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ORIGINAL ARTICLE

Salivary chromogranin A levels correlate with disease severity but do not reflect anxiety or personality of adult patients with atopic dermatitis

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ABSTRACT

Stress-induced scratching is an issue in patients with adult atopic dermatitis (AD). Although itching and stress are believed to be intimately related, no objective index is available; therefore, most evaluations are subjective. Using saliva, which is easily collected, we investigated the degree to which AD severity and patient stress levels are reflected in stress proteins in the saliva. Here, we evaluated the severity (Scoring Atopic Dermatitis [SCORAD] score), stress (State–Trait Anxiety Index [STAI] score), personality (Tokyo University Egogram [TEG] II score) and quality of life (Dermatology Life Quality Index [DLQI] score) of 51 patients with AD who were examined in the Department of Dermatology of Shimane University between April and December 2015. We collected saliva and measured salivary chromogranin A (CgA), amylase and cortisol. The amount of salivary CgA per protein in patients with AD was correlated with their SCORAD score ($r = 0.458$, $P < 0.001$). There was no correlation between cortisol or amylase levels and SCORAD score. SCORAD score was correlated with DLQI ($r = 0.390$, $P = 0.006$). CgA per protein was correlated with DLQI ($r = 0.393$, $P = 0.004$). There was no correlation between scores for the anxiety component of the STAI, TEG II or DLQI. Our results suggested that patients with more severe AD may have high stress levels. The personalities of these patients with AD tended to involve elevated anxiety levels.

Key words: **atopic, chromogranin A, dermatitis, saliva, stress marker.**

INTRODUCTION

Atopic dermatitis (AD) is a form of chronic intractable eczema that is associated with itching.[1] AD may be aggravated by various factors, with stress-induced scratching a particular problem in adult patients. Stress occurs when various external stimuli ("stressors") impose a physical or mental burden on an individual, resulting in "stress" that then causes a range of physical disorders. The body and mind have been known to be intimately interrelated since comparatively ancient times as expressed in the Japanese proverb *Yamai ha kikara* ("Illness arises from the spirit"). The disease activity of skin disorders is also greatly affected by the patient's mental state in many cases.[2] As most assessments of stress are subjective, an objective stress marker is desirable. Saliva samples can be collected non-invasively, making them useful for the diagnosis of specific oral pathologies[3,4] as well as more general ones.[5–7] Salivary chromogranin A (CgA),[8] cortisol[9,10] and amylase[11] are used as psychological stress markers.

Chromogranin A is an acidic glycoprotein dissociated from chromaffin granules in the adrenal medulla that reflect the secretion of catecholamines in the blood and provides a marker of the sympathetic adrenomedullary system activity. CgA is present in the submandibular gland ducts, from where it is released into the saliva upon autonomic nervous stimulation. Salivary CgA is attracting attention as a new indicator of psychological stress.[8] Cortisol, the main glucocorticosteroid secreted by the adrenal medulla, is involved in glucose metabolism as well as protein and fat metabolism, exerting a range of effects on the immune, vascular and central nervous systems in the maintenance of homeostasis, and is an important hormone in maintaining both mental and physical states of health.[9] Cortisol is secreted in large quantities in stressful situations, and salivary cortisol has been found to be correlated with Scoring Atopic Dermatitis (SCORAD) scores in patients with AD.[10] Salivary amylase is believed to be secreted by the sympathetic nervous system.[11] Salivary amylase activity has been found to increase in response to unpleasant stimuli and conversely to decrease in response to pleasant ones, making it

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a novel indicator of the sympathetic nervous system and suggesting that salivary amylase may enable the distinction between pleasant and unpleasant stimuli.[12]

Therefore, we focused on these stress markers in saliva to study correlation with SCORAD score, and stress type with the aim of creating and utilizing objective biomarkers.

METHODS

Subjects

The study subjects included 51 patients with AD (29 men, 22 women; mean age, 32.2 years; age range, 16–57) examined in the Department of Dermatology, Shimane University Hospital, between April and December 2015 who consented to participate. Patient data was anonymized prior to the analysis. The 51 patients (48 outpatients, three inpatients) included patients with mild (n = 18), moderate (n = 22), severe (n = 9) and very severe (n = 2) AD, as classified by the severity scale proposed by the Ministry of Health, Labor and Welfare Research Group. This study on the relationship between AD and stress was approved by the ethics committee of Shimane University and the Dean of the Faculty of Medicine (approval no. 1773).

