposed [3]. However, there are few reliable biomarkers at present, and the American Academy of Dermatology even states that there are no specific biomarkers that can be recommended for diagnosis and/or assessment of disease severity [4].

Squamous cell carcinoma antigens (SCCAs) are serine proteinase inhibitors that belong to the serpin superfamily of proteins [5]. They are expressed in various epithelial tissues [6] and may be involved in epidermal barrier homeostasis [7, 8]. They were originally purified from squamous cell carcinoma of the uterine cervix [9] and have been utilized as markers in various cancers [10-14]. Later, SCCA serum levels were found to be elevated in various inflammatory skin diseases, including AD [15-18]. Since SCCAs were found to be induced by Th2 cytokines, such as interleukin-4 (IL-4) and IL-13 [16], they may be potential biomarkers for AD as downstream markers of Th2-type immune responses. Several studies suggested that measurement of SCCA1 and SCCA2 in the serum may be promising for evaluating/monitoring the clinical severity of AD [16, 19-23].

Recently, we and others in a multicenter study [23] reported the clinical utility of SCCA2 in a relatively large number of pediatric AD patients. However, the marker was not measured in patients with comorbid allergic diseases such as asthma and allergic rhinitis (AR), which may confound interpretation of the data in AD since most children with AD have multiple allergic diseases. Here, we conducted a cross-sectional study to assess the utility of SCCA1 and SCCA2 in the pediatric population, focusing especially on comorbid allergies. We also assessed the relationship between their serum levels and the disease severity/treatment responses in patients with severe AD.

MATERIALS AND METHODS

Study participants and outcomes

Volunteers aged less than 18 years were recruited through the Mie National Hospital website. Subjects were excluded from the study if they had a nonallergic chronic disease or an acute infectious disease. All volunteers completed the questionnaires of the International Study of Asthma and Allergies in Childhood [24]. For this study, we used the validated Japanese version [25]. Based on the answers to the questions, the presence or absence of current (the most recent 12 months) symptoms of AD, bronchial asthma (BA), and AR was determined, and the volunteers were classified into the following 4 groups: healthy volunteers without AD, BA or AR (healthy group); those with BA but not AD (BA group); those with AR but not AD or BA (AR group) and those with AD (AD group 1). We also recruited patients who needed to be hospitalized because of severe AD (AD group 2). During hospitalization, patients were treated with emollients and topical corticosteroids according to clinical practice guidelines [1].

Blood samples were obtained from the study participants to measure the baseline serum levels of SCCA1 and SCCA2. Blood samples were obtained twice (i.e., at the beginning and end of hospitalization) from some patients with severe AD, and the serum levels of thymus and activation-regulated chemokine (TARC), as well as SCCA1 and SCCA2, were measured. TARC is a member of the Th2 type chemokine family and was reported to be a useful biomarker for AD [26-28]. The serum levels of TARC, SCCA1 and SCCA2 were measured using specific enzyme-linked immunosorbent assays [21, 26]. The disease severity in the patients with severe AD was also assessed at the beginning and end of hospitalization using the severity scoring of atopic dermatitis (SCORAD) index [29].

The study protocol was approved by the Ethics Committee of Mie National Hospital (approval number: 24-1). All guardians of the participants provided written informed consent.

Statistical analyses

Baseline serum levels of SCCA1 and SCCA2 were summarized as the geometric mean and standard deviation (SD). The logarithmically transformed means were compared among the participant groups by analysis of variance. Tukey multiple comparison test was used to assess all pairwise differences between the participant groups. For the severe AD patients, we calculated Spearman correlation coefficients between the SCORAD index and TARC, SCCA1, and SCCA2 levels. A linear regression model was constructed to predict the decrease in the SCORAD index from the decrease in each of the logarithmically transformed biomarker levels. All data were analyzed using GraphPad Prism 8 (GraphPad Software, Inc., San Diego, CA, USA). All reported *p* values are 2-sided.

RESULTS

Characteristics of subjects

A total of 576 participants (547 volunteers and 29 severe AD patients) were enrolled in the study (**Fig. 1**). All participants were included in the analyses. **Table 1** summarizes the demographics, sex, age, and allergic comorbidities of the subjects. The patients were relatively younger than the volunteers, with mean (SD) ages of 4.0 (4.9) years in AD group 2, and ranging from 6.7 (2.1) to 9.3 (3.2) years in the other groups.

