Update on Epidemiology and Clinical Assessment Tools of Cutaneous Lupus Erythematosus and Dermatomyositis

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Abstract Cutaneous Lupus Erythematosus (CLE) and Dermatomyositis (DM) are cutaneous autoimmune diseases that have been among the least systematically studied, due in part to the lack of validated outcome instruments in the past. More recent epidemiologic studies have elucidated the incidence and prevalence of these diseases and their subtypes. In addition, the advent of validated clinical outcome measures, including the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), has led to an objective means of measuring activity and damage of the disease. These outcome measures have established the framework for evaluating responsiveness and therapeutic efficacy in clinical trials as well as longitudinal studies to study disease course.

Keywords Cutaneous Lupus Erythematosus · Systemic Lupus Erythematosus · Epidemiology · CLE Disease Activity and Severity (CLASI) · Drug-Induced CLE · Refractory CLE · Skindex-29 · Short-Form 36 (SF-36) · Physician Global Assessment (PGA) · Visual Analogue Scale (VAS) · Dermatomyositis (DM) · Clinically amyopathic dermatomyositis (CADM) · Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) · The Dermatomyositis Skin Severity Index (DSSI) · The Cutaneous Assessment Tool (CAT)

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Cutaneous Lupus Erythematosus

Incidence/Prevalence

Cutaneous Lupus Erythematosus (CLE) is a heterogeneous group of rare autoimmune skin diseases that includes skin symptoms of Systemic Lupus Erythematosus (SLE) and cutaneous-limited LE. Over 80 % of patients with SLE have cutaneous involvement; skin manifestations may be specific or nonspecific [1•]. Large-scale, population-based epidemiological studies reporting the incidence of isolated CLE have been rare [2•]. Due to the chronic and heterogeneous nature of this disease, it is hard to reliably designate where patients are in their disease process, and thus, incidences may be skewed based on the population and resources available. However, population-based studies on CLE have shown some consistency, even in different populations. The incidence of CLE is estimated to be about the same as that of SLE [2•]. A recent study of 1,088 patients in Sweden reported an incidence of CLE of 4.0/100,000 with a female-to-male ratio of 3:1 and a mean age of onset of 54 years. In this study, a quarter of the patients (24 %) were already diagnosed with SLE at the time of CLE diagnosis, and an additional 18 % developed SLE during the 3-year observation period [1•]. These results are consistent with a prior study from 1965–2005 in the United States that examined the incidence of CLE in Olmsted County, Minnesota, and found an incidence rate of 4.3/100,000 with 19 % of patients progressing to SLE over a 20-year period [2•]. Another recent prospective study of 196 CLE patients at the University of Pennsylvania demonstrated 56.6 % of patients with CLE only and 43.4 % of patients already diagnosed with SLE in addition to CLE at the first visit [3]. In this study, of 85 CLE-only patients who had more than one visit, 13 (15.3 %) went on to meet SLE criteria, with a mean time from CLE diagnosis to SLE of 8.03 years [3]. This study revealed that patients with CLE who

developed SLE did so mostly by meeting the mucocutaneous ACR criteria, and only 38.46 % were considered to have developed new moderate to severe systemic disease, with only two patients (15.38 %) developing renal disease and four patients (30.77 %) developing hematologic abnormalities [3]. Limitations to this study were a short observation period and a small sample size. Of note, in the Minnesota study, patients were enrolled at time of CLE diagnosis and followed for 40 years [2••], while in the recent study patients enrolled after having their CLE for a mean of 6.62 years (based on self-report) and were followed for a mean of 2.81 years [3]. Thus, it is challenging to make a direct comparison of the numbers between these different studies because of discrepancies in follow-up time.