Evaluation of severity of AD, anxiety, personality and life quality

Scoring Atopic Dermatitis score, objective SCORAD score, serum lactate dehydrogenase (LDH), serum level of thymus and activation regulated chemokine (TARC) and serum level of immunoglobulin E (IgE) were evaluated.

Patients were asked to complete the following questionnaires during their examination: the State–Trait Anxiety Index (STAI), an objective assessment of anxiety; the new Tokyo University Egogram [TEG] II, a personality test; and the Dermatology Life Quality Index (DLQI) survey. The STAI is divided into state anxiety and trait anxiety. State anxiety is a transient state of anxiety associated with factors such as autonomic nervous excitement, while trait anxiety is a tendency for anxiety to be aroused in response to stressful situations and is understood to be a comparatively stable personality trait.[13] The inventory measures the two scales simultaneously. The TEG II expresses the relationship between the various ego states of the individual's personality and the amount of psychic energy released externally as five bar graphs that visualize personality characteristic and behavior patterns. The five scales of the TEG II correspond to the five ego states of the critical parent (CP), nurturing parent (NP), adult (A), free child (FC) and adapted child (AC).[14] The correlation between the high and low values of each scale provide an understanding of personality characteristics. Ego states are not "good" or "bad", but they have some aspects that can be understood to be advantageous and others that can be understood to be detrimental. The DLQI enables measurement and comparison of the quality of life (QOL) of various skin diseases. With a total of 10 questions, it comprises six scales covering symptoms, feelings, daily life, leisure, work, school, interpersonal relationships and treatment. The various subscale scores and the total score (0–30 points) can be calculated.[15]

Measurements of stress markers in saliva

The subjects were instructed to avoid the following daily procedures before saliva collection: taking caffeine, sugar or acidic foods shortly prior; consuming dairy products for 20 min; brushing their teeth for 45 min; eating for 1 h; taking alcohol for 12 h; and dental treatment for 2 days before sample collection. Each individual was issued a saliva collection kit. When these conditions were met, the subjects rinsed out their mouths three times with water, were allowed to accumulate saliva in their mouths for the next 10 min, leaned forward to allow it to flow into a container, and repeated this process until at least 1 mL of saliva was collected. The collected saliva was centrifuged at 905 g for 15 min, transferred to a polypropylene tube and frozen at −20°C until measurement.

Chromogranin A concentration, cortisol concentration and amylase concentration in the saliva were measured by a YK070 Human Chromogranin A EIA Kit (Yanaihara Institute, Shizuoka, Japan), a Corticosterone ELISA Kit (Salimetrics, State College, PA, USA) and a 12S001579 Salivary Amylase Monitor (Nipro, Osaka, Japan), respectively.

Statistical analysis

Experimental results are given as mean ± standard deviation (SD). R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. The median number and 25–75 percentile of anxiety were calculated. Correlations were investigated by calculating Pearson's product–moment correlation coefficient with a 5% significance level.

RESULTS

Results of SCORAD, objective SCORAD, serum LDH, serum TARC level, serum IgE, STAI, TEG II, DLQI, salivary CgA, salivary cortisol and salivary amylase are summarized in Table 1. There was no correlation between AD serum disease severity markers (TARC, LDH and total IgE) and salivary CgA, cortisol or amylase levels (Table 2). Correlation data for all subject parameters about salivary stress markers are summarized in Table 3.

Correlation between SCORAD score and salivary CgA, amylase and cortisol

Salivary CgA levels and CgA levels per protein were correlated with their SCORAD score and their objective SCORAD score (Fig. 1). There was no correlation between SCORAD score and salivary cortisol or amylase levels (Table 3).

Correlation between salivary CgA, amylase and cortisol levels and anxiety scale scores

Chromogranin A levels were correlated with DLQI scores (Fig. 2), but there was no correlation between STAI scores and CgA, amylase or cortisol levels (Table 3).

Correlation between SCORAD score and anxiety scale scores (STAI, TEG II and DLQI)

Scoring Atopic Dermatitis scores were correlated with DLQI scores (Fig. 3) but not with STAI scores (Table 3).