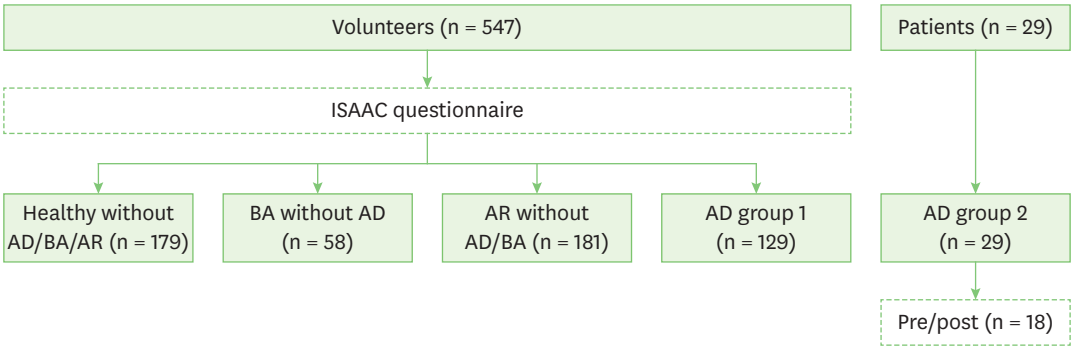

Fig. 1. Subjects enrolled in the study. ISAAC, International Study of Asthma and Allergies in Childhood; AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis.

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Table 1. Baseline characteristics of the study participants

Characteristic	Volunteers				Patients
	Healthy group (n = 179)	BA group (n = 58)	AR group (n = 181)	AD group 1 (n = 129)	AD group 2 (n = 29)
Male sex	86 (48)	35 (60)	97 (54)	63 (49)	15 (52)
Age (yr)	7.5 ± 2.8	6.7 ± 2.1	9.3 ± 3.2	8.0 ± 3.5	4.0 ± 4.9
Comorbidity					
Atopic dermatitis (AD)	0 (0)	0 (0)	0 (0)	-	-
Bronchial asthma (BA)	0 (0)	58 (100)	0 (0)	6 (5)	2 (7)
Allergic rhinitis (AR)	0 (0)	38 (66)	65 (100)	65 (50)	4 (14)

Values are presented as number (%) or mean ± standard deviation.
Healthy group, healthy volunteers without allergic diseases; BA group, volunteers with BA; AR group, volunteers with AR; AD group 1, volunteers with AD; AD group 2, patients who needed to be hospitalized because of severe AD.

Serum levels of SCCA1 and SCCA2 in each allergic disease group

Fig. 2 and **Supplementary Table 1** show the serum levels of SCCA1 and SCCA2 in the 5 groups. **Supplementary Table 1** summarizes the pairwise comparisons between the groups. While the serum levels of SCCA1 and SCCA2 were similar among the healthy, BA and AR groups, they were significantly higher in AD groups 1 and 2 than in the healthy group ($p < 0.0001$) and also significantly higher ($p < 0.0001$) in AD groups 1 and 2 than in the BA and AR groups. Finally, those serum levels were significantly higher in AD group 2 than in AD group 1 ($p < 0.0001$). The differences in their geometric means were 6.6 ng/mL for SCCA1 and 20.0 ng/mL for SCCA2.

Reference and cutoff values for SCCA1 and SCCA2

The healthy children were further divided into 3 age groups: 1–5, 6–10, and 11–17 years old. **Supplementary Table 2** summarizes the descriptive statistics of SCCA1 and SCCA2 in those groups. Although SCCA1 and SCCA2 were slightly higher in the 2 younger groups, there were no significant differences among the groups. Next, we calculated the geometric mean and SD for all healthy volunteers. As a result, the reference values (geometric mean − 2SD to geometric mean + 2SD) of SCCA1 and SCCA2 were 0.45 to 1.91 ng/mL and 0.21 to 1.93 ng/mL, respectively.