SLE Progression in CLE Subtypes

A recent review reports that the risk of SLE is highest in Acute Cutaneous Lupus Erythematosus (ACLE), followed by Subacute Cutaneous Lupus Erythematosus (SCLE), and lowest in Chronic Cutaneous Lupus Erythematosus (CCLE) [4]. One recent Swedish study demonstrated that the probability of being diagnosed with SLE during the first 3 years after SCLE diagnosis was 24.7 %, and for Discoid Lupus Erythematosus (DLE) the probability was 16.7 % [1••]. Older studies, however, have shown a higher progression of DLE to SLE [4] than in this study [1••], but the discrepancy could be explained by differences in follow-up. In DLE patients, generalized in contrast to localized DLE may be a prognostic sign for SLE development [4–7]. SLE development was demonstrated in 13 % of generalized DLE patients compared with 1 % of localized DLE patients in Barcelona, Spain ($p=0.003$) [6]. In a retrospective study of CLE patients in Thailand, 51.9 % of generalized DLE patients compared to 18.4 % of localized DLE patients developed SLE [7]. Among DLE patients, certain clinical and laboratory indicators, such as arthralgias/arthritis, nail changes, anemia, leukopenia, high erythrocyte sedimentation rate (ESR) and high titers of antinuclear antibody (ANA), have been associated with progression to SLE [6, 8].

Gender in CLE

A study of CLE patients of African descent in France demonstrated a female-to-male ratio of 3.5:1, suggesting sex ratios are similar for black and white populations [9]. Recent studies have suggested possible differences in the expression of CLE between male and female patients with respect to the type of lesions, systemic features, and immunological findings. A study of CLE patients in Spain demonstrated female patients had a significantly higher prevalence of Raynaud's phenomenon, chilblain lupus, arthralgias, and SLE, as well as a higher ESR, higher ANA titers, and decreased levels of C3 [10]. Another study has shown that the proportion of CLE females

diagnosed with SLE up to 1 year after CLE diagnosis was 14 % compared to 6.7 % of CLE males, and this gender difference was even larger after 3 years (20.7 % vs 10.4 %, respectively) [1••]. However, the clinical significance of these differences in terms of worsened quality of life, disease severity, or morbidity/mortality was not studied. A recent longitudinal study at the University of Pennsylvania demonstrated a higher percentage of patients who worsened in disease activity over a period of at least 2 years were male (58 %) compared to those with improved or stable disease course (OR 3.9, CI 1.244 to 12.2784) [11•]. More studies must be done to evaluate gender differences in disease course and prognosis.

Subtypes of CLE

The most common form of CLE is DLE in both the U.S. and in other countries, including Sweden, France and Korea, ranging from 50 to 80 % depending on the population being studied [1••, 9, 12••, 13]. SCLE has been reported to occur in 7–27 % of the CLE population depending on the population studied. One recent cross-sectional database study from the University of Pennsylvania was composed of 18.4 % SCLE patients [12••]. Most of the subjects with SCLE were white, which is consistent with an earlier report that indicated that 85 % of the involved SCLE population is of white origin [12••]. Most of the SCLE patients have papulosquamous rather than annular-polycyclic lesions [6, 12••]. Most patients with ACLE are women, with prior studies showing female to male ratio of 8–9.2:1, compared with female-to-male ratios of 3–4:1 in patients with SCLE and CCLE [12••, 13].

The severity and disease course of the different CLE subtypes have been elucidated further with the advent of clinical outcome measures of disease activity/damage, as we will discuss below.

Drug-Induced Lupus Erythematosus

About one-third of all SCLE cases may be attributed to previous drug exposure [14•]. Previous case reports have recognized that drug-induced SCLE (DI-SCLE) is a clinical entity, immunologically, histopathologically and clinically indistinguishable from idiopathic SCLE. However, a recent study from Italy of SCLE patients from 2001 to 2010 states that drug-induced SCLE may be differentiated by certain distinctive features [15]. The study found that the cutaneous picture was widespread in 82 % of patients with DI-SCLE compared to 6 % of those with idiopathic SCLE ($p=0.0001$), and bullous and erythema multiforme-like lesions were present in 45 % of DI-SCLE compared to only 1 % of those with idiopathic SCLE ($p=0.0001$). In addition, vasculitic lesions and malar rash were observed more often in DI-SCLE (45 % vs 3 %, $p=0.0001$, and 45 % vs 6 %, $p=0.001$, respectively) [15]. The time from drug exposure to onset of SCLE varies widely, ranging from

