Reliability of scar assessments performed with an integrated skin testing device – The DermaLab Combo®

T.U. Gankande a,*, J.M. Duke a, P.L. Danielsen a, b, H.M. Dejong a, c, F.M. Wood a, c, H.J. Wallace a

a Burn Injury Research Unit, School of Surgery, The University of Western Australia, Australia
b Department of Dermatology, Bispebjerg University Hospital, Denmark
c Burn Outcomes Centre, Royal Perth Hospital, Australia

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A B S T R A C T

Background: The DermaLab Combo® is a device with potential to make objective measurements of key scar components – pigmentation, vascularity, pliability and thickness. This study assessed the inter-rater and test–retest reliability of these measurements.

Method: Three raters performed scar assessments on thirty patients with burn scars using the DermaLab Combo®. Measurements of pigmentation, vascularity, pliability and thickness were made and intra-class correlation coefficients (ICC) were derived for inter-rater and test–retest reliability.

Results: Inter-rater reliability was found to be “excellent” in the ‘best’ and ‘worst’ areas of the index scar and normal skin for pigmentation (ICC: 0.94–0.98) and thickness (ICC: 0.86–0.96). Test–retest reliability was also “excellent” for pigmentation (ICC: 0.87–0.89) and thickness (ICC: 0.92–0.97) in all areas. Vascularity showed “good” to “excellent” inter-rater reliability (ICC: 0.66–0.84) in all areas however test–retest reliability was “low” (ICC: 0.29–0.42). Test–retest reliability was “excellent” for pliability (ICC: 0.76–0.91). Technical limitations were encountered making measurements in some scars for thickness, and in particular, pliability.

Conclusion: The DermaLab Combo® measured pigmentation, thickness and pliability with “excellent” reliability. If future studies provide protocols to improve test–retest reliability of vascularity measurements and obtain pliability measurements more successfully, the DermaLab Combo® will be valuable device for scar assessment.

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1. Introduction

Scarring is a consequence of burn with the potential for long-term physical and psychological impacts on patients [1]. Systematic scar assessment enables clinicians to monitor scar progression and researchers to evaluate interventions and factors influencing scar outcome.

Current scar assessment methods used in clinical practice are subjective and may have low inter-rater reliability [2]. The
inter-rater reliability of the modified Vancouver Scar Scale (mVSS), for example, varies depending on which scar component is being measured [3]. Objective scar measurements are likely to provide more reliable data for clinical and research purposes, enabling more robust comparisons within and between patients [4–6].

Scar assessment includes measurement of four key components – pigmentation, vascularity, pliability and height (thickness) of the scar. Many individual devices have been tested to obtain objective measurements of these components, but none have been broadly adopted within a clinical setting. The most likely reason is that most devices only measure one individual component [7–9]. For example, in Oliveira and others [9], objective measurements for the four scar components were obtained using four separate devices.

Scar measuring devices can be broadly categorised into three groups, assessing colour (pigmentation and vascularity), pliability (elasticity) and height (thickness) [8]. To date no device capable of measuring all four scar components has been tested for reliability [7,8]. The DermaLab Combo® (Cortex Technologies, Denmark) [10] is a commercially available skin testing device that has the potential capability to measure all four scar assessment components. It was primarily designed for skin testing in the cosmetic field and does not claim to be a medical device. However, it is a high-specification device based on proven technologies (see Section 2).

This study was designed to test the reliability (inter-rater reliability and test–retest reliability) of the DermaLab Combo® device to measure the four components of the mVSS in burn scars: pigmentation, vascularity, pliability and height (thickness) [11]. The study was conducted at Royal Perth Hospital (RPH) burns outpatient clinic, Western Australia.

### 2. Methods

#### 2.1. Subjects

Thirty adult patients who attended the RPH burns outpatient clinic for routine follow-up assessments and were able to attend a follow-up appointment within 10 days of the first assessment were recruited consecutively. Participation was voluntary. Subjects were included in the study if they met the following inclusion criteria: at least 18 years of age; able to provide informed written consent; had a healed burn scar with an area of at least 3 cm × 6 cm; the scar was a minimum of three months post burn; and there was a contralateral, normal skin area of at least 3 cm × 3 cm with the same degree of sun exposure.

Subjects were excluded from the study if they could not provide informed written consent. If the subject wore a pressure garment, the rater responsible for recruiting the subject made a subjective assessment on the level of sun exposure of the contralateral normal skin and asked supplementary questions to confirm a similar level of sun exposure on both scar and contralateral normal skin areas.

All subjects were provided with a patient information sheet and a verbal explanation of the study after which written informed consent was sought.

#### 2.2. Study design

The study was a single-arm observational study using three independent raters. For the inter-rater reliability study, all three raters made measurements of the scar and contralateral normal skin (control) areas for each parameter on the same day. For the test–retest reliability study, the same three raters made the same measurements on a second occasion within 10 days of the initial baseline assessment. The study was approved by Royal Perth Hospital (RPH) and University of Western Australia (UWA) Human Research Ethics Committees.

#### 2.3. Raters

The three raters had comprehensive training in the use of the DermaLab Combo® under the supervision of an experienced user of the DermaLab Combo® (HW). Each training session was 3 h in duration and the raters undertook three sessions of training over a three week period. The training session consisted of the raters familiarising themselves with the use of the probes and the study protocol to measure the four components of scar assessment on each other. Subsequent to this training, each rater used the DermaLab Combo® device on patients with burn scars to conduct at least 10 independent assessments of scars using the study protocol prior to the start of the study. In this paper the raters are referred to as raters R1, R2 and R3.

#### 2.4. Materials

The DermaLab Combo® was used to assess melanin (pigmentation), erythema (vascularity), elasticity (pliability) and thickness (height) of post-burn scars. The DermaLab Combo® consists of a main unit with screen and multiple separate probes. The three probes used in this study had separate channel connectors and were each attached to the main unit with separate tubes (Fig. 1).

2.4.1. The colour probe

The colour measurement of the DermaLab Combo® is based on the principle of narrow-band reflectance spectrophotometry (550 nm ± 30 nm and 660 nm ± 60 nm for haemoglobin [erythema or vascularity] and melanin [pigmentation] respectively). The colour probe has an optical focussing on 7 mm diameter target area with a clear front for accurate positioning and is illuminated by two angled white light emitting diode (LED) lights. The probe displays four readings (three individual measurements with their average) separately for erythema (vascularity) and melanin (pigmentation) using Commission Internationale de l’Eclairage (CIE) – luminance (L), red-green axis (a) and blue-yellow axis (b) [CIELab] values.