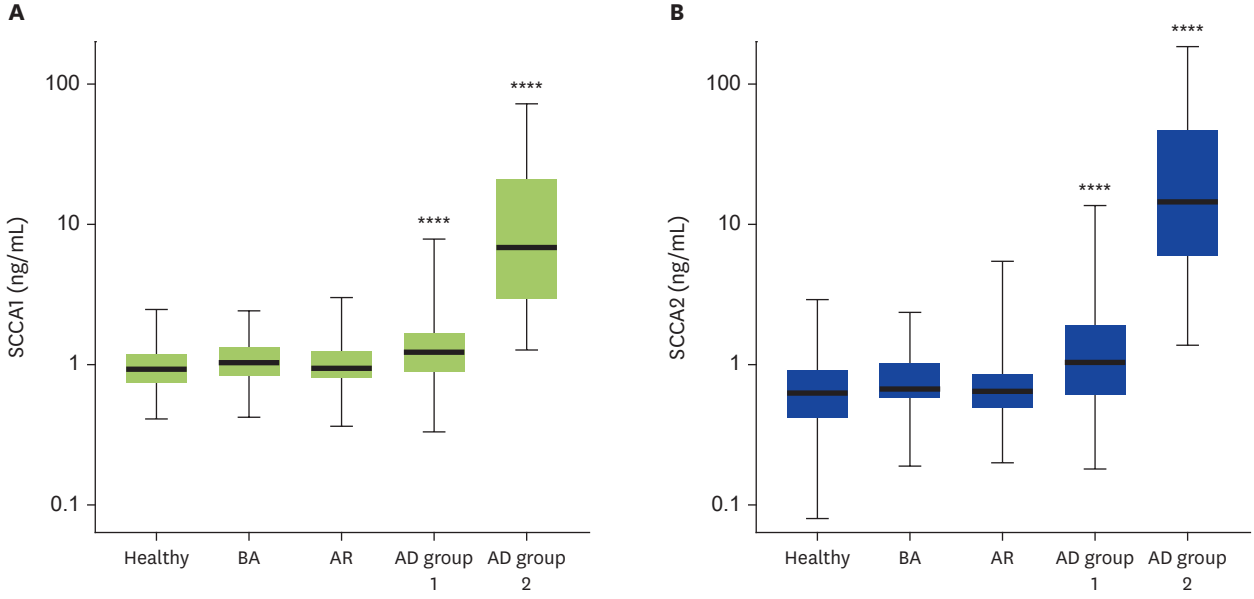

Fig. 2. Baseline serum levels of SCCA1 (A) and SCCA2 (B) in the study participants. The geometric mean serum levels of SCCA1 and SCCA2 differed among the 5 participant groups ($p < 0.0001$; analysis of variance). SCCA, squamous cell carcinoma antigen; AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis. ****$p < 0.0001$ (Tukey multiple comparison test) SCCA1 (A) and SCCA2 (B) in AD groups 1 and 2 were significantly higher than those in Healthly, BA and AR groups.

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Table 2. Diagnostic performance of SCCA1 and SCCA2 for AD in the volunteer population

	AUC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV†	NPV†
SCCA1	0.676 (0.613–0.738)	1.09	0.62 (0.53–0.70)	0.68 (0.61–0.75)	0.38	0.85
		1.65	0.26 (0.19–0.35)	0.95 (0.91–0.98)	0.62	0.81
SCCA2	0.715 (0.657–0.774)	0.84	0.61 (0.52–0.70)	0.71 (0.64–0.77)	0.39	0.86
		1.50	0.35 (0.27–0.44)	0.95 (0.91–0.98)	0.68	0.83

SCCA, squamous cell carcinoma antigen; AD, atopic dermatitis; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
†PPV and NPV were calculated based on the prevalence of AD in the volunteer population.

ROC analysis was performed to determine the diagnostic performance of the biomarkers in identifying AD in the volunteer groups. The area under the curves were 0.676 for SCCA1 and 0.715 for SCCA2. The cutoff levels based on the highest Youden index were 1.09 and 0.84 ng/mL, respectively. The cutoff levels at 95% specificity were 1.65 and 1.5 ng/mL, respectively (**Table 2**).