3 days to 11 years with a median latency of 6 weeks [14•, 16], and a median time to resolution of 4 weeks [16]. The latency seems to differ between drug classes, where longer periods are reported for thiazides and calcium channel blockers and shorter periods for terbinafine and chemotherapeutic drugs [14•]. Although anti-histone antibodies are strongly associated with drug-induced SLE, they are reported positive in only one-third of drug-induced SCLE cases [16].

More than 40 commonly used drugs from various classes have been implicated. Triggering drugs can fall into different categories, including antihypertensives, antifungals, proton pump inhibitors (PPIs), tumor necrosis factor- α (TNF α) inhibitors, and antiepileptics [14•, 16–20]. In a Swedish case-control study, the odds ratio of drug-induced SCLE was determined for terbinafine (OR=52.9), TNF α inhibitors (OR=8.0), antiepileptics (OR=3.4), and PPIs (OR=2.9) [14•].

Refractory CLE

A cross-sectional analysis of 114 patients found 9.6 % patients to be refractory to conventional therapies, meaning that their skin lesions remained active despite aggressive medical treatment with immunosuppressives and/or thalidomide [12••]. Patients with generalized DLE appear to be more refractory to current therapies than those with localized DLE or SCLE [12••]. In addition, current smokers are more likely to be refractory to all treatments [12••]. Prior studies have suggested that smoking may interfere with the efficacy of antimalarial agents in CLE, but more recent studies have not confirmed this [21, 22]. However, given the high association of smoking with cutaneous lupus and the fact that a subset of smokers are predominant in the group that is refractory to conventional therapies, smoking cessation in CLE is recommended [12••, 23, 24•]. A recent prospective longitudinal study at the University of Pennsylvania of 218 patients with CLE or SLE with cutaneous involvement showed that current smokers had worse disease activity and worse quality of life [24•]. Of note, this study demonstrated that individuals in the CLE-only group had a higher percentage of current smokers than did the SLE with cutaneous involvement group, suggesting greater association of smoking with CLE than even SLE.

Cancer Risk in CLE patients

Patients with CLE have been shown to have an increased risk of certain types of cancers. A Swedish study of 3,663 CLE patients found an overall increased cancer risk of 1.8, with a fourfold increased risk for buccal cancer, lymphoma, respiratory cancer, and nonmelanoma skin cancer [25••]. This increased risk remained even when excluding those patients with concomitant SLE. Case studies and a recent review have also suggested an increased risk of squamous cell carcinoma

in DLE patients, with a predilection for the lips [26–30]. In addition, case studies have suggested an association between SCLE and cancers, including hepatocellular carcinoma [31], lung cancer [32, 33], and breast cancer [33, 34].

Clinical Assessment Tools and Outcome Measures:

The CLASI

Until recently, there had been no adequate validated disease severity measures available specifically for CLE to allow better characterization of disease severity, assessment of disease course, and conduction of large controlled trials. The CLE Disease Area and Severity Index (CLASI) was designed in 2005 by Dr. Victoria P. Werth, an author of this review article, to convert subjective observations into objective data by means of a scoring system that measures activity and damage of the disease, taking into account the amount of erythema, scale/hypertrophy, mucus membrane involvement, hair loss, dyspigmentation, scarring and alopecia [35]. A conscious decision was made not to include surface area in the assessment because of the difficulty of assessing surface area accurately when evaluating small, scattered lesions [36–38]. Indeed, while there are many potential elements to measure, one must choose just a few that can be well validated as demonstrating responsiveness in the context of prospective studies.