Table 1. Subject characteristics

Parameters	*n*	Mean ± SD
SCORAD	49	33.35 ± 15.58
Objective SCORAD	50	26.99 ± 13.25
LDH (IU/L)	28	226.2 ± 55.6
TARC (pg/mL)	30	1956.8 ± 1868.2
IgE (IU/mL)	33	9634.7 ± 10517.3
STAI state	51	44. 65 ± 9.03
STAI trait	51	49.75 ± 10.85
TEG II CP	51	9.98 ± 4.82
TEG II NP	51	13.51 ± 4.96
TEG II A	51	11.39 ± 5.56
TEG II FC	51	10.71 ± 5.69
TEG II AC	51	13.12 ± 5.66
DLQI	51	6.627 ± 5.26
Salivary CgA (pmol/mL)	51	22.25 ± 38.1
Salivary CgA/protein (pmol/mL)	51	12.12 ± 22.5
Salivary cortisol (ng/mL)	51	137.62 ± 99.1
Salivary cortisol/protein (ng/mL)	51	89.55 ± 86.7
Salivary amylase (KIU/L)	51	293.4 ± 312.1
Salivary amylase/protein (KIU/L)	51	137.79 ± 100.9

A, adult; AC, adapted child; CgA, chromogranin A; CP, critical parent; DLQI, Dermatological Life Quality Index; FC, free child; IgE, immunoglobulin E; LDH, lactate dehydrogenase; NP, nurturing parent; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation; STAI, State–Trait Anxiety Index; TARC, thymus and activation regulated chemokine; TEG, Tokyo University Egogram.

Anxiety scales

There was a significant correlation between STAI and TEG II and DLQI scores (Fig. 4). Correlation data for all subject parameters about SCORAD, STAI, TEG II and DLQI scores are summarized in Table 4.

DISCUSSION

Stress may be physical or psychological, but this can be difficult to distinguish. The increasing number of patients with AD presenting at approximately 18 years of age may be due not only to the psychological stress of entrance examinations but also due to the increase in physical stressors associated with studying for these examinations, including a lack of sleep and chronic fatigue.[16] Studies have also found that patients with AD are unable to deal appropriately with psychosocial challenges,[17] and repeatedly scratching an itch may represent a behavioral change in response to such psychosocial stress.[18] In cases of severe AD, a stress–scratch cycle develops over and above the itch–scratch cycle,[19] producing a recurring cycle resulting in intensification of addictive scratching as an abnormal behavior rooted in psychosocial stress. The management approach taken to address this stress–scratch cycle is considered extremely important.[20] Such stress may have a wide variety of causes; although "stress" is considered an aggravating factor for AD, the type, level and manner of stress that aggravates AD remain unclear.

Recently, there have been advances in the analysis of stress biomarkers in saliva. Acute pain is more of a physical stress factor than a mental one and does not produce an increase in salivary CgA, whereas the concentration of salivary CgA reportedly increases in response to feelings of fear.[3] Cortisol is believed to indicate a reaction to physical stress, while CgA indicates a reaction to psychological stress.[21] We focused on saliva, which is easy to collect, to investigate whether factors such as AD SCORAD score and patients' stress levels are reflected in stress proteins in the saliva. Previous studies found that patients undergoing initial evaluation for AD have significantly higher levels of salivary CgA compared with patients without AD undergoing an initial examination as well as patients with AD undergoing repeat examinations,[22] and that high salivary cortisol in patients with AD is correlated with severity.[10] Although no study has addressed the question of salivary amylase levels in patients with AD, these levels are high in patients with schizophrenia, a phenomenon that is believed to be associated with stress.[23] Our results demonstrated a correlation between salivary CgA and AD SCORAD scores, but not between SCORAD scores and salivary cortisol or amylase levels. This suggests that the AD SCORAD score, which is considered

Table 2. Correlations between disease severity markers and salivary stress markers