SCCA1 and SCCA2 in severe AD patients

Blood samples were obtained at the beginning and end of hospitalization of 18 severe AD patients. During the treatment in the hospital, the serum levels of TARC, SCCA1 and SCCA2 decreased significantly in all patients (**Fig. 3A–C**, respectively) and correlated significantly with the SCORAD index (**Fig. 3D–F**, respectively). Spearman correlation coefficients were 0.6856, 0.7513, and 0.7885, respectively. We also assessed the relationship between the decrease in the SCORAD index and the decreases in the serum levels of TARC, SCCA1, and SCCA2 (**Fig. 3G–I**, respectively). Among these biomarkers, a decrease in the SCCA2 level most strongly predicted improvement in the severity, i.e., a decrease in the SCORAD index, with R^2=0.476.

DISCUSSION

In this study, children and adolescents with AD showed significantly higher serum levels of SCCA1 and SCCA2 compared with healthy volunteers. The levels were not elevated in those with BA or AR without AD, indicating that SCCAs are specific markers for AD in allergic children. Their levels were higher in AD group 2 (patients with severe AD) than in AD group 1 (volunteers with AD, presumably mild disease). We also found that the serum levels of SCCAs in AD group 2 correlated significantly with the SCORAD index, and decreases in their levels during treatment correlated well with decreases in the SCORAD index. The correlation indices were highest for SCCA2 compared with SCCA1 and TARC. These results indicate that SCCAs are reliable biomarkers for AD, and that the serum levels of SCCAs, especially SCCA2, predict the disease severity and treatment response.

TARC has been regarded as the most reliable biomarker of the severity of AD [3]. TARC is a ligand for CC chemokine receptor 4, which is selectively expressed on Th2 type cells. It is produced by dendritic cells, endothelial cells and keratinocytes, and its overproduction leads to Th2 type cell accumulation at inflammation sites [30]. In contrast, SCCAs are induced by Th2 type cytokines such as IL-4 and IL-13 [16]. Therefore, SCCAs may reflect the downstream of the immune response, which might lead to superiority of SCCAs in our study. The reason for the stronger correlation of the SCCA2 level with disease severity remains unclear. An earlier study showed that keratinocytes produced mainly SCCA2 upon stimulation with IL-4 or IL-13 [21]. This result may in part explain the superiority of SCCA2 over SCCA1 for disease activity.

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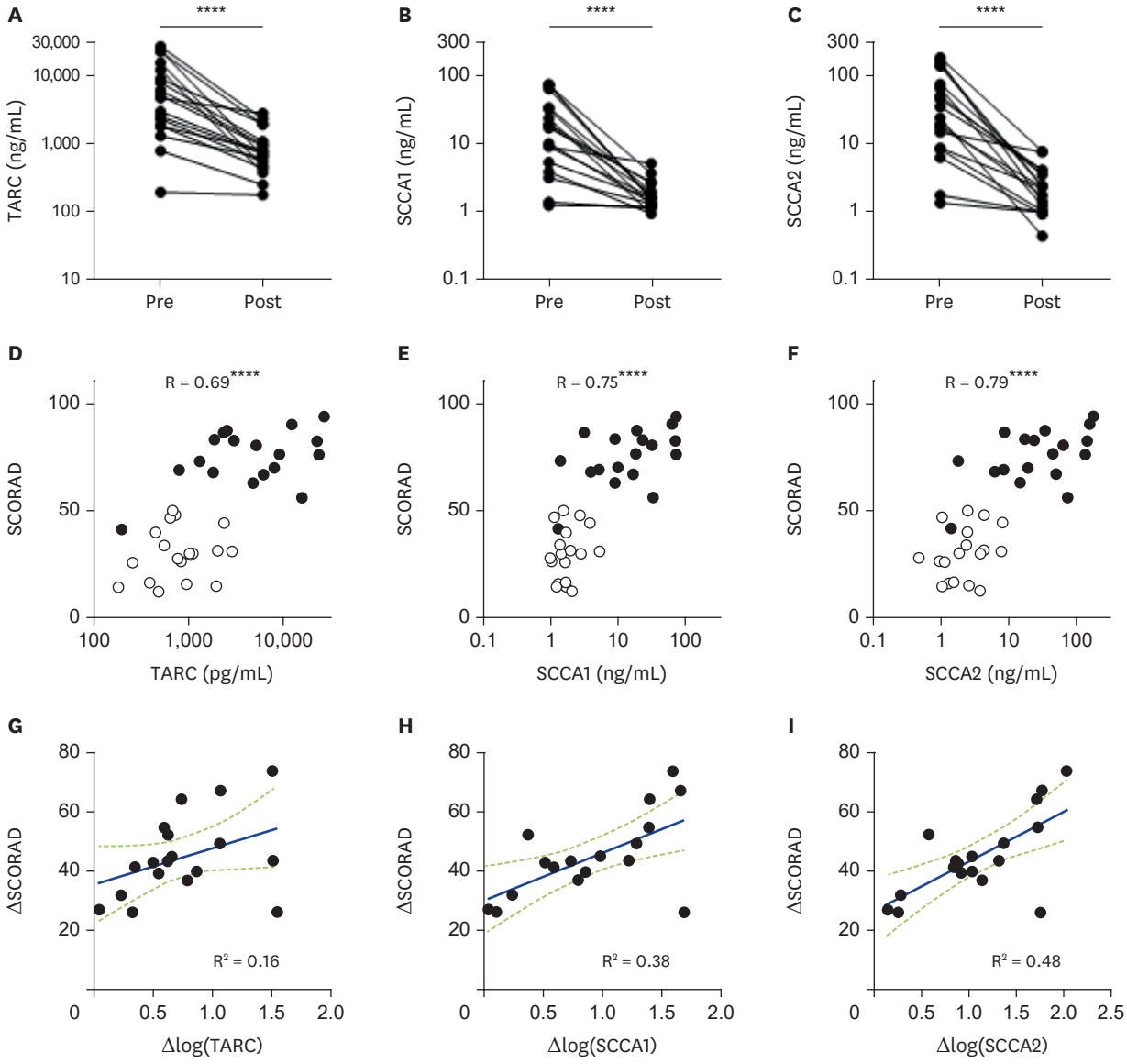

