The Objective Severity Assessment of Atopic Dermatitis Score

An Objective Measure Using Permeability Barrier Function and Stratum Corneum Hydration With Computer-Assisted Estimates for Extent of Disease

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Objectives: Clinical scores used to assess the severity of atopic dermatitis (AD) rely entirely on subjective criteria to evaluate the severity of lesions and the extent of involvement. The aim of this study was to develop an objective measure of AD severity by measuring stratum corneum (SC) functions and by using computer-assisted estimates of involved body surface areas (BSAs).

Design: Barrier function of the SC was assessed by measuring transepidermal water loss, and SC hydration was assessed by measuring capacitance. The extent of disease was assessed using a computer-assisted algorithm.

Patients: A total of 38 sequential volunteers aged 4 months to 18 years (25 girls, 13 boys) with mild to severe AD at a university outpatient pediatric dermatology clinic.

Main Outcome Measures: The computer-assisted method for estimating BSA was compared with estimates using the “rule of nines.” The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score, derived from measurements of SC barrier function and SC hydration and normalized for extent of disease was compared with the Scoring Atopic Dermatitis (SCORAD) index.

Results: Measurements of epidermal permeability barrier function and SC hydration correlated with clinical estimates of disease severity. The computer-assisted measurements of the extent of disease correlated with estimates derived from the rule of nines. The OSAAD scores correlated with the currently used instrument for AD severity, the SCORAD index.

Conclusion: The OSAAD is a new AD severity score that avoids the pitfalls of currently used subjective scoring systems by using objective measures.

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A TOPIC DERMATITIS (AD) is a common chronic inflammatory disease of childhood caused by an interplay of local, immunologic, genetic, and environmental factors. Assessment of disease activity is complicated by variable lesional morphology, poorly margined lesions, and concurrent lesions of varying severity. Moreover, “uninvolved” skin in not entirely normal but is variably dry and may show spongiosis histologically. There is a striking lack of standardization in measures that assess these clinical features to determine disease severity. A recent review evaluated 13 AD severity scales, all of which relied on subjective assessment of clinical signs and symptoms, and concluded that the only scale for which validity, reliability, sensitivity, and acceptability had been evaluated was the Scoring of Atopic Dermatitis (SCORAD) index. The SCORAD is an index composed of (1) clinical observations of lesional morphology; (2) estimation of extent of involvement using the “rule of nines”; and (3) patient (or parent) assessments of symptoms. While SCORAD is widely used as the current gold standard, concerns of interobserver and intraobserver variability have been raised because of SCORAD’s reliance solely on subjective criteria. Moreover, the method used for estimating extent of body surface area (BSA) affected, the rule of nines, is also subjective and plagued by interobserver variability, even among trained observers. Recently, a new assessment tool, the Eczema Area and Severity Index (EASI), was introduced to assess the extent and activity of AD, but again, this index relies on subjective parameters.

In the present study, we asked whether objective measures of stratum corneum (SC) function, namely, permeability barrier function and SC hydration, both of which can be rapidly and noninvasively assessed using well-described bioengineer-
ing technology, could be used to assess AD severity. Transepidermal water loss (TEWL) rates, a direct measure of the permeability barrier, are increased in AD, both on uninvolved skin and on involved skin in relation to severity. The barrier defect has been attributed to decreased content of SC ceramide, a key lipid of the intercellular lamellae that form the permeability barrier. Whether the barrier defect in AD is intrinsic or secondary to another pathogenic factor is unknown, but in either case it would contribute to disease amplification through increased percutaneous absorption of antigens and irritants and through release of proinflammatory cytokines. Patients with AD also have an impaired ability of SC to bind and hold water. This is due to decreased content of osmotically active amino acids in corneocytes (impairing their ability to attract and bind water) and abnormal SC lamellae that cannot trap water within the corneocytes. Like barrier function, SC hydration, as measured by corneometry (CM), correlates well with AD severity and is also abnormal on dry, uninvolved skin.

Thus, in the present study, we sought to use these 2 objective measures of SC function, TEWL and CM, as proxies for disease activity in AD. We reasoned that a summation of these measures on uninvolved and involved skin over the body surface might provide an objective score of AD severity. Furthermore, to more objectively define the areas of involvement, we developed a novel computer-assisted system.