2.4.2. The elasticity probe

The elasticity measurement of the DermaLab Combo® is based on the principle of vertical suction applied on the surface of scar. The probe has a measuring aperture of 10 mm diameter and adheres to the skin by a double adhesive sticker. Elasticity measurements are expressed in terms of Young’s modulus in megaPascals (MPa). For the purpose of this paper, elasticity measurements will be referred to as ‘pliability’.
2.4.3. The skin thickness probe
The DermaLab Combo® skin thickness measurement probe is based on the principle of high frequency ultrasound (20 MHz) and has a resolution of 60 μm × 200 μm with a penetration capacity of 3.4 mm with a fully adjustable gain settling (±10 dB). The probe has a rotating transducer, scan length 17 mm, footprint 11 mm, and the capacity to display actual and stored measurements side-by-side.

In contrast to the VSS height measurement that measures scar height above the pre-injury ‘baseline’ surface of the skin, this probe measures the thickness of the whole scar including the scar above and below the baseline surface of the skin. For the purpose of this paper, scar height measurements will be referred to as ‘thickness’.

2.5. Procedure

2.5.1. Inter-rater reliability
All pressure garments and bandages were removed at least 15 min before the start of the assessment to reduce any blanching effect that may influence measurements. All assessments were carried out in the same room where the subjects were exposed to similar environmental conditions at the time of assessment. All assessments were carried out with the subjects in a sitting position. The anatomical body part containing the scar was placed in a nondependent position; if the scar was on a leg – both legs were elevated to rest on another chair, if the scar was on an arm – both arms were rested parallel to each other on a table.

One index scar of at least 6 cm × 3 cm in size was identified per eligible participant. The index scar was defined as the scar with the largest percentage of body surface area on a body site (head/neck; chest; back; left arm; right arm; left leg; right leg) with a contralateral anatomically matched normal skin area available (minimum surface area 3 cm × 3 cm). Within the index scar, one nominated rater selected a 3 cm × 3 cm scar area deemed to be the ‘best’ area of the scar (lowest mVSS score) and a 3 cm × 3 cm area of the same scar deemed to be the ‘worst’ area of the scar (highest mVSS score) using the mVSS [11]. These two areas were marked by this rater with a semi-permanent skin marker and photographed. A 3 cm × 3 cm contralateral anatomically matched normal skin area was also identified and marked.

All three raters assessed these three marked areas using the DermaLab Combo®. Each scar component was assessed at three sites within the identified 3 cm × 3 cm scar areas (see Fig. 2). These individual measurements as well as the average of the three measurements were recorded and used in the analysis. The three independent raters performed the scar assessments on each subject on the same day. In the case of pliability measurement, suction applied by the DermaLab Combo® elasticity probe alters the biomechanical properties of the skin, hence repeat measurements on the same location are not recommended by the manufacturer at less than 1 h intervals. Due to this extended wash-out period the elasticity probe was used only by one rater (R1) and pliability measurements were excluded from the inter-rater reliability analysis.

2.5.2. Test–retest reliability
All study subjects were asked to attend a repeat assessment within 10 days of the initial baseline assessment. Two or three
of the original raters performed the repeat DermaLab Combo® scar assessment on each subject. The repeat assessment was carried out under the same conditions as the initial assessment. Subjects were asked about anything that may have affected their scar between the time of the initial baseline assessment and the repeat assessment (for example, use of different skin moisturiser, a new therapeutic measure such as a different pressure garment or excessive sun exposure). If the three marked scar areas were not visible they were re-marked with the semi-permanent skin marker with the help of the baseline photographs.

As for the initial baseline assessment, each scar parameter was assessed on three sites within each marked area (Fig. 2) and the individual measurements as well as the average of the three measurements were recorded. The raters performed the repeat scar assessments on each participant on the same day. Due to the extended wash-out period (1 h) with the elasticity probe, only rater 1 conducted the repeat pliability assessment.

### 3. Data collection and analysis

Data were collected over a 6-month period, from July 2012 to January 2013. Each rater was blinded to the results of the other raters and independently recorded results in a separate Scar Assessment Form (Appendix I). Each rater recorded four measurements on the data collection sheet for each parameter in the three 3 cm × 3 cm areas: one measurement for each site and the average of the three measurements. All forms were filed separately until the data collection was complete.

Throughout the paper we refer to the 3 cm × 3 cm squares marking the ‘best’ and ‘worst’ parts of the index scar and contralateral normal skin as “areas” and the probe placement locations for measurements within the areas as “sites”.

For the purpose of the reliability analyses the measurements for each site were considered as independent units for analysis. Analyses were also conducted using the average measurement of the three sites in the three 3 cm × 3 cm areas for inter-rater reliability. All data analyses were performed using SPSS version XX (Chicago, Inc) and Stata V12 statistical software (StataCorp LP, College Station, TX).

#### 3.1. Inter-rater reliability

Inter-rater reliability is the extent of agreement among raters scoring the same subjects under the same conditions [12]. The inter-rater reliability of individual measurements and the average measurement for each component were calculated for each rater pair (R1 vs. R2, R1 vs. R3, and R2 vs. R3) for the ‘best’ and ‘worst’ area of each index scar and the contralateral normal skin area on each subject.

Measurements obtained with the DermaLab Combo® device were continuous variables. The Bland Altman (BA) method and plots of the difference in measurements vs. average of scores, for each rater pair were generated with mean difference and 95% limits of agreement. BA plots and results were examined for any patterns of variation to change with the magnitude of the measurement. In the absence of such patterns inter-rater reliability was established using two-way random effects ANOVA to derive the intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) for all rater combinations. These methods are fully described in Gankande and others [3]. ICC were interpreted using the Rosner interpretation (0-0.40: marginal agreement; >0.40-0.75: good agreement; >0.75: excellent agreement) [13].

#### 3.2. Test–retest reliability

Test–retest reliability refers to the reliability or the consistency of a measurement over time [14]. Repeat scar assessments were done within 10 days of the initial baseline assessment, during which time no significant change in scar was
anticipated. ICC were used as the measure of test-retest reliability [15,16].

Test-retest reliability of individual site measurements for each component was calculated for the ‘best’ and ‘worst’ area of each index scar and the contralateral normal skin area on each subject.

As for inter-rater reliability, the BA method was applied and test-retest reliability was assessed using two-way random effects ANOVA to derive ICC with 95% confidence intervals. ICC were interpreted using the Rosner interpretation [13].