	SCORAD	Objective SCORAD	TARC (pg/mL)	LDH (IU/L)	IgE (IU/mL)
Salivary CgA (pmol/mL)	$r = 0.419$ $P = 0.003$	$r = 0.349$ $P = 0.013$	$r = 0.269$ $P = 0.150$	$r = 0.220$ $P = 0.261$	$r = 0.060$ $P = 0.739$
Salivary CgA/protein (pmol/mL)	$r = 0.458$ $P = 0.001$	$r = 0.385$ $P = 0.006$	$r = 0.309$ $P = 0.097$	$r = 0.222$ $P = 0.256$	$r = 0.086$ $P = 0.634$
Salivary cortisol (ng/mL)	$r = 0.082$ $P = 0.575$	$r = 0.078$ $P = 0.588$	$r = -0.021$ $P = 0.912$	$r = 0.158$ $P = 0.422$	$r = 0.002$ $P = 0.990$
Salivary cortisol/protein (ng/mL)	$r = 0.138$ $P = 0.345$	$r = 0.125$ $P = 0.389$	$r = -0.008$ $P = 0.968$	$r = 0.035$ $P = 0.858$	$r < 0.001$ $P = 0.999$
Salivary amylase (KIU/L)	$r = -0.192$ $P = 0.186$	$r = -0.177$ $P = 0.218$	$r = -0.165$ $P = 0.385$	$r = -0.063$ $P = 0.749$	$r = 0.051$ $P = 0.779$
Salivary amylase/protein (KIU/L)	$r = -0.162$ $P = 0.267$	$r = -0.141$ $P = 0.329$	$r = -0.162$ $P = 0.393$	$r = -0.097$ $P = 0.624$	$r = 0.240$ $P = 0.178$

Underlining indicates significant data. CgA, chromogranin A; IgE, immunoglobulin E; LDH, lactate dehydrogenase; SCORAD, Scoring Atopic Dermatitis; TARC, thymus and activation regulated chemokine.

Table 3. Correlations between AD patients parameters and salivary stress marker

(a)	DLQI	STAI state	STAI trait
Salivary CgA (pmol/mL)	$r = 0.347$ $P = 0.013$	$r = -0.029$ $P = 0.843$	$r = 0.118$ $P = 0.411$
Salivary CgA/protein (pmol/mL)	$r = 0.393$ $P = 0.004$	$r = -0.037$ $P = 0.795$	$r = 0.087$ $P = 0.545$
Salivary cortisol (ng/mL)	$r = 0.259$ $P = 0.067$	$r = 0.005$ $P = 0.970$	$r = 0.205$ $P = 0.149$
Salivary cortisol/protein (ng/mL)	$r = 0.261$ $P = 0.064$	$r = -0.174$ $P = 0.220$	$r = 0.156$ $P = 0.273$
Salivary amylase (KIU/L)	$r = -0.076$ $P = 0.595$	$r = 0.145$ $P = 0.310$	$r = 0.215$ $P = 0.131$
Salivary amylase/protein (KIU/L)	$r = -0.147$ $P = 0.305$	$r = 0.111$ $P = 0.436$	$r = 0.175$ $P = 0.218$

(b)	TEG II CP	TEG II NP	TEG II A	TEG II FC	TEG II AC
Salivary CgA (pmol/mL)	$r = 0.022$ $P = 0.878$	$r = 0.058$ $P = 0.686$	$r = 0.257$ $P = 0.068$	$r = 0.112$ $P = 0.435$	$r = 0.206$ $P = 0.147$
Salivary CgA/protein (pmol/mL)	$r = 0.050$ $P = 0.729$	$r = 0.106$ $P = 0.461$	$r = 0.254$ $P = 0.073$	$r = 0.159$ $P = 0.265$	$r = 0.149$ $P = 0.298$
Salivary cortisol (ng/mL)	$r = 0.026$ $P = 0.855$	$r = -0.160$ $P = 0.263$	$r = -0.003$ $P = 0.982$	$r = -0.132$ $P = 0.355$	$r = 0.050$ $P = 0.727$
Salivary cortisol/protein (ng/mL)	$r = 0.117$ $P = 0.414$	$r = 0.016$ $P = 0.910$	$r = 0.015$ $P = 0.917$	$r = 0.053$ $P = 0.711$	$r = -0.010$ $P = 0.942$
Salivary amylase (KIU/L)	$r = -0.129$ $P = 0.367$	$r = -0.213$ $P = 0.133$	$r = -0.093$ $P = 0.519$	$r = -0.288$ $P = 0.040$	$r = 0.271$ $P = 0.054$
Salivary amylase/protein (KIU/L)	$r = -0.132$ $P = 0.357$	$r = -0.054$ $P = 0.709$	$r = -0.124$ $P = 0.386$	$r = -0.285$ $P = 0.043$	$r = 0.181$ $P = 0.205$

Underlining indicates significant data. A, adult; AC, adapted child; AD, atopic dermatitis; CgA, chromogranin A; CP, critical parent; DLQI, Dermatological Life Quality Index; FC, free child; NP, nurturing parent; STAI, State–Trait Anxiety Index; TEG, Tokyo University Egogram.