METHODS

COMPUTER-ASSISTED BSA ESTIMATES

Estimates of BSA involvement were obtained by shading the involved areas on a representational image of a child (Figure 1). One figure was shaded in all affected areas, and another was shaded on more severely affected areas only. The drawings were scanned and the images analyzed using the Scion (Frederick, Md) Image beta 4.02 (National Institutes of Health–based image analyze shareware: www.scioncorp.com/frames/fr_scion_products.htm), which calculated the percentage of BSA involved in all types of lesions and the percentage of BSA with more severe lesions. The percentage of BSA with milder involvement was obtained by subtraction. Estimation of BSA involvement by the rule of nines and the shading of figures for the computer-assisted BSA calculation were performed by the same physician. Scanning of drawings and computer-assisted calculation of the involved BSA were performed by an independent and blinded person.

VALIDATION OF COMPUTER-ASSISTED BSA CALCULATIONS

We performed a validation study of the computer-assisted method using 3 different clinical pictures from the Dermatology Online Atlas (DOIA: www.dermis.net) showing full body images of AD, mycosis fungoides, and psoriasis. Board-certified dermatologists (n=7) and dermatology residents (n=5) completed the study. The involved areas were drawn onto templates and scanned, and the percentage of BSA involved was calculated as described above. In parallel, the participants calculated the percentage of involved BSA using the rule of nines. Reproducibility was analyzed by the coefficient of variance.

ASSESSMENT TOOLS

Transepidermal water loss was assessed with the open loop system Tewameter TM 210 (Courage and Khazaka, Cologne, Germany). The probe gathered continuous TEWL measurements for 45 to 60 seconds and averaged them. The measured values are expressed in grams per square meters per hour. Capacitance as a parameter for SC hydration was assessed with a Corneometer CM 825 (Courage and Khazaka). Three individual CM measurements from the same site were averaged. The CM 825 values are expressed as arbitrary units. Established guidelines for TEWL and CM measurements were followed except that room temperatures were slightly higher because of our study participants' young age and the requirement that they be at least partially undressed for about 30 minutes. The SCORAD index was determined as described and was obtained prior to measurement of TEWL and CM.

PILOT STUDY

Volunteers with moderate to severe AD (n=8) were studied. Multiple body sites (12-20 sites per patient) with differing mor-
phologic characteristics and degrees of severity were assessed with TEWL and CM. Lesions were defined as more severe, moderately severe, or milder based on relative erythema, lichenification, excoriation, and crusting. Severity was defined relatively in each patient. The goal of this pilot study was to determine the minimum number of involved and uninvolved sites that should be measured to obtain a consistent measure of TEWL and CM in each category.

PATIENTS

The subjects undergoing Objective Severity Assessment of Atopic Dermatitis (OSAAD) evaluation were sequential volunteers (n=38) with mild to severe AD seen at a University outpatient pediatric dermatology practice (mean age, 5.6 years; age range, 4 months to 18 years; 25 girls and 13 boys). Thirty-four percent of the patients were Asian, 29% white, 13% African American, 11% Filipino, 11% Hispanic, and 2% mixed Hispanic and Asian. Volunteers were instructed not to use any topical products within 4 hours of their visit. Patients who had applied topical agents within 4 hours of the study time were excluded. Written informed parental consent was obtained for all subjects. The study was approved by the committee for human research at the University of California, San Francisco.

Study measurements were performed immediately following the subject’s clinic appointment. The room temperature was 21.9°C±2°C with an average humidity of 39.3% (range, 23%-53%). All subjects were acclimatized in the study room for at least 20 minutes before testing began. The measurements, including the recording of involved BSA, required approximately 5 minutes per patient. To minimize regional anatomic differences, the ventral forearm was used as the measuring site whenever possible. Excoriated sites were excluded. The study was carried out from November through February; all participants resided in northern California.

OSAAD CALCULATION

The OSAAD score was constructed by multiplying TEWL and CM for unaffected, mildly affected, and severely affected areas by the extent of BSA involvement for these areas. To obtain a score that would be zero or negative in completely resolved AD, we baseline adjusted TEWL (∆TEWL) and CM (∆CM) measurements by subtracting one SD of normal for each parameter for healthy children without AD. Therefore, 10 was used as the baseline adjustment for TEWL (mean plus 1 SD) and 64 was used for CM (mean minus 1 SD). Since SC hydration is inversely correlated with disease severity, ∆CM was multiplied by minus 1. The OSAAD was calculated according to the following formula: OSAAD=A+B+C+D+E+F, where A=∆TEWL_uninvolved×percent of BSA_uninvolved; B=∆TEWL_mild×percent of BSA_mild; C=∆TEWL_severe×percent of BSA_severe; D=∆CM_uninvolved×percent of BSA_uninvolved; E=∆CM_mild×percent of BSA_mild; and F=∆CM_severe×percent of BSA_severe.