The CLASI has been shown to have good content validity, inter-rater validity, and intra-rater validity [39]. The CLASI score can demonstrate responsiveness in all subsets of CLE, including localized and generalized DLE as well as SCLE [40–43]. In addition, this clinical tool has been shown to have practical applicability for CLE by dermatologists and rheumatologists [39, 44] as well as for SLE. With the design and validation of the CLASI complete, more recent work has focused on practical applications of the CLASI.

A recent study showed that the CLASI may also be used to classify patients into groups according to disease severity. Mild, moderate, and severe disease corresponded with CLASI activity scores of 0 to 9, 10 to 20, and 21 to 70, respectively [45••]. This classification of disease severity with CLASI has been used to better characterize the epidemiology of this disease, with a study demonstrating that 76.5 % of patients with CLE and concomitant SLE had none-to-mild systemic disease, and 23.5 % had moderate to severe disease [3]. Of the CLE and SLE patients, 13.4 % went on to have severe systemic symptoms during the study [3]. In contrast, none of the 72 CLE-only patients developed new moderate to severe systemic disease [3]. A greater percentage of patients with CLE who converted to SLE during the study developed moderate to severe systemic symptoms when compared to patients with longstanding SLE or CLE alone, suggesting a need for continued monitoring of CLE patients [3].

The CLASI has also been found to be sensitive to clinical improvement, with clinically significant improvement defined as a 4-point or 20 % decrease in the CLASI activity score [45•]. A recent prospective longitudinal cohort study using this CLASI definition evaluated therapeutic response in patients using antimalarials [46•]. These studies laid the foundation for studies in both CLE and lupus-specific cutaneous lesions in SLE that use CLASI as a primary endpoint in demonstrating efficacy of a drug [41–43, 46•, 47–53], with 14 clinical trials currently underway using CLASI [54]. The CLASI has been used in clinical trials for hydroxychloroquine [47, 48], thalidomide [52], pulsed dye laser [41], and topical tacrolimus and clobetasol [53]. Included are studies from different countries, including Japan, Thailand, Germany and India, demonstrating the wide geographic applicability of this clinical outcome measure.

The CLASI activity score is currently being evaluated for its utility in assessment of disease progression. A multicenter longitudinal study including 96 patients from the CLE database was conducted at the University of Pennsylvania evaluating CLE disease course over a period of at least two years [11•]. The study evaluated disease course using three variables, including average disease activity (area under the curve/year), overall progression (slope, or change in CLASI over time), and variability (flares/year) with flares defined as an increase in CLASI of 4 points or 20 %. In this study, a majority of patients had mild disease activity [CLASI 0–9] (74 %) and stable disease course (67 %), defined by slope <2, over an average of 3.3 years. Those with mild disease activity tended to have stable disease, fewer flares per year, and better quality of life on average than those with moderate–severe disease [11•].

Controversially, a study from Germany evaluating the use of CLASI for different subtypes of CLE suggested that the CLASI does not give an accurate assessment of the different disease parameters in each of the CLE subtypes [55, 56]. The study demonstrated that CLASI activity scores accurately assessed high disease activity in ACLE and CCLE and high damage scores in CCLE compared to SCLE and LET. However, it suggests that the CLASI excludes some characteristic signs of CLE, specifically edema for LET [56]. However, our experience has shown LET makes up only a small percentage of CLE patients and that they tend to have erythematous lesions and to respond to antimalarials [4]. The goal of CLASI was to have a standard, unified measure of disease rather than a separate measure for each CLE subtype. In addition, with the prospect of other specialties including rheumatology using CLASI, especially in SLE clinical trials, accurate measurement of induration and edema may be difficult.

QOL in CLE

There have been few studies until recently about quality of life (QOL) in patients with CLE. A study from the University of

Pennsylvania using QOL surveys including the Skindex-29 and SF-36 demonstrated severely impaired QOL in all subscales in CLE patients, particularly from an emotional perspective [57•]. Patients with CLE were found to have worse QOL than those with other common dermatologic conditions, like acne, non-melanoma skin cancer, and alopecia. In terms of mental and physical health, patients with CLE had worse or similar scores in comparison to systemic disease like hypertension, type 2 diabetes mellitus, recent myocardial infarction, and congestive heart failure [57•]. A recent multi-center cross-sectional study compared the CLE populations from University of Texas Southwestern and the University of Pennsylvania in terms of QOL and found similar results. There was increased impairment in Skindex Functioning and Lupus-specific sub-domains, as well as SF-36 physical functioning and general health subscales at the UT Southwestern relative to the University of Pennsylvania [58].