4. Results

4.1. Subjects and descriptive statistics

Of the 30 subjects, 12 (40%) were female and 18 (60%) were male. The median age of study subjects was 43 years (interquartile range [IQR]: 25.0–54.3 years; minimum (min)–maximum (max): 18–81 years). The median time since injury among subjects was 4.5 months (IQR: 3–6 months; min–max: 3–648 months). The locations of the assessed scars were: arm (n = 12), leg (n = 13), chest (n = 3), abdomen (n = 1) and back (n = 1). Twenty-seven out of the 30 subjects had a mVSS assessment performed. The median mVSS score in the ‘best’ area of scar was 2 (IQR: 1–2; min–max: 0–7) and 3 (IQR: 2–5; min–max: 1–10) in the ‘worst’ area of scar. The distributions of the scar component measurements at baseline for pigmentation, vascularity, thickness and pliability are described in Table 1.

4.2. Inter-rater reliability

ICC and 95% CI for all rater pairs (R1 vs. R2, R1 vs. R3 and R2 vs. R3) for pigmentation, vascularity and thickness measurements are presented for individual measurements (Table 2) and average measurements (Table 3).

### Table 1 – Range of scar measurements at baseline for pigmentation, vascularity, thickness and pliability measured with the DermaLab Combo® for the 30 study subjects.

<table>
<thead>
<tr>
<th>Component</th>
<th>Minimum measurement</th>
<th>Maximum measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>‘Best’ area of scar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>26.00</td>
<td>93.00</td>
</tr>
<tr>
<td>Vascularity</td>
<td>10.00</td>
<td>45.00</td>
</tr>
<tr>
<td>Thickness</td>
<td>1001.00</td>
<td>2109.00</td>
</tr>
<tr>
<td>Pliability</td>
<td>177.00</td>
<td>3240.00</td>
</tr>
<tr>
<td><strong>‘Worst’ area of scar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>28.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Vascularity</td>
<td>7.00</td>
<td>51.00</td>
</tr>
<tr>
<td>Thickness</td>
<td>1132.0</td>
<td>2433.00</td>
</tr>
<tr>
<td>Pliability</td>
<td>264.00</td>
<td>9438.00</td>
</tr>
<tr>
<td><strong>Normal skin area</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>26.00</td>
<td>66.00</td>
</tr>
<tr>
<td>Vascularity</td>
<td>9.00</td>
<td>43.00</td>
</tr>
<tr>
<td>Thickness</td>
<td>342.00</td>
<td>1870.00</td>
</tr>
<tr>
<td>Pliability</td>
<td>246.00</td>
<td>4704.00</td>
</tr>
</tbody>
</table>

Pigmentation had “excellent” inter-rater reliability in all the tested areas for all rater pairs, with ICC of 0.98, 0.94, 0.95 in the ‘best’ area of the scar, 0.96, 0.95, 0.97 in the ‘worst’ area of the scar and 0.95, 0.92, 0.91 in the contralateral normal skin area. When the average measurements for pigmentation were used in the analysis the inter-rater reliability was marginally greater among all rater combinations.

Vascularity showed “good” to “excellent” inter-rater reliability in all three areas measured. ICC of 0.74, 0.66 and 0.78 in the ‘best’ scar area and 0.84, 0.67 and 0.73 in the ‘worst’ scar area correspond to “good” to “excellent” inter-rater reliability. In the contralateral normal skin area the inter-rater reliability was only “good” and the ICC varied between rater pairs. Rater pairs R1 vs. R2 and R1 vs. R3 had higher inter-rater reliability (ICC 0.73) than the rater pair R2 vs. R3 (ICC 0.54). As

### Table 2 – Inter-rater reliability for pigmentation, vascularity and thickness components based on individual site measurements (all rater combinations).

<table>
<thead>
<tr>
<th>Component</th>
<th>R1 vs. R2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R1 vs. R3&lt;sup&gt;b&lt;/sup&gt;</th>
<th>R2 vs. R3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>‘Best’ scar area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>0.98 (0.96, 0.98)</td>
<td>0.94 (0.90, 0.96)</td>
<td>0.95 (0.92, 0.98)</td>
</tr>
<tr>
<td>Vascularity</td>
<td>0.74 (0.60, 0.83)</td>
<td>0.66 (0.48, 0.79)</td>
<td>0.78 (0.66, 0.85)</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.95 (0.92, 0.96)</td>
<td>0.86 (0.78, 0.91)</td>
<td>0.93 (0.89, 0.95)</td>
</tr>
<tr>
<td><strong>‘Worst’ scar area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>0.96 (0.94, 0.98)</td>
<td>0.95 (0.93, 0.97)</td>
<td>0.97 (0.95, 0.98)</td>
</tr>
<tr>
<td>Vascularity</td>
<td>0.84 (0.76, 0.89)</td>
<td>0.67 (0.50, 0.78)</td>
<td>0.73 (0.59, 0.82)</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.95 (0.91, 0.97)</td>
<td>0.91 (0.85, 0.95)</td>
<td>0.96 (0.92, 0.97)</td>
</tr>
<tr>
<td><strong>Normal skin area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>0.95 (0.93, 0.97)</td>
<td>0.92 (0.87, 0.95)</td>
<td>0.91 (0.86, 0.94)</td>
</tr>
<tr>
<td>Vascularity</td>
<td>0.73 (0.58, 0.82)</td>
<td>0.73 (0.58, 0.82)</td>
<td>0.54 (0.30, 0.69)</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.94 (0.91, 0.96)</td>
<td>0.92 (0.88, 0.95)</td>
<td>0.95 (0.92, 0.97)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ICC (95% CI): intra-class correlation coefficient (95% confidence interval).

<sup>b</sup> Raters 1–3.

<sup>c</sup> 3 site measurements for one subject were not included in the analysis (reached maximum measurement).

<sup>d</sup> 33 site measurements not included in the analysis (reached maximum measurement).
with pigmentation, there was marginally higher inter-rater reliability for vascularity when the average measurement was used in the analysis.

For about one-third of the 30 subjects (11/30), the thickness measurement in the 'worst' area of scar reached the maximum thickness of 2.5 mm. Only one of the 30 subjects reached the maximum thickness in the 'best' area of the scar. When thickness was able to be measured, it achieved “excellent” inter-rater reliability in all the tested areas for all rater pairs with ICC values of 0.95, 0.86 and 0.93 in the 'best' area of scar, 0.95, 0.91 and 0.96 in the 'worst' area of scar and 0.94, 0.92 and 0.95 in the contralateral normal skin area. Again, there was marginally higher inter-rater reliability when the average measurement was used in the analysis.