Fig. 3. Serum levels of TARC, SCCA1, and SCCA2 before and after treatment of severe AD patients. Changes in the serum levels of TARC (A), SCCA1 (B) and SCCA2 (C) between the beginning and end of hospitalization. ****$p < 0.0001$, Wilcoxon matched-pairs signed-rank test.
Relationships between the decrease in the severity scoring of atopic dermatitis (SCORAD) index and the decreases in serum levels of TARC (D), SCCA1 (E), and SCCA2 (F) during hospitalization. Closed and open circles indicate the values at the beginning and end of hospitalization, respectively. ****$p < 0.0001$, Spearman correlation test. The *x*-axes show the decrease in the SCORAD index, while the *y*-axes show the decrease in the logarithmically transformed serum levels of TARC (G), SCCA1 (H), and SCCA2 (I), respectively. TARC, thymus and activation-regulated chemokine; SCCA, squamous cell carcinoma antigen.

In addition, serum TARC levels are high in children, especially infants [26]. Thus, it is necessary to have different reference and cutoff values for TARC in different age groups for clinical use. On the contrary, the serum levels of SCCAs in healthy children were similar among the different age groups in our study. Although the levels were slightly higher in the 2 younger groups, the differences were not statistically significant and were much smaller than those found for TARC [26]. In our previous report [23], we demonstrated the validity of a single cutoff at 1.6 ng/mL for SCCA2. We also determined the normal ranges and cutoff levels of SCCA1 and SCCA2, irrespective of age, which may be helpful in clinical application.

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Because different subject groups were recruited for determination of cutoff levels, i.e., only mild AD in this study and more severe AD in the previous study, the cutoff levels of SCCA2 were different. However, the cutoff level at 95% specificity was 1.5 ng/mL in this study is close to the 1.6 ng/mL in the previous study.

An important finding in this study was that the serum levels of SCCAs correlated with the severity of AD. It is sometimes difficult to assess the severity and evaluate the outcome of a certain treatment because physicians' visual examinations are not always accurate [28]. Various instruments have been developed to measure the symptoms of AD, and several have been recommended as core outcome sets [31]. However, the main objective of the recommendation was to define the core outcome sets that should be used in clinical trials. These instruments are not suitable for use in daily clinical practice because their scoring systems are complex [32]. Accordingly, a simple and reliable biomarker for assessing disease severity would be a great breakthrough.