Factors associated with poor QOL include female gender, generalized disease, increased severity of disease, distribution of lesions, younger age, low income, low education, and presence of SLE [57•, 58]. In terms of distribution, facial lesions and inflammatory alopecia were correlated with worse QOL. Another recent study at the University of Pennsylvania on the effects of photosensitivity on CLE demonstrated participants with higher photosensitivity had greater impairments in QOL in terms of functioning, symptoms, and emotions than did participants with lower photosensitivity [59•]. Of note, psychiatric impairment and high prevalence of depression and anxiety in this dermatologic population warrants screening for psychiatric distress and suicidal ideation [57•].

QOL is worse in those with increased disease severity, as classified by CLASI activity score [45•]. Studies have demonstrated a linear correlation between CLASI activity score and Skindex 29+3 subdomain scores with Spearman $r=0.22$ for Skindex emotion, $r=0.35$ for Skindex symptoms, and $r=0.32$ for Skindex function [58]. These studies imply that therapeutic goals should encompass improving both skin disease activity and QOL. In fact, a recent prospective study of 39 patients demonstrated that therapeutic response in disease activity was accompanied by an improvement in skin-specific quality of life measures [60].

Limitations of Clinical Outcome Measures in Mild Disease

Recently, a study has demonstrated the limited use of clinical outcome measures and QOL measures in those patients with mild disease activity. The study demonstrated a weak correlation between the currently used outcome measures in CLE, including CLASI, PGA, VAS, and Skindex scores, when measuring changes in disease at lower ends of disease activity [61]. This may be due to a “floor effect” in which data cannot take on a value lower than a particular number,

called the “floor.” Thus, in patients with mild disease activity at baseline, there is less room for improvement in all clinical outcome measures. This has been shown to be a property of outcome measures for many different cutaneous and systemic diseases as well, including Rheumatologic pain scores [62, 63] and Psoriasis (PASI) [64, 65].

Interestingly, recent studies have demonstrated CLASI responsiveness in patients with mild skin disease using the definition of 4 points or 20 % decrease in CLASI activity. In a Japanese study, 23 of 27 patients (85 %) were categorized as responders according to the definition of improvement in CLASI, and a majority of these patients (52 %) had baseline mild disease (CLASI <9) [48]. The study demonstrated an improvement rate of 22.6 % in those with CLASI <9 at baseline, suggesting that CLASI may be sensitive to improvement [47]. A separate study demonstrated improvement in CLE patients with SLE with median CLASI activity score changing from 8 (2–22) to 4 (2–10) [47]. A prospective longitudinal cohort study at the University of Pennsylvania showed that, of 11 patients initiated on hydroxychloroquine, six patients (55 %) were responders with a decrease in median activity scores from 8 to 3 [46•]. This study suggests that patients with mild CLE disease activity may demonstrate improvement in disease based on a decrease in CLASI score that is not detectable by other external outcome measures.

Thus, clinical and quality of life outcome measures like the CLASI and Skindex-29 have been recently established for their validity, and more recent studies have established its clinically meaningful use in clinical trials. However, we must keep in mind certain limitations in interpretation of outcome measures when ascertaining clinically significant improvement in the CLE and SLE trials, especially at the mild end of disease activity. In addition to responsiveness, CLASI may be used in further longitudinal studies to study disease activity over time and clinical parameters that define disease course and prognosis.