4.3. Test–retest reliability

Repeat scar assessments were completed for 19 out of the 30 subjects. For measurement of pigmentation, vascularity and thickness, 12 subjects had repeat testing conducted by three raters while 7 were assessed by only two raters, resulting in a total of 50 repeat tests for analysis. As per the protocol, each rater took measurements at 3 sites of each area of assessment (‘best’ and ‘worst’ area of index scar and the contralateral normal skin area). For analysis of individual measurements (3 sites per area in 50 repeat tests), up to 150 paired data sets were available for test–retest analysis. All subjects confirmed to the rater team that nothing had affected their scar since the first assessment including different topical preparations, pressure therapy or excessive sun exposure.

The results of the test–retest reliability ICC and 95% CI for pigmentation, vascularity and thickness are presented in Table 4. The number of data pairs included in each analysis is indicated.

Pigmentation had “excellent” test–retest reliability in the ‘best’ and ‘worst’ areas of the scar and the contralateral normal skin area (ICC 0.87, 0.89, 0.83 respectively).

Vascularity demonstrated varying levels of test–retest reliability. In the ‘worst’ area of the scar test–retest reliability for vascularity was “good” (ICC 0.42). In the 'best' area of scar and the contralateral normal skin area test–retest reliability was “marginal” with ICC 0.29 and 0.39 respectively.

Thickness also showed “excellent” test–retest reliability in all the three areas: the 'best' area of the scar (ICC 0.97), 'worst' area of the scar (ICC 0.92) and the contralateral normal skin area (ICC 0.86).

<table>
<thead>
<tr>
<th>Table 3 – Inter-rater reliability for pigmentation, vascularity and thickness components using average measurements of each area (all rater combinations).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Component</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>'Best' scar area</td>
</tr>
<tr>
<td>Pigmentation (n = 30)</td>
</tr>
<tr>
<td>Vascularity (n = 30)</td>
</tr>
<tr>
<td>Thickness (n = 29)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>'Worst' scar area</td>
</tr>
<tr>
<td>Pigmentation (n = 30)</td>
</tr>
<tr>
<td>Vascularity (n = 30)</td>
</tr>
<tr>
<td>Thickness (n = 19)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normal skin area</td>
</tr>
<tr>
<td>Pigmentation (n = 30)</td>
</tr>
<tr>
<td>Vascularity (n = 30)</td>
</tr>
<tr>
<td>Thickness (n = 30)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ICC (95% CI): intra-class correlation coefficient (95% confidence interval).
<sup>b</sup> Raters 1-3.
<sup>c</sup> 1 subject not included in the analysis (reached maximum measurement).
<sup>d</sup> 11 subjects not included in the analysis (reached maximum measurement).

<table>
<thead>
<tr>
<th>Table 4 – Test–retest reliability for pigmentation, vascularity and thickness components using individual site measurements.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement area</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>'Best' area of scar</td>
</tr>
<tr>
<td>'Worst' area of scar</td>
</tr>
<tr>
<td>Normal skin area</td>
</tr>
</tbody>
</table>

<sup>a</sup> ICC (95% CI): intra-class correlation coefficient (95% confidence interval).
<sup>b</sup> n = number of test–retest data pairs included in analysis.
<sup>c</sup> 51 test–retest data pairs not included in the analysis (at least one measurement reached maximum limit).
5. Discussion

The main purpose of this study was to measure scar components analogous to those measured in the subjective Vancouver Scar Scale (VSS), namely, pigmentation (melanin), vascularity (erythema), pliability (elasticity) and height (thickness), using the DermaLab Combo® device. These objective measurements were analysed to assess the inter-rater and test–retest reliability and the capability of the DermaLab Combo® device in conducting burn scar assessments.

The DermaLab Combo® is a relatively new commercially available integrated skin testing device primarily designed for skin testing in the cosmetic field. The advantages of this device are that it is user-friendly and measures multiple components, including those assessed in the VSS. Therefore, there is potential for this device to be used for clinical and research purposes if it is shown to be reliable in measuring scar components.

The narrow measuring head aperture of the DermaLab Combo® may be a source of potential bias when measuring large scars. A series of measurements are needed to obtain an average score representative of the entire scar [17]. The current study recorded and used three individual site measurements within 3 cm x 3 cm areas representing the ‘best’ and ‘worst’ areas of the index scar and contralateral normal skin. The individual site measurements and average of the three site measurements were both used for the purpose of analysis.

The results of this study show “excellent” inter-rater and test–retest reliability for DermaLab Combo® measurements of pigmentation. This is a marked improvement compared to the modified VSS (mVSS) assessment of pigmentation in our previous study [3] that demonstrated only “marginal” to “good” inter-rater reliability (weighted Kappa [kw] 0.02–0.33) in the ‘worst’ area of scar and “good” inter-rater reliability (kw 0.45–0.57) in the ‘best’ area of scar. No technical issues were encountered making pigmentation measurements.

Vascularity assessment indicated “good” to “excellent” inter-rater reliability in all scar areas. This represents a marginal improvement compared to the inter-rater reliability of the mVSS reported for the ‘best’ area of the scar in our previous study; “good” to “excellent” inter-rater reliability (kw 0.64–0.76) in the ‘worst’ area of the scar, and “good” inter-rater reliability (kw 0.44–0.71) in the ‘best’ area of the scar [3]. However, test–retest reliability for the vascularity component using the DermaLab Combo® was low and failed to achieve an acceptable level of reliability.

The inter-rater reliability of the vascularity measurements was not as high as we had expected, and test–retest reliability was particularly poor. This was in sharp contrast to the “excellent” reliability of the pigmentation measurements. Spectrophotometry, the measuring principle used in the DermaLab Combo® has been in use for over 50 years and is considered to be a reliable and objective method for skin colour assessment [18,19]. Compared to the human observer, reflectance spectrophotometry can detect very small changes in vascularity (erythema) or pigmentation [20]. This sensitivity may have been responsible for the lower than expected reliability for vascularity. The protocol of the current study did not specify with what pressure the probe should be applied and excessive pressure may cause blanching of the skin. Conversely, the measurement of pliability with the suction probe within a short space of time before erythema measurement may have increased the degree of erythema. These sources of variation require investigation in future studies, and could be avoided by modifications to the measurement protocol. Therefore, we recommend that protocols of future studies of scar assessment use the colour probe first followed by the ultrasound probe and finally the pliability probe to avoid possible influence on the other measurements. In addition, changes in the skin chromophore concentrations (melanin and haemoglobin) induce changes in both the melanin index (MI) and the erythema index (EI) in narrow-band spectrophotometry, making it difficult to separate the contribution of each component [18]. This may cause problems for the measurement of skin pigmentation and vascularity after an intervention (e.g. after suction), or over time (e.g. test–retest) where one or both skin chromophores at a location may be altered [18]. Calibration of the colour probe was repeated each day of testing as recommended by the manufacturer, but any issues in the calibration process would also manifest as poor test–retest reliability.