The serum levels of SCCAs were similar between healthy volunteers and those with BA or AR. In a study that included children with acute asthma, serum SCCA levels increased only in the acute phase of asthma exacerbation, while in the recovery phase they were similar to those in age-matched healthy children [33]. Another study found the SCCA levels to be elevated in BA patients compared with controls, but the difference was only 1 ng/mL [34]. Furthermore, serum SCCA levels in adult patients with AR caused by cedar pollen were similar to those in healthy adult volunteers, and the median level in patients with AR caused by *Dermatophagoides farinae* was only 0.20 ng/mL higher than that in healthy volunteers [35]. Our present findings are consistent with those earlier results. However, serum levels of SCCAs were reported to be elevated in patients with psoriasis [17], so special attention needs to be paid to differential diagnosis of AD from psoriasis.

This study has several limitations. First, we used the SCORAD index as a severity scale, but that is not considered to be a gold-standard severity scale [4]. Second, we did not assess the relationship between the disease severity and the serum levels of biomarkers in patients with mild or moderate AD. However, we previously reported the SCCA2 levels in that population of AD patients [23], and one of the purposes of this study was to clarify utility of SCCAs in AD children with comorbidities.

In conclusion, the serum levels of SCCA1 and SCCA2 were elevated in children and adolescents with AD. In addition, the SCCA2 level correlated more strongly with the SCORAD index than the TARC or SCCA1 level. We think that SCCA2 has potential as a useful and reliable biomarker for assessing the severity of AD in children and adolescents and their responses to treatment.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Differences in serum levels of SCCA1 and SCCA2 between groups

Click here to view

Supplementary Table 2

Serum levels of SCCA1 and SCCA2 in healthy volunteers without allergic diseases by age group

Click here to view

REFERENCES

1. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, Shimojo N, Tanaka A, Nakahara T, Nagao M, Hide M, Fujita Y, Fujisawa T, Futamura M, Masuda K, Murota H, Yamamoto-Hanada K. Clinical practice guidelines for the management of atopic dermatitis 2018. J Dermatol 2019;46:1053-101.
PUBMED | CROSSREF
2. Tang TS, Bieber T, Williams HC. Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? J Allergy Clin Immunol 2014;133:1615-25.e1.
PUBMED | CROSSREF
3. Thijs J, Krastev T, Weidinger S, Buckens CF, de Bruin-Weller M, Bruijnzeel-Koomen C, Flohr C, Hijnen D. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. Curr Opin Allergy Clin Immunol 2015;15:453-60.
PUBMED | CROSSREF
4. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.
PUBMED | CROSSREF
5. Silverman GA, Bird PI, Carrell RW, Church FC, Coughlin PB, Gettins PG, Irving JA, Lomas DA, Luke CJ, Moyer RW, Pemberton PA, Remold-O'Donnell E, Salvesen GS, Travis J, Whisstock JC. The serpins are an expanding superfamily of structurally similar but functionally diverse proteins. Evolution, mechanism of inhibition, novel functions, and a revised nomenclature. J Biol Chem 2001;276:33293-6.
PUBMED | CROSSREF
6. Cataltepe S, Gornstein ER, Schick C, Kamachi Y, Chatson K, Fries J, Silverman GA, Upton MP. Co-expression of the squamous cell carcinoma antigens 1 and 2 in normal adult human tissues and squamous cell carcinomas. J Histochem Cytochem 2000;48:113-22.
PUBMED | CROSSREF
7. Sivaprasad U, Kinker KG, Ericksen MB, Lindsey M, Gibson AM, Bass SA, Hershey NS, Deng J, Medvedovic M, Khurana Hershey GK. SERPINB3/B4 contributes to early inflammation and barrier dysfunction in an experimental murine model of atopic dermatitis. J Invest Dermatol 2015;135:160-9.
PUBMED | CROSSREF
8. Sakata Y, Arima K, Takai T, Sakurai W, Masumoto K, Yuyama N, Suminami Y, Kishi F, Yamashita T, Kato T, Ogawa H, Fujimoto K, Matsuo Y, Sugita Y, Izuhara K. The squamous cell carcinoma antigen 2 inhibits the cysteine proteinase activity of a major mite allergen, Der p 1. J Biol Chem 2004;279:5081-7.
PUBMED | CROSSREF
9. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer 1977;40:1621-8.
PUBMED | CROSSREF
10. Shimura K, Mabuchi S, Yokoi T, Sasano T, Sawada K, Hamasaki T, Kimura T. Utility of serum squamous cell carcinoma antigen levels at the time of recurrent cervical cancer diagnosis in determining the optimal treatment choice. J Gynecol Oncol 2013;24:321-9.
PUBMED | CROSSREF