to represent physical stress, is correlated with psychological stress. This is an extremely interesting finding with regards to the role of stress in AD. However, cortisol is known to exhibit diurnal fluctuations and it is possible that this might have resulted in the lack of an observable correlation. In routine clinical practice, tests are performed at almost every examination, suggesting that CgA may be more useful for investigating stress. Patients with very high CgA levels may have had such high levels because their AD was sufficiently severe to warrant possible hospitalization. CgA was also correlated with DLQI scores (Fig. 2), suggesting that it may be an important stress marker in the saliva.

Stress and anxiety are normally assessed using questionnaires. In this study, we also used questionnaires to evaluate patients with AD for anxiety and personality type but were unable to identify any correlation with stress markers in the saliva. The personality test, however, did reveal some trends specific to patients with AD: those with higher NP and FC scores tended to exhibit lower levels of state anxiety (temporary anxiety), whereas those with high AC scores tended to exhibit higher levels of trait anxiety (susceptibility to anxiety). These analyses may also play a useful role when providing patients with guidance. Other studies have also found that patients with AD score highly on the AC scale,[24] and the fact that our study corroborates this tendency further reveals its association with anxiety.

This study is medically important because it identified an objective association between saliva, which is easily sampled during examinations, and AD severity. This finding has important potential clinical applications, including measuring changes in salivary CgA levels after therapeutic interventions or for use in patients with other inflammatory diseases. It may also be useful in stress management for patients, although we must first understand what type of stress is involved. Although this may appear to be a simple question, the true cause is rarely established. In many cases, hints can be found in the answers to ordinary medical history questionnaires; therefore, the technique involved in taking a medical history is important. Establishing a good doctor–patient relationship is a basic prerequisite for such stress management, and 28 of 189 study subjects (14.8%) emphasized this point in the free comment section of the questionnaires.[25] Our analysis of the use of saliva as an objective stress marker may offer a useful future tool for stress management and stress coping.

Our results suggest that severe AD is associated with higher stress levels. Simple salivary CgA measurements may be useful as an objective assessment of patient stress. Here, we found an association between the personality of patients with

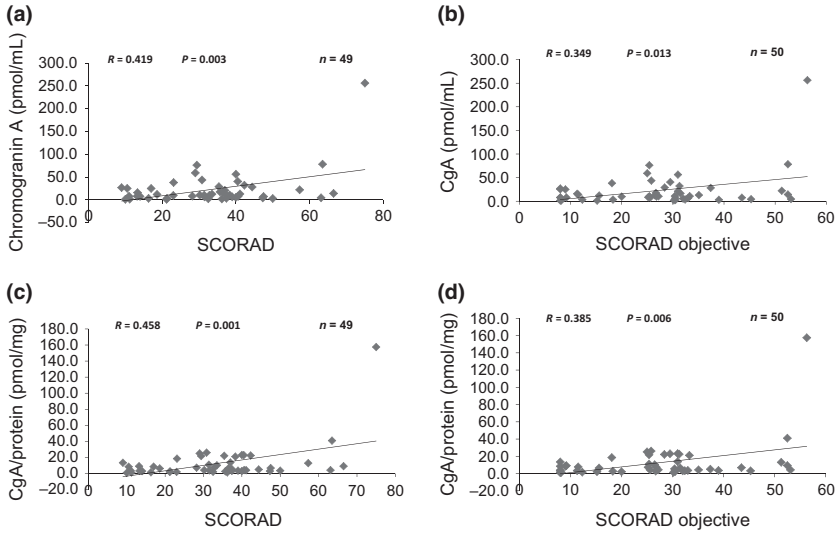

Figure 1. Correlation between Scoring Atopic Dermatitis (SCORAD) scores and salivary chromogranin A (CgA) amylase and cortisol. (a) There was significant correlation between SCORAD score and salivary CgA levels (r = 0.419, P = 0.003). (b) There was significant correlation between SCORAD objective score and salivary CgA levels (r = 0.349, P = 0.013). (c) There was significant correlation between SCORAD score and salivary CgA levels per protein (r = 0.458, P < 0.001). (d) There was significant correlation between SCORAD objective score and salivary CgA levels per protein (r = 0.385, P = 0.006).