Dermatomyositis

Incidence/Prevalence

Dermatomyositis (DM) is included in a group of rare immune-mediated diseases called idiopathic inflammatory myopathies characterized by inflammatory skin lesions and weakness of skeletal muscle. The current diagnostic criteria for DM excludes patients without muscle involvement, yet distinct subtypes of DM including amyopathic DM (ADM), hypomyopathic DM (HDM), and drug-induced DM (DI-DM) may only have cutaneous manifestations with little or no muscle involvement. A population study from Olmsted, Minnesota demonstrated an overall age- and sex-adjusted incidence of

DM including all subtypes of 9.63 per million (95 % CI, 6.09–13.17); age-adjusted incidence was 13.98 per million (95 % CI, 8.08–19.89) for females and 4.68 per million (95 % CI, 1.15–8.20) for males [66]. A population study in Taiwan demonstrated that overall annual incidence of DM was 7.1 (95 % CI 6.6–7.6) cases per million population. The incidence of both DM and PM increased with age and reached a peak at age 50–59 years [67].

Clinically Amyopathic DM (CADM)

Prior analyses suggest that the CADM subphenotype is more common than has been previously thought, with 21 % of DM patients overall having CADM, and with such patients comprising a relatively high proportion of DM patients followed by dermatologists [66]. A study at the University of Pennsylvania demonstrated a significant difference in DM presentation in dermatology and rheumatology departments. In a 3-year study period of DM patients seen in the rheumatology department, 89 % had classical DM (CDM), 6 % had HDM, and 4 % had ADM [68•]. This differed significantly from dermatology department, which saw 33 % CDM, 28 % HDM, and 40 % ADM patients [68•]. In another study on QOL with DM at the dermatology department of University of Pennsylvania, 28 of 42 (66.7 %) enrolled patients had ADM [69•]. Thus, ADM may be an entity within the spectrum of DM that is under-recognized in fields outside of dermatology, largely because the current DM criteria prevent definitive diagnosis of ADM and because these patients are more frequently seen in dermatology [68•]. Limitations of these studies include a population of small size and from a tertiary Dermatology center that may not be representative of the general population. These studies suggest a need for revision of the current definition of DM.

ADM patients appear to be at risk of developing the same potentially fatal disease associations and complications for which CDM patients are at risk. A systematic review demonstrated that 36 of 291 (13 %) of identified CADM patients developed interstitial lung disease (ILD). In addition, an associated internal malignancy was found in 41 of 291 (14 %) of the identified CADM cases [70]. Another study from Penn showed there was no difference in the rates of ILD between CDM and ADM ($P=.30$) in patients seen both by the rheumatology department and those seen by the dermatology department [68•].

Systemic features

ILD is the most common internal organ manifestation that affects the prognosis of DM patients. In addition to PFTs, the development and routine use of HRCT in those with abnormal PFTs enables early detection of interstitial changes in the lung. As a result, the prevalence of ILD has increased over the last few years [71, 72]. In recent cohort studies, the

prevalence of ILD in myositis has reached close to 50 %, ranging from 21 % to 78 % [70]. Some studies suggest that ILD can lead to death from chronic respiratory insufficiency in 30–66 % of cases [71].

DM patients have a higher risk of malignancy, including cancers of the ovary, lung, pancreas, stomach, breast, and nasopharynx, with overall standardized incidence ratio (SIR) ranging from 2.17 to 14.2 in recent studies [73–77]. The types of malignancies vary with gender, ethnicity, and geographic location. Recently, the South Australian (SA) myositis database registered all patients with biopsy-proven inflammatory myositis from 1980–2009 and found a trend toward overall increased risk for malignancy in DM (SIR 2.17), with lung cancer the most common malignancy (16.3 %) followed by prostate cancer (14 %), and then colon and hematological malignancies [73]. In contrast, nasopharyngeal carcinomas were by far the most common malignancy in Chinese countries, with one study showing an SIR of 140 [74, 77, 78]. Gastric cancer was highest in a Japanese population [75], lung cancer was highest in a Korean population [76], and ovarian cancer the most frequently reported malignancy in females with DM [73]. Studies have shown most cancers were detected in the first year of observation, with 72.1 % of all malignancies occurring within 5 years of myositis diagnosis [73, 74]. The risk of cancer decreases with observation time yet remains elevated compared with the general population in both study groups after 5 years of follow-up [74].