11. Williams M, Swampillai A, Osborne M, Mawdsley S, Hughes R, Harrison M, Harvey R, Glynne-Jones RMount Vernon Colorectal Cancer Network. Squamous cell carcinoma antigen: a potentially useful prognostic marker in squamous cell carcinoma of the anal canal and margin. Cancer 2013;119:2391-8.
PUBMED | CROSSREF

12. Yin M, Hou Y, Zhang T, Cui C, Zhou X, Sun F, Li H, Li X, Zheng J, Chen X, Li C, Ning X, Li K, Lou G. Evaluation of chemotherapy response with serum squamous cell carcinoma antigen level in cervical cancer patients: a prospective cohort study. PLoS One 2013;8:e54969.
PUBMED | CROSSREF

13. Chen IH, Liao CT, Wang HM, Huang JJ, Kang CJ, Huang SF. Using SCC antigen and CRP levels as prognostic biomarkers in recurrent oral cavity squamous cell carcinoma. PLoS One 2014;9:e103265.
PUBMED | CROSSREF

14. van Zijl FVWJ, Monserez DA, Korevaar TIM, Bugter O, Wieringa MH, Baatenburg de Jong RJ, Hardillo JAU. Postoperative value of serum squamous cell carcinoma antigen as a predictor of recurrence in sinonasal inverted papilloma. Clin Otolaryngol 2017;42:528-35.
PUBMED | CROSSREF

15. Campbell B, De'Ambrosis B. Squamous cell carcinoma antigen in patients with cutaneous disorders. J Am Acad Dermatol 1990;22:639-42.
PUBMED | CROSSREF

16. Mitsuishi K, Nakamura T, Sakata Y, Yuyama N, Arima K, Sugita Y, Suto H, Izuhara K, Ogawa H. The squamous cell carcinoma antigens as relevant biomarkers of atopic dermatitis. Clin Exp Allergy 2005;35:1327-33.
PUBMED | CROSSREF

17. Watanabe Y, Yamaguchi Y, Komitsu N, Ohta S, Azuma Y, Izuhara K, Aihara M. Elevation of serum squamous cell carcinoma antigen 2 in patients with psoriasis: associations with disease severity and response to the treatment. Br J Dermatol 2016;174:1327-36.
PUBMED | CROSSREF

18. Horiuchi Y, Tsukahara T, Otoyama K. Immunohistochemical study of elevated expression of squamous cell carcinoma (SCC)-related antigens in erythrodermic epidermis. J Dermatol 1994;21:67-72.
PUBMED | CROSSREF

19. Kawashima H, Nishimata S, Kashiwagi Y, Numabe H, Sasamoto M, Iwatsubo H, Takekuma K, Hoshika A. Squamous cell carcinoma-related antigen in children with atopic dermatitis. Pediatr Int 2000;42:448-50.
PUBMED | CROSSREF

20. Yamane Y, Moriyama K, Yasuda C, Miyata S, Aihara M, Ikezawa Z, Miyazaki K. New horny layer marker proteins for evaluating skin condition in atopic dermatitis. Int Arch Allergy Immunol 2009;150:89-101.
PUBMED | CROSSREF

21. Ohta S, Shibata R, Nakao Y, Azuma Y, Taniguchi K, Arima K, Suzuki S, Shiraishi H, Iwasaka T, Izuhara K. The usefulness of combined measurements of squamous cell carcinoma antigens 1 and 2 in diagnosing atopic dermatitis. Ann Clin Biochem 2012;49(Pt 3):277-84.
PUBMED | CROSSREF