Thickness measurements achieved “excellent” inter-rater and test–retest reliability across all measured areas. Van der Kerckhove and others [21] used a DermaScan C® (high frequency ultrasound, Cortex Technologies, Denmark) [10] to measure scar thickness, and also obtained “excellent” results for inter-rater reliability (ICC 0.88). The DermaLab Combo® device shows superior inter-rater reliability for measuring scar thickness compared to the subjective mVSS which demonstrated only “good” to “excellent” inter-rater reliability in both the ‘worst’ and ‘best’ areas of the scar (kw 0.72-0.76) [3].

Despite achieving “excellent” reliability (both inter-rater and test–retest) of the thickness measurement, a technical limitation was encountered regarding the maximum thickness measurement using the DermaLab Combo®. The manufacturer’s specifications for the DermaLab Combo® ultrasound probe indicate a 3.4 mm penetration capacity. However, the maximum scar thickness that could be measured during our study was 2.5 mm. Approximately one-third of the 30 study subjects had readings in the ‘worst’ area of the scar that reached the maximum measurement. The authors understand an additional ultrasound probe is currently in development which may address this limitation.

The test–retest reliability of pliability using the DermaLab Combo® was “excellent” in the scar areas, but only “good” in
normal skin. In this study we did not assess inter-rater reliability of pliability, but Anthonissen and others [22] using a similar device, the DermaLab™ (Cortex Technologies, Denmark), found that inter-rater reliability of pliability of burn scars to be “excellent” for both scars and normal skin (grafted scar: ICC 0.86; spontaneously healed skin and normal skin: ICC 0.93), similar to the inter-rater reliability of pliability measurements made with the mVSS (‘best’ area of scar: kw 0.82–0.84; ‘worst’ area of scar: kw 0.77–0.86) [3]. A direct comparison between the DermaLab Combo® and the DermaLab™ studies is not possible because the two studies measured different types of reliability and the devices were not identical. Despite the “excellent” test-retest reliability of pliability measurements with the elasticity (pliability) probe in scar areas, the probe had limitations. The raters found scar assessment with the probe was not achievable on approximately half of the ‘worst’ scar areas, suggesting the probe may not have appropriate specifications for making measurements on rigid tissue. Anthonissen and others [22] also discuss the potential limitations of the elasticity (pliability) probe of the DermaLab™ device to measure rigid scars. Difficulties were also observed obtaining successful measurements on the legs and we speculate that this may be due to the greater thickness of the epidermis of the leg skin. In addition, the probe was ineffective in obtaining a proper grip with the skin with its adhesive tape when the subjects had a rough growth of body hair. The influence of body hair may help explain the low test-retest reliability for normal skin, as normal skin has more hair than scar. Protocols of future studies should include shaving the area prior to use of the elasticity probe.

A major strength of this study is the identification and systematic evaluation of a device with the potential capability of measuring four scar components considered important in scar assessment in an objective manner. This study has translated the DermaLab Combo® device, currently used in the cosmetic industry, to the area of burn scar assessment with some success. Pigmentation measurement was highly reliable, showing a substantial improvement compared to the mVSS assessment of pigmentation, and no technical issues were encountered. Scar thickness measurement was also highly reliable; however, for about one-third of the scars measured the thickness reached the maximum capacity of the device in its current version. Pliability measurement offered only a modest improvement in inter-rater reliability compared to the mVSS and was limited in its capacity to make measurements in approximately half of the burns scars tested. We are of the view that the vasularity assessment using the DermaLab Combo® did not reach its full potential in the current study.

6. Conclusion

The DermaLab Combo® is an easy to use and commercially available device, making it a viable option for scar assessment in both clinical and research settings. It provides objective and reliable measurements for pigmentation, thickness and pliability. However, the device has limitations in making measurements of thickness and pliability in some burn scars. Thickness can be measured in all scars but reaches a maximum measurement. The problems encountered obtaining successful measurements of pliability and reliable vasularity measurements are being examined further. If future studies provide protocols to improve test-retest reliability of vasularity measurements and obtain pliability measurements more successfully, the DermaLab Combo® will be a valuable option for scar assessment and monitoring.

Conflict of interest statement

All authors declare no conflict of interest.

Acknowledgements

The authors acknowledge the funding support of the Wound Management Innovation Cooperative Research Centre and Sugeesh Ariyaratna for his contribution in proof reading of this paper.

Appendix 1

| ROYAL PERTH HOSPITAL BURNS UNIT |
| DERMALAB COMBO - SCAR ASSESSMENT |

Affix patient sticker

<table>
<thead>
<tr>
<th>Colour</th>
<th>Elasticity(PD only)</th>
<th>Height</th>
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<tr>
<td>Best</td>
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<tr>
<td>Melanin</td>
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REFERENCES


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& kosmetologie

fortbildung
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Messung hautphysiologischer Parameter

Markus Steinert – Laserklinik Dres. Steinert, Biberach


**Grundlagen der Methoden**

**Hautfeuchtigkeit**

Die Hautfeuchtigkeit ist ein wichtiger Parameter zur Charakterisierung, ob trockene oder feuchte Haut vorliegt. Um die Feuchtigkeit der Hornschicht schnell und reproduzierbar messen zu können, gibt es verschiedene Analysemethoden: Messung der Desquamation, Impedanzmessung, nuklearer magnetischer Resonanzmessung, Infrarotspektroskopie, Resonanzfrequenzmessung oder die kapazitive (Konduktanz-)Messung. Physikalische Grundlage dieser Messmethode ist die lineare Abhängigkeit zwischen der elektrischen Kapazität der Epidermis und ihrem Wassergehalt.

**Hautfett (Sebum)**


**Transeidermaler Wasserdampfverlust**


1 DermaLab® Combo, Cortex-Technology-Hauptgerät mit Analyse-Sonden. (Mit freundlicher Genehmigung von Cortex Technology)
Elastizität der Haut

Oberflächenstruktur von Haut und Haaren

Hautfärbung/Pigmentierung

Präzise Hautanalyse mit hochauflösendem Ultraschall

Praktische Durchführung der Messung
Zur Charakterisierung des Hauttyps sind alle Messungen zunächst an der unbehandelten Haut durchzuführen. Deswegen sollten die Analysen ca. 20 min nach der Hautreinigung erfolgen, damit sich die durch den Abschmink- und Reinigungsprozess modifizierten Eigenschaften der Haut, wie z.B. die Hautfeuchtigkeit oder Fettgehalt der Hautoberfläche regenerieren können.