Clinical Assessment Tools

The cutaneous manifestations of DM are among the least systemically studied aspects of the disease, in part due to the lack of validated tools. Several outcome instruments that have been developed to systematically measure DM include the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), the Dermatomyositis Skin Severity Index (DSSI) and the Cutaneous Assessment Tool (CAT) skin indices [79]. The CDASI was developed by Dr. Victoria Werth, one of the co-authors. Briefly, it has four activity (erythema, scale, excoriation, ulceration) and two damage (poikiloderma, calcinosis) measures for 15 anatomical locations, with scores from 0 to 148. The CDASI total score captures overall disease state, while the activity score is expected to reflect the current inflammatory state of disease. It describes the extent of disease in terms of the severity of involvement, but does not record the percentage of body surface area or the number of lesions. DSSI assesses activity based on body surface area and severity (redness, induration, and scale) on a scale of 0 to 72 [79]. CAT is an eight-page instrument that uses 21 activity and damage items for a range of 0 to 175 for activity and 0 to 33 for damage. The modified CAT is a one-page instrument that allows for recording specific features of activity and damage as present or not [79].

One study comparing the reliability and validity of the CDASI, CAT, and DSSI demonstrated that the CDASI displayed higher inter- and intra-rater reliability relative to CAT [79]. CDASI and DSSI demonstrated near perfect inter- and intra-rater reliability based on interclass correlation. All scales correlated better with physician than patient global skin measures [79]. A more recent study evaluating the CDASI and CAT-binary method (CAT-BM), a modified version of the CAT, found the CDASI to have a higher inter- and intra-rater reliability and to demonstrate better responsiveness than the CAT-BM [80•]. The nature of the instruments themselves may lend to the CDASI having higher inter-rater reliability. For example, a larger number of items that contributes to the overall activity score in the CDASI may allow one disagreement among physicians over an item to have less impact on the overall reliability of the outcome measure than the CAT-BM. In addition, the CDASI specifically goes through all anatomical parts and allows for a gradation of activity in each part, allowing for higher reliability and responsiveness [80•]. The small patient population may limit the external validity of the findings observed in these two studies.

Interestingly, inter-rater reliability of damage measurements is lower in terms of CDASI, CAT-BM, and PGA, suggesting that physicians have difficulty agreeing with one another in assessment of damage [80•]. This may be that the definition of certain terms like poikiloderma varies among physicians [79, 80•], which may need to be more clearly defined.

The CDASI was found to be the favored outcome instrument compared to the CAT and DSSI for clinical appropriateness among physicians in terms of ease of use [79]. Another important factor in the practicability is its completion time. The mean completion time for the CDASI was not significantly higher than the CAT-BM, at 4.76 and 3.19 minutes, respectively [80•]. The psychometric properties of these outcome measures have been reviewed by Rider et al. [81] and are included in Table 1.

QOL measures

Measuring not only disease activity and damage, but also QOL, is important in inflammatory skin diseases like DM. Prior to this past year, only one published report had been done on the impact of DM on QOL. This study had used skin-specific QOL measures, including Skindex and Dermatology Life Quality Index (DLQI), rather than global health QOL measures and found more severe QOL impairment in DM than other skin conditions including psoriasis and atopic dermatitis [82]. The DLQI is a 10-question measure that captures skin-related QOL as an overall score, but does not have the ability to measure subscales, such as emotion [81]. The Skindex 29+3 is a 29-item QOL measure that assesses three subscores for emotion, symptoms, and function [81].