22. Okawa T, Yamaguchi Y, Kou K, Ono J, Azuma Y, Komitsu N, Inoue Y, Kohno M, Matsukura S, Kambara T, Ohta S, Izuhara K, Aihara M. Serum levels of squamous cell carcinoma antigens 1 and 2 reflect disease severity and clinical type of atopic dermatitis in adult patients. Allergol Int 2018;67:124-30.
PUBMED | CROSSREF

23. Nagao M, Inagaki S, Kawano T, Azuma Y, Nomura N, Noguchi Y, Ohta S, Kawaguchi A, Odajima H, Ohya Y, Fujisawa T, Izuhara K. SCCA2 is a reliable biomarker for evaluating pediatric atopic dermatitis. J Allergy Clin Immunol 2018;141:1934-6.e11.
PUBMED | CROSSREF

24. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8:483-91.
PUBMED | CROSSREF

25. Futamura M, Ohya Y, Akashi M, Adachi Y, Odajima H, Akiyama K, Akasawa A. Age-related prevalence of allergic diseases in Tokyo schoolchildren. Allergol Int 2011;60:509-15.
PUBMED | CROSSREF

26. Fujisawa T, Nagao M, Hiraguchi Y, Katsumata H, Nishimori H, Iguchi K, Kato Y, Higashiura M, Ogawauchi I, Tamaki K. Serum measurement of thymus and activation-regulated chemokine/CCL17 in children with atopic dermatitis: elevated normal levels in infancy and age-specific analysis in atopic dermatitis. Pediatr Allergy Immunol 2009;20:633-41.
PUBMED | CROSSREF

27. Tamaki K, Kakinuma T, Saeki H, Horikawa T, Kataoka Y, Fujisawa T, Sato S, Takehara K, Nakahara T, Fukagawa S, Furue M. Serum levels of CCL17/TARC in various skin diseases. J Dermatol 2006;33:300-2.
PUBMED | CROSSREF

28. Kataoka Y. Thymus and activation-regulated chemokine as a clinical biomarker in atopic dermatitis. J Dermatol 2014;41:221-9.
PUBMED | CROSSREF

29. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
PUBMED | CROSSREF

30. Saeki H, Tamaki K. Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. J Dermatol Sci 2006;43:75-84.
PUBMED | CROSSREF

31. Gerbens LA, Prinsen CA, Chalmers JR, Drucker AM, von Kobyletzki LB, Limpens J, Nankervis H, Svensson Å, Terwee CB, Zhang J, Apfelbacher CJ, Spuls PI; Harmonising Outcome Measures for Eczema (HOME) initiative. Evaluation of the measurement properties of symptom measurement instruments for atopic eczema: a systematic review. Allergy 2017;72:146-63.
PUBMED | CROSSREF

32. de Bruin Weller MS, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Evaluation of the child with atopic dermatitis. Clin Exp Allergy 2012;42:352-62.
PUBMED | CROSSREF

33. Nishi N, Miyazaki M, Tsuji K, Hitomi T, Muro E, Zaitsu M, Yamamoto S, Inada S, Kobayashi I, Ichimaru T, Izuhara K, Nagumo F, Yuyama N, Hamasaki Y. Squamous cell carcinoma-related antigen in children with acute asthma. Ann Allergy Asthma Immunol 2005;94:391-7.
PUBMED | CROSSREF

34. Yuyama N, Davies DE, Akaiwa M, Matsui K, Hamasaki Y, Suminami Y, Yoshida NL, Maeda M, Pandit A, Lordan JL, Kamogawa Y, Arima K, Nagumo F, Sugimachi M, Berger A, Richards I, Roberds SL, Yamashita T, Kishi F, Kato H, Arai K, Ohshima K, Tadano J, Hamasaki N, Miyatake S, Sugita Y, Holgate ST, Izuhara K. Analysis of novel disease-related genes in bronchial asthma. Cytokine 2002;19:287-96.
PUBMED | CROSSREF

35. Suzuki K, Inokuchi A, Miyazaki J, Kuratomi Y, Izuhara K. Relationship between squamous cell carcinoma antigen and the clinical severity of allergic rhinitis caused by Dermatophagoides farinae and Japanese cedar pollen. Ann Otol Rhinol Laryngol 2010;119:22-6.
PUBMED | CROSSREF