STATISTICAL ANALYSIS

Statistical analyses were performed with SAS 6.12 software (SAS Institute Inc, Cary, NC) and Prism 3.0 (GraphPad Software, San Diego, Calif). Results are shown as means±SDs. The chosen level of significance is P<.05. The 3 groups (uninvolved, mildly involved, and severely involved) were compared by performing an analysis of variance (Friedman test) for each parameter (TEWL and SC hydration). When P<.05 for analysis of variance, a post hoc pairwise comparison with the Dunn test was calculated. When box plots are used, the box extends from the 25th percentile to the 75th percentile, with a line at the median. The whiskers show the highest and lowest values.

VALIDATION OF COMPUTER-ASSISTED ESTIMATE OF BSA

Using photographic images of AD, psoriasis, and mycosis fungoides, the percentage of involved BSA calculated by the rule of nines and our computer-assisted method correlates significantly (P<.001; Spearman coefficient, r=0.82). The percentage of involved BSA in the images of AD and psoriasis showed no significant differences between the 2 methods. The mycosis fungoides example had very extensive disease and showed higher values when calculated using the rule of nines: 39.6% with the rule of nines vs 30.8% using our computer-assisted method (P=.006). The scattering of data in all 3 examples was lower in the computer-assisted score, suggesting less interobserver variability with this method (Figure 2). Thus, our computer-assisted method correlates well with the rule of nines, and the latter may overestimate the extent of disease when a large percentage of the body is involved. A significant correlation (P<.001; Spearman coefficient, r=0.93) between the BSA assessed by the rule of nines and the computer-assisted BSA calculation was also detected in the OSAAD study population (n=38) (Figure 3).

PILOT STUDY

We measured TEWL and CM on multiple sites (n=8) to determine the range of values in regions clinically assessed as uninvolved and involved from mildly to severely. In a particular patient, lesions judged to be more severe all had TEWL values that were similar (within 10%); the same was true of more mildly involved skin and uninvolved skin (data not shown). Addition of an intermediate level (moderate) involvement greatly increased the complexity of clinical decision making without giving a clear benefit. We concluded that 1 set of measurements each from uninvolved, more mildly involved,
and more severely involved areas, as defined clinically in each patient, was sufficient.

**PERMEABILITY BARRIER FUNCTION**

In uninvolved areas, TEWL ranged between 4.2 and 42.9 g/m² per hour. In more mildly affected areas, it ranged between 11.3 and 67.4 g/m² per hour, while in more severely affected areas it ranged between 20.8 and 85.3 g/m² per hour (Figure 4). There was overlap in TEWL rates between patients with areas designated as uninvolved or mildly or severely involved. However, in a given patient, TEWL rates in areas clinically judged to be uninvolved were always lower than in mildly involved areas, and they were always lower in mildly involved areas than in those judged to be more severely involved. Analysis of variance findings were significant ($P < .001$), with $P < .01$ for all 3 Dunn test–adjusted post hoc pairwise comparisons (TEWL_uninvolved vs TEWL_mild, TEWL_uninvolved vs TEWL_severe, TEWL_mild vs TEWL_severe).

**SC HYDRATION**

The CM values correlated closely with disease severity. In the uninvolved areas, CM ranged between 17.3 and 57.0 arbitrary units, reflecting a wide range of dry skin severity in our sample (Figure 5). Despite overlapping values between patients, in a given patient, the CM values in areas clinically judged as severe were always lower than those in mild or uninvolved areas. Analysis of variance findings were significant ($P < .001$), with $P < .01$ for all 3 Dunn test–adjusted post hoc pairwise comparisons (CM_uninvolved vs CM_mild, CM_uninvolved vs CM_severe, CM_mild vs CM_severe).

**OSAAD SCORE**

The OSAAD score was calculated according to a formula that incorporated the adjusted values for TEWL and CM on uninvolved and mildly and severely involved skin areas multiplied by the respective percentage of BSA, and it was compared with SCORAD values. The values derived from OSAAD show comparable scattering with those derived from SCORAD. The correlation of the OSAAD with the SCORAD scores was significant ($P < .001$) with a Spearman coefficient of $r = 0.63$ (Figure 6).