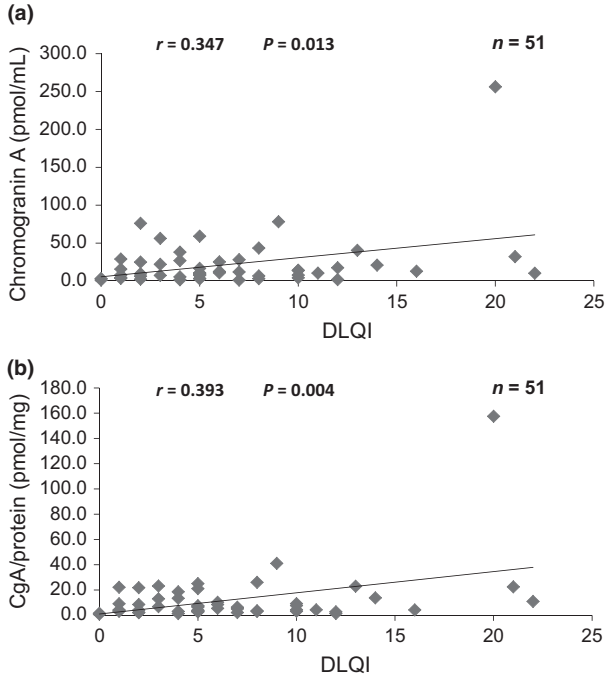

Figure 2. Correlation between salivary chromogranin A (CgA), amylase and cortisol levels and anxiety scales. (a) There was significant correlation between Dermatological Life Quality Index (DLQI) and salivary CgA levels (r = 0.347, P = 0.013). (b) There was significant correlation between DLQI and salivary CgA levels per protein (r = 0.393, P = 0.004).

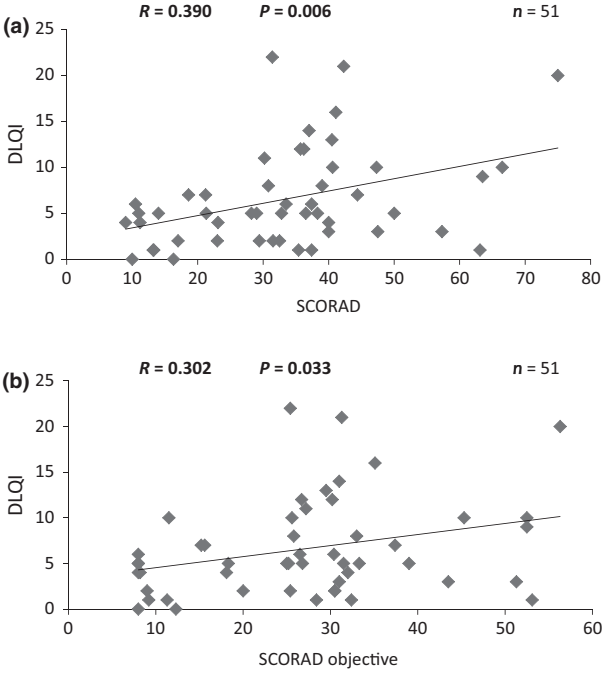

Figure 3. Correlation between Scoring Atopic Dermatitis (SCORAD) scores and anxiety scale scores (State–Trait Anxiety Index [STAI], Tokyo University Egogram [TEG] II and Dermatological Life Quality Index [DLQI]). (a) There was significant correlation between SCORAD score and DLQI (r = 0.390, P = 0.006). (b) There was significant correlation between SCORAD objective score and DLQI (r = 0.302, P = 0.033).