Table 1 Psychometric Properties of DM Outcome Measures

Outcome measure	Reliability evidence	Validity evidence	Ability to detect change	Cautions
CDASI	Good to excellent inter- and intra-rater reliability. Better inter- and intra-rater reliability than CAT and CAT-BM	Content validity adequate by participating dermatologists. Moderate to excellent construct validity	Responsiveness strong in a group of patients with recognized change	Need appropriate training. Does not measure every aspect of DM disease, but focuses on elements in the skin likely to be responsive in the context of therapeutic interventions. Not validated in other Myositis subgroups
CAT	Total activity score has good internal consistency, test–retest and inter-rater reliability. Total damage score has fair to good internal consistency, test–retest and inter-rater reliability. Reliability of individual activity and damage items are more variable	Strong evidence for construct validity in juvenile IIM and more limited in adult DM. Content validity not assessed	Responsiveness moderate to strong in children with juvenile DM with recognized change	Requires training to Administer. Some concerns about reliability of some items. Not validated in other myositis subgroups
DSSI	Good intra-rater reliability. Moderate to good Inter-rater reliability. Good to excellent test–retest stability	Content validity was evaluated by a panel of experts. Moderate but limited construct validity	N/A	BSA may not be reliable or responsive to change. Does not assess skin damage. Not validated in other myositis subgroups
DLQI	Not assessed in Myositis	Moderate to low construct validity in DM and amyopathic DM. Content and criterion validity not established in myositis	Not assessed in myositis	Focus on disability, response distribution has ceiling effects, and dimensionality and item bias are problems. Not yet studied in other myositis subgroups

Table adapted from Rider et al. [81]

A recent study based both on skin-specific QOL instruments, including Skindex and DLQI, and on global health QOL instruments, including the Short Form-36 (SF-36) and Health Assessment Questionnaire-Disability Index (HAQDI), demonstrated that patients with DM had a significantly worse QOL in all subscores except bodily pain and in overall mood than patients when compared to 12 other dermatologic and seven nondermatologic conditions [68•]. A substantial percentage of DM patients had psychiatric disease, especially depression and anxiety, ranging from approximately 20 to 40 % of patients with DM, compared with 11 to 30 % of healthy persons, respectively [68•]. Another study on QOL in CLE demonstrated that CLE and DM patients both have similarly negative impacts on QOL, worse than other common skin diseases like non-melanoma skin cancer, acne, and alopecia as well as nondermatologic diseases like hypertension, type 2 diabetes, congestive heart failure, and recent myocardial infarction (MI) [57•]. According to the CDASI, increased cutaneous severity is correlated with a poorer QOL [68•]. This demonstrates the importance of recognizing and treating psychiatric illnesses in this patient population.

Prior studies have shown that pruritus, an under-recognized symptom of DM, is a large component of the impact on QOL [82]. DM patients were found to have a significantly higher median pruritus score than CLE [68•].

The best QOL measure to use for DM has not yet been established. DLQI significantly correlates with Skindex 29+3

(Skindex-29 symptoms $r=0.6323$, Skindex-29 emotion $r=0.6744$, Skindex-29 function $r=0.8598$; all p values <0.0001), while it is simple and shorter, which may make it a more clinically practical skin-specific index. However, DLQI correlates better with Skindex-29 function subscore than with Skindex-29 emotion subscore, while emotion is usually more significantly affected by DM, which may make its use less reliable in DM. The SF-36 has been shown to correlate more with the Skindex-29 emotional subscore ($r=0.6336$, $p=0.02$) and capture more mild disease than the HAQ-QI, suggesting it may be a better global QOL assessment [68•]. In conclusion, CDASI appears to be the best validated measure of DM severity and responsiveness while the best QOL clinical measure has yet to be determined.

Conclusion

Cutaneous Lupus Erythematosus and Dermatomyositis are among the least systematically studied of the autoimmune diseases. However, the establishment of multicenter databases have allowed for collection of patient data and epidemiology studies to be conducted. New standardized, validated cutaneous outcome measures including the CLASI and CDASI have been used in clinical trials to find better treatments for these diseases. In addition, they have been used to correlate worse disease activity with impaired quality of life to determine the clinical

impact of these diseases. More studies are currently underway to expand the clinical applicability of these outcome measures.

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- Of importance
- Of major importance

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