Die Feuchtigkeitsmessung
Zur Messung der Wasserbindungskapazität im Stratum corneum wird die Sonde senkrecht auf die Hautoberfläche aufgesetzt. Ein Federdruck löst die Messung automatisch aus. Nach wenigen Sekunden werden die Leitwerte in relativen Einheiten (Feuchtigkeitseinheiten 0–9,999 μS) auf dem Touch-Screen angezeigt. Das Design der Pin-Sonde gewährleistet mit den acht Pins selbst bei trockener und behaarter (Kopf-)Haut trotz störender Haare eine zuverlässige, reproduzierbare Messung. Beim Messgerät DermaLab® Combo können acht Messungen hintereinander gemacht werden, deren Mittelwert automatisch angezeigt wird.

Die Sebum-Messung

Die Beurteilung von Hautbarriereeigenschaften mit der TEWL-Sonde
Der TEWL wird über den Diffusionsgradienten ermittelt. Zwei Sensoren in der offenen Messkammer messen nach dem senkrecht aufsetzen auf die Hautstelle sowohl Feuchtigkeit und Temperatur in Echtzeit und zeigen die Werte am Bildschirm an. Die Kurve der Echtzeitmessung wird am Monitor angezeigt. Nachdem sich der transpidermale Wasserverlust stabilisiert hat (normalerweise nach 30–40 s) stoppt die Messung automatisch. Unter idealen Raumbedingungen (22–24°C, 40–60% Luftfeuchtigkeit) kann der TEWL (0–250 g/m²/h) mit einer Auflosung von 0,1 g/m²/h (Standardabweichung 5%) berechnet werden. Die Messungen der letzten 5 s werden als Häutwert angezeigt.

Elastizitätsmessung mit dem Saugtechnikprinzip
Dazu wird die 10 mm große, ca. 7 g leichte Sonde mit doppelseitigen Kleberungen an die Haut geklebt. Anschließend wird die Haut mit Vakuum maximal 2,5 mm angesaugt, gedeckt und wieder relaxiert. Zwei Detektoren in der Sonde begrenzen das Messfeld auf 1,5 mm. Sobald die Haut die Detektoren passiert hat, werden die grüne und eine rote Linie am Monitor sichtbar. Nach Beendigung der Messung werden drei verschiedene Parameter angezeigt.
1. Viskoelastizität (VE) als Maß für die Rückstellung der Haut,
2. Young’s Modulus (E) zeigt die Steifigkeit der Haut,
3. Retraktionszeit (R) ist die gemessene Zeit für die Rückstellung.

Für die Ermittlung der Elastizität ist nur eine Messung notwendig.

Die Analyse der Oberflächenstruktur der Haut mit dem Videoscope
Das elektronische Video-Mikroskop (Videoscope) mit integrierter LED-Beleuchtung liefert qualitativ hochwertige Aufnahmen der Hautoberfläche mit einer 20–50-fachen Vergrößerung.

Messung von Hautfärbung, Hautrötung und Bräunungsgrad mit dem ColorMeter


Visualisierung der Gewebestrukturen mit Ultraschall

Zur Visualisierung der Haut wird die 20-MHz-Ultraschall-Sonde senkrecht auf die Hautoberfläche aufgesetzt. Der Transducer in der Sonde vollzieht eine einzelne rotierende Bewegung von 17,6 mm. Mit einer Auflösung von 376 × 256 Pixeln werden Strukturen der Haut bis 3,37 mm Eindringtiefe am Bildschirm angezeigt. Das ermöglicht die sofortige Beurteilung von Dermis und Subkutis (Dichte, Dicke, Übergang, Kollagendichte, Hautschädigungen) sowie eine objektive Bewertung und Dokumentation von Veränderungen der Haut, die äußerlich nicht erkennbar sind (UV-Schäden, Hautalterung, Hautverjüngung). Kollagen- und Elastizitätsverlust lassen sich durch die Intensität der Reflektion ermitteln. Da Schall in Wasser weitergeleitet wird, wird die Sonde mit destilliertem Wasser und einer Membran vorbereitet, die das Auslaufen des Wassers verhindert.

Apparative Ausstattung


Wertung der Methode für die Praxis


Abrechnungshinweise

Die einzelnen Messungen sind reine Selbstzahlerleistungen und werden nach der GOÄ abgerechnet.

Hinweise zur Erlernung der Methode


www.cortex.de; Kontaktadresse: Cortex Technology, Büro Deutschland, Ökonomierat-Peritzmeier-Platz 2–4, 59065 Hamm

Korrespondenzadresse
Dr. Markus Steinert
Laserklinik Dres. Steinert GmbH
Holzmarkt 6
88400 Biberach
Prof@DrSteinert.de

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ISBN: 978-3662434260
Hardcover: 89,99 €

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Ablative Versus Non-Ablative Treatment of Perioral Rhytides. A Randomized Controlled Trial With Long-Term Blinded Clinical Evaluations and Non-Invasive Measurements

L. Hedelund, MD,1* P. Bjerring, MD, MSc,2 H. Egekvist, MD, PhD,2 and M. Haedersdal, MD, PhD, DMsc1
1Department of Dermatology, Copenhagen University Hospital, Bispebjerg Hospital, Denmark
2Department of Dermatology, Aarhus University Hospital, Denmark

Background and Objective: To compare efficacy and side effects of CO2 laser resurfacing and intense pulsed light (IPL) rejuvenation for treatment of perioral rhytides.

Methods: Twenty-seven female subjects with perioral rhytides (class I–III) were randomly treated with either CO2 laser or IPL (three monthly treatments). Efficacy was evaluated by patient self-assessments and blinded photographs up to 12 months postoperatively. Side effects were assessed clinically. Non-invasive measurements included: trans epidermal water loss (TEWL), skin reflectance, skin elasticity, and ultrasound.

Results: CO2 laser resurfacing resulted in higher degrees of patient satisfaction and clinical rhytide reduction compared to IPL rejuvenation up to 12 months postoperatively (patient evaluations, P < 0.05) (observer evaluations, P < 0.008). Laser-induced side effects included erythema, dyspigmentation, and milia whereas no side effects were observed after IPL rejuvenation. Non-invasive measurements showed a significant higher reduction of the subepidermal low-echogenic band in CO2 laser treated areas versus IPL treated areas (12 months postoperatively, P < 0.001). Skin elasticity (expressed as Young’s modulus) increased in both groups (P = ns). One month postoperatively a significant increase in TEWL values (P < 0.009) and skin redness% (P < 0.02) was found in CO2 laser treated patients versus IPL treated patients. No significant differences were seen in skin pigmentation% during the observation period.