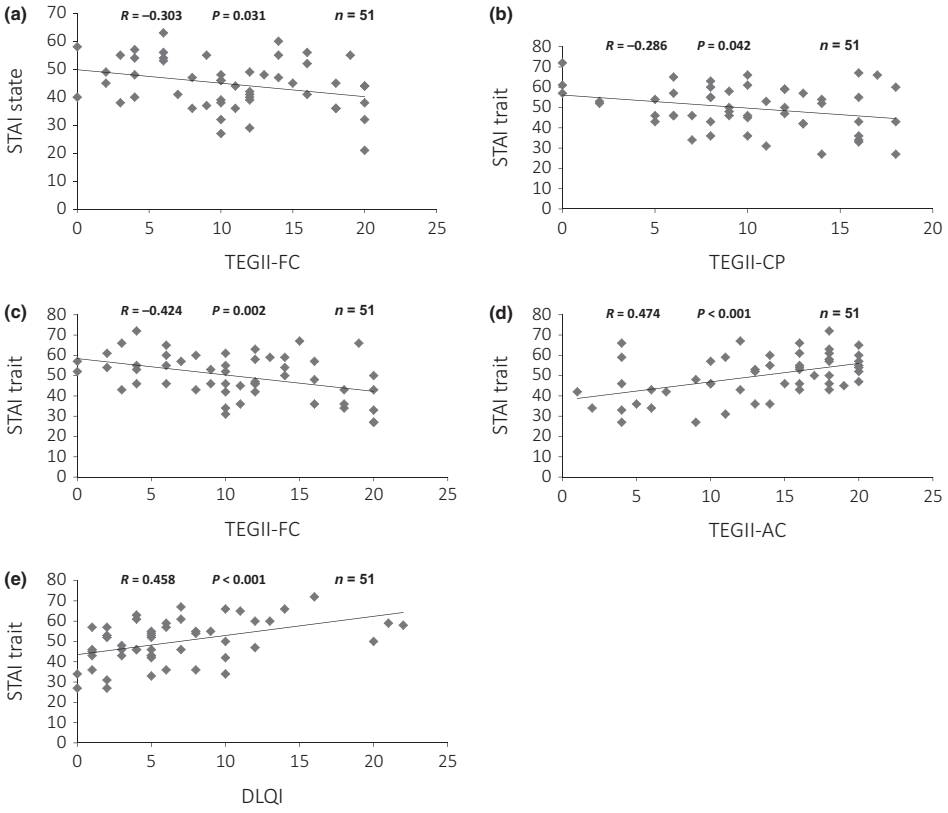

Figure 4. Correlation among anxiety scale scores (State–Trait Anxiety Index [STAI], Tokyo University Egogram [TEG] II and Dermatological Life Quality Index [DLQI]). (a) There was significant correlation between STAI state and TEG II free child (FC) ($r = -0.303$, $P = 0.031$). (b) There was significant correlation between STAI trait and TEG II critical parent (CP) ($r = -0.286$, $P = 0.042$). (c) There was significant correlation between STAI trait and TEG II FC ($r = -0.424$, $P = 0.002$). (d) There was significant correlation between STAI trait and TEG II adapted child (AC) ($r = -0.474$, $P < 0.001$). (e) There was significant correlation between STAI trait and DLQI ($r = 0.458$, $P < 0.001$).

Table 4. Correlations of subject parameter

	SCORAD	Objective SCORAD			
DLQI	r = 0.390 P = 0.006	r = 0.302 P = 0.033	DLQI		
STAI state	r = 0.049 P = 0.737	r = 0.024 P = 0.871	r = 0.188 P = 0.187	STAI state	
STAI trait	r = 0.029 P = 0.844	r = −0.018 P = 0.900	r = 0.458 P < 0.001	n.d.	STAI trait
TEG II CP	r = 0.019 P = 0.898	r < 0.001 P = 0.998	r = 0.127 P = 0.373	r = −0.155 P = 0.276	r = −0.286 P = 0.042
TEG II NP	r = −0.021 P = 0.888	r = 0.050 P = 0.729	r = 0.055 P = 0.702	r = −0.271 P = 0.054	r = −0.224 P = 0.114
TEG II A	r = 0.204 P = 0.159	r = 0.173 P = 0.230	r = 0.151 P = 0.291	r = −0.232 P = 0.101	r = −0.179 P = 0.210
TEG II FC	r = 0.137 P = 0.347	r = 0.128 P = 0.376	r = 0.043 P = 0.076	r = −0.303 P = 0.031	r = −0.424 P = 0.002
TEG II AC	r = 0.037 P = 0.802	r = −0.013 P = 0.931	r = 0.153 P = 0.282	r = 0.142 P = 0.321	r = 0.474 P < 0.001

Underlining indicates significant data. A, adult; AC, adapted child; CP, critical parent; DLQI, Dermatological Life Quality Index; FC, free child; n.d., not done; NP, nurturing parent; STAI, State–Trait Anxiety Index; TEG, Tokyo University Egogram.
TEG, Tokyo University Egogram; STAI, State–Trait Anxiety Index.

AD and anxiety but not between anxiety and salivary stress markers.

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CONFLICT OF INTEREST: None declared.

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