In the present study we have developed a novel measure of AD severity, the OSAAD score, where “O” stands for
“objective" to distinguish it from other scoring schemes that rely on subjective data. Objective measures are internally consistent, and hence objective data–based scales should minimize problems of interobserver and intraobserver variability. It will be important in future studies to examine the interobserver variability in using the OSAAD. Yet subjective interpretations of disease activity are not without merit; it is often important to know how patients, parents, and clinicians interpret disease severity. In these instances, OSAAD could be used in parallel with a subjective measure such as SCORAD and/or quality-of-life instruments.24–25

The manifestations of AD range on a continuum from severely inflamed plaques to very mild lesions and from the "uninvolved but dry" to truly normal-appearing skin. While the ideal objective system might obtain data from all areas and compute the aggregate score, this is too cumbersome in practice. We determined that lesions judged to be more severe on a particular individual all had TEWL and CM values that were similar, respectively, and without overlap. The same held true for milder lesions and uninvolved skin. Therefore, measuring TEWL or CM on a single site in each of the 3 severity categories greatly simplified the data collection.

The differences in TEWL and CM values from severe, mild, and uninvolved skin between patients were also significant (Figures 4 and 5), but because judgments of lesional severity were relative to a patient’s own disease state, there was some overlap of values. However, because the data obtained are objective, the resulting OSAAD scores lend themselves well to comparisons between patients, as demonstrated by their correlation with SCORAD scores (Figure 6). An important advantage of using an objective measure like TEWL or CM is that interobserver variability in the subjective components, namely, in recognizing lesional severity or in defining lesional boundaries, should be amenable to improvement by feedback training, although this remains to be determined in clinical testing.

In addition to improved validity and reliability, the ideal objective measure of AD severity would have the following features: it should be easy to perform, noninvasive, and inexpensive. Both TEWL and CM measurements can be obtained quickly (eg, in approximately 5 minutes once the initial instrument equilibration has been established) and noninvasively and thus are methods well suited for use in children. The major expense incurred is in the initial investment in the instrumentation. In addition, the method should be sensitive throughout the entire range of disease activity. Transepidermal water loss appears to be sensitive to disease expression throughout the lesional severity range of AD, while CM appears to be particularly sensitive in the milder end of the disease spectrum.11 Finally, the parameter being measured should be directly relevant to the disease process. Even if AD proves to be primarily caused by immune dysregulation, the disease is manifested in the epidermis, and dry skin with an impaired barrier is an integral component of AD disease expression; thus, TEWL and CM are meaningful measures of disease activity.

This point is underscored by consideration of a close relative of AD, asthma, which, while primarily an immune-mediated process, is nonetheless monitored through functional responses of the target organ (ie, volumes and airway resistance in the lung). A recent examination of the ability of certain serum and urinary markers of inflammation to track AD severity concluded that their utility was impaired by their lack of specificity.26 This is likely to be a particular problem in AD, where other atopic conditions may coexist and use the same inflammatory pathways. Hence, a strictly dermatologic measure of disease severity like the OSAAD is particularly attractive.

In the present study, we also developed a novel computer-assisted method for estimating the extent of disease and demonstrated that the method compared well with the commonly used rule of nines (Figures 2 and 3). The primary advantage in using our computer-assisted method is that it removes the subjective component involved in estimating percentage of lesional involvement. There remains a subjective component in the clinical delineation of lesional boundaries, although, as noted above, this is amenable to improvement through feedback training. Errors may also be introduced when the examiner transfers his/her mental image of a patient onto a 2-dimensional template. Future modifications using a computer-generated 3-dimensional model system may minimize this source of error.

Our computer-assisted system could also be applied in assessing extent of disease in other clinical settings (eg, psoriasis, mycosis fungoides, and thermal burns). We envision many applications for the OSAAD in clinical practice, providing clinicians and patients with an objective measure of clinical progress, analogous to use of pulmonary function studies in management of chronic respiratory diseases.

In summary, we have developed an objective method for measuring lesional severity in AD and joined this to a more objective method for determining extent of disease. The score obtained, the OSAAD score, compares well with the SCORAD index. If future testing confirms our prediction of improved interobserver variability, the OSAAD will provide a reliable means for physicians to evaluate their patients’ condition over time and in response to therapeutic interventions.

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