Key words: CO2 laser; intense pulsed light; skin elasticity; skin reflectance; trans epidermal water loss; ultrasound

INTRODUCTION

Ablative CO2 laser resurfacing is used in the treatment of facial rhytides. The clinical improvement occurs through a well-organized wound healing response leading to formation of new collagen [1]. Unfortunately, the clinical efficacy of ablative laser resurfacing has been limited by potential unwanted side effects and significant postoperative inconvenience [2,3]. Non-ablative skin rejuvenation techniques, which improve the skin quality without affecting the overlying epidermis have, therefore, been investigated with great interest. By selectively targeting haemoglobin or tissue water as the primary chromophores the mechanism of action is supposed to be based on formation of a dermal repair zone followed by dermal remodeling [4,5].

Several randomized controlled trials have documented a significant reduction of facial rhytides after CO2 laser resurfacing [6–8]. Moreover, from randomized and non-randomized controlled trials it seems that non-ablative lasers and IPL systems induce a minor to moderate short-term improvement of facial lines and rhytides [4,9,10]. CO2 laser resurfacing and non-ablative skin rejuvenation are not traditionally performed on the same group of patients, since the risk of side effects after CO2 laser resurfacing does not justify treatment of only mild photodamaged skin. Therefore, the present study is the first trial, which directly compares efficacy and side effects of ablative and non-ablative skin rejuvenation in a homogeneous group of patients.

Several treatment techniques and technical diverse systems including vascular lasers (532–595 nm), mid-infrared lasers (1,064–1,540 nm), and IPL systems (500–1,200 nm) have been used to obtain non-ablative remodeling. In the present study efficacy and side effects of three monthly treatments with IPL was compared with CO2 laser resurfacing for treatment of perioral rhytides. The treatment outcome was evaluated by patient self-assessments and blinded evaluations of photographs. Objective non-invasive measurements were performed in order to support the clinical findings.

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Region of Copenhagen, the Faroe Islands and Greenland.

*Correspondence to: L. Hedelund, MD, Department of Dermatology-D92, Copenhagen University Hospital, Bispebjerg Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark. E-mail: LH20@bbh.hosp.dk

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Materials and Methods

Twenty-seven healthy female volunteers with ages from 38 to 70 years (average age, 56 years) Fitzpatrick skin type II and class I–III wrinkles in the perioral region were treated. The patients were recruited from the community via advertisements in local newspapers and all gave informed consent to participate in the study. The study was approved by the institutional review board (human study committee) and conducted from November 2002 to January 2003. Exclusion criteria included any signs of infection or inflammatory skin disease, previous formation of hypertrophic scars or keloids, pregnancy, use of oral isotretinoin in the past 12 months, current use of acetylsalicylic or non-corticosteroidal anti-inflammatory drugs, exposure to ultraviolet irradiation within the last 4 weeks, and previous skin rejuvenation procedures in the perioral area. CO₂ laser treated patients were prescribed prophylactic acyclovir (400 mg three times daily starting 1 day prior to laser treatment for 7 days) and dicloxacillin (500 mg twice daily beginning the day of laser treatment for 7 days). Prior to treatment, the patients received nerve blocks and local infiltration anaesthesia (lidocaine–adrenaline 20 mg/ml) in the perioral area. Postoperative care included plain petrolatum combined with 2% fusidic acid cream. Prior to IPL treatment, the area to be treated was covered with a transparent gel to optimize optical coupling between light-guide and skin.

Patients were randomly allocated to receive either one treatment with CO₂ laser or three monthly treatments with IPL. Randomization was carried out prior to treatment by patients drawing lots between 37 opaque sealed envelopes containing CO₂ laser or IPL marked cards. An independent nurse assigned patients to treatment. Twelve of 18 patients allocated to intervention with CO₂ were treated (three patients were not treated because of illness, one patient was found after randomization not to satisfy the entry criteria, one patient did not show up because of lack of time and one patients had regrets about the treatment). Of 19 patients allocated to intervention with IPL, 15 patients completed all three treatments (one patient had regrets about the treatment, one patient moved, and two patients did not want to continue because of lack of time) (Fig. 1). CO₂ laser treatments were performed by a MedArt® 450 CO₂ laser with a MedArt® 456 scanner attached to the laser unit (ASAH Medico, Valseholmen, DK). The setting parameters were 10.1 W, 572–846 J, scan area 1.0 cm², scan time 1.1 seconds, dwell time 0.9 milliseconds. Two passes were delivered. Wiping was performed with saline saturated gauze pads between passes. IPL

Fig. 1. Flow chart.
treatments were performed with a second generation IPL system (Ellipse Flex, DDD, Denmark). Energies varied between 8.5 and 9 J/cm² delivered at two 2.5 millisecond pulses with a 10 milliseconds interpulse delay. Dual mode filters restricted the emitted light to a wavelength band from 530 to 750 nm, inhibiting shorter and longer wavelengths. As longer wavelengths from 750 to 1,200 nm were removed, the emitted fluence levels were significantly lower than in comparable IPL systems.

Postoperative evaluations were performed 1, 3, 6, and 12 months after the final treatment. Patient satisfaction with the overall treatment result was assessed on visual analogue scales (VAS; 0 = unsatisfied to 10 = maximum satisfaction) [11]. Photodocumentation was performed before treatment and at each postoperative control. The photographs were evaluated by means of the Fitzpatrick photodamage classification (an arbitrary scale from 0 to 9 representing increased severity of wrinkles) [12]. Photos were evaluated by two independent dermatologists and by the patients themselves in a blinded fashion, i.e., the photographs were mixed intra-individually and the dermatologists as well as the patients were unaware of whether the photographs were preoperative or postoperative. Potential side effects such as wounds, erythema, hypopigmentation, and scars were evaluated by clinical on-site evaluations on a four-point scale of none, mild, moderate, and severe.

Photographs were taken with a Canon Digital Camera (EOS D30) equipped with a lens mounted ring flash (Canon Macro Lens EF 100 mm 1:2.8 USM). All photographs were taken in raw format under identical conditions and camera settings. Standardized views (en face and 45° oblique) were used and a single laboratory processed all photographs.

Non-invasive measurements included: (1) measuring of Trans Epidermal Water Loss (TEWL); (2) skin reflectance measurements; (3) skin elasticity measurements; and (4) ultrasonographic examinations. Measurements were performed on the left side of the upper lip and on an adjacent control area before treatment and at each postoperative control (TEWL measurements were only performed preoperatively and 1 and 3 months postoperatively). Specific landmarks ensured that measurements were continually taken at the same skin area.

TEWL was measured by a Dermalab® system (Cortex Technology, Hadsund, Denmark). TEWL refers to the total amount of water loss through the skin and reflects the integrity of the skin barrier. The procedure was undertaken in accordance with the guidelines of the European Society of Contact Dermatitis [13].

Objective measurements of skin pigmentation% and skin redness% were performed by skin reflectance spectroscopy (UV-Optimize, Model 550/660 nm, PBI Medical, Ringsted, Denmark). The instrument measures pigmentation (melanin) and redness (hemoglobin) in human skin and relates the results to biological relevant scales. Thus, 0% pigmentation corresponds to absolutely white skin with no melanin pigmentation at all whereas 100% pigmentation corresponds to theoretically absolutely black skin without any reflection. Zero% redness is found in skin that has been drained from blood whereas 100% redness% is found in skin with highly intense blood flow [14,15].

Skin elasticity was measured by a DermaLab® system (Cortex Technology). The DermaLab® skin elasticity system uses a suction chamber method. Thus, the suction probe gradually exposes the skin to a growing amount of stress and the instrument calculates the applied stress (vacuum, Pa) needed to achieve an elevation of the skin of 1.5 mm. The result is expressed as Young's modulus (E) [16].

For ultrasonographic examinations a 20 MHz dermascan system (Dermascan C® Cortex Technology) was used to obtain cross-sectional images of the skin (B-mode). For all recordings, the gain compensation curve was fixed in a constant oblique position at 15–32 dB. The axis of the probe was placed horizontal to the skin surface and with constant thickness of the ultrasonic-coupling gel of 1 mm. The subepidermal low-echogenic band (SLEB) was defined as a clearly visual lowechogenic band in the upper dermis immediately below the epidermal entrance echo [17,18]. Quantification of SLEB was performed by calculating the number of low echogenic pixels (LEPs) (range 0–30, total range 0–255) in the upper dermis (LEP_u) relative to the number of LEPs in the lower dermis (LEP_l) [19].

The LEP_u and the LEP_l were determined separately by dividing the dermal layer into two parts of equal size. The dermal thickness was defined as the distance between the epidermal entrance echo and the interface between the dermis and the subcutis at five predefined places in each image. Cut-off points were determined using A-scan function on the B-mode image, and the mean thickness was calculated. All images were analyzed in a blinded fashion with the evaluator having no access to patient data.

Statistics

Aiming for a significance level of 0.05 and a power of 90% and based on the assumption that the smallest clinically important median difference between CO2 laser and IPL treatment was 1 unit on Fitzpatrick wrinkle assessment scale we calculated that a sample of 21 patients would be required in total. All patients who received the allocated treatment were included for statistical analysis. Non-parametric statistical methods were used. For paired comparisons: Friedman test and Wilcoxon matched pairs test were used. Unpaired comparisons were performed by Kruskal-Wallis test and Mann-Whitney U test. Data are presented as medians (interquartile range (IQR)). Calculations of TEWL, skin redness%, skin pigmentation%, skin elasticity, and LEP_u, LEP_l are based on absolute changes (postoperative minus preoperative values).

RESULTS

Clinical Evaluations

The patient satisfaction was significantly higher among CO2 laser treated patients than among IPL treated patients (P < 0.05). The levels of patient satisfaction remained constant during the entire observation period (Table 1).

Clinical evaluations of perioral rhytides by the patients themselves and by the dermatologists showed a signi-
TABLE 1. Patient Satisfaction Evaluated on VAS Scale (0–10)

<table>
<thead>
<tr>
<th>Time</th>
<th>CO₂ laser median (IQR)</th>
<th>IPL median (IQR)</th>
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<tr>
<td>1 month</td>
<td>9.3 (8.5–9.7)*</td>
<td>4.2 (1.2–6.7)</td>
</tr>
<tr>
<td>3 months</td>
<td>8.8 (7.4–9.5)*</td>
<td>4.5 (1.6–6.4)</td>
</tr>
<tr>
<td>6 months</td>
<td>9.0 (7.4–9.5)*</td>
<td>5.0 (0.7–7.3)</td>
</tr>
<tr>
<td>12 months</td>
<td>8.3 (5.1–9.4)*</td>
<td>3.6 (1.0–5.7)</td>
</tr>
</tbody>
</table>

Stars illustrate significant differences between CO₂ laser and IPL treated patients 1, 3, 6, and 12 months postoperatively (*P < 0.05). Abbreviation: IQR, interquartile range, 25% to 75%.

Patients treated with CO₂ laser developed erythema, hyperpigmentation, hypopigmentation, and milia (Table 3). No side effects were observed in IPL treated patients.

Non-Invasive Measurement

In control areas TEWL values, skin redness%, skin pigmentation%, skin elasticity, and LEPu/l remained constant and no significant differences were found between CO₂ laser treated and IPL treated patients at any assessment. In CO₂ laser treated areas, TEWL values were significantly increased 1 month postoperatively compared to IPL treated areas (median, 5.60 g/m²-hour; IQR, 2.70 to 6.85 g/m²-hour vs. –1.60 g/m²-hour; IQR, –2.95 to 0.05 g/m²-hour) (P < 0.009) (Fig. 3). One month postoperatively a significant increase in skin redness% were found in CO₂ laser treated areas versus IPL treated areas (median, 7.30; IQR, 3.40 to 10.20 vs. –7.15; IQR, –10.90 to 5.05) (P < 0.02). No significant differences were seen in skin pigmentation% during the observation period (Fig. 4). CO₂ laser treatment resulted in a long-term reduction of LEPu/l and 12 months postoperatively LEPu/l values were significantly reduced in CO₂ laser treated areas versus IPL treated areas (–0.77; IQR, –1.20 to –0.22 vs. 0.52; IQR, 0.09 to 1.09) (P < 0.001) (Fig. 5). Both treatment modalities induced an increase in skin elasticity, which increased from 1 to 12 months postoperatively, and no significant differences were seen between CO₂ laser treated patients versus IPL treated patients at any time (4.83 MPa; IQR, 2.20 to 5.93 MPa vs. 4.37 MPa; IQR, –2.45 to 5.91 MPa) (12 months postoperatively, P = ns) (Fig. 6).

DISCUSSION

In the present study, CO₂ laser resurfacing resulted in a higher degree of patient satisfaction and clinical rhytide reduction compared to IPL rejuvenation at all assessments up to 12 months. A relatively high rate of side effects was observed after CO₂ laser treatment, which might be related to a longer dwell time of the scan than used of most resurfacing scanned lasers today. No side effects were observed after IPL rejuvenation. Non-invasive measurements supported the clinical findings showing a decrease in LEPu/l up to 12 months postoperatively in CO₂ laser treated patients compared to IPL treated patients. However, both treatment modalities induced a long-term improvement of skin elasticity and no significant differences were seen. One month postoperatively TEWL values and skin redness increased in CO₂ laser treated patients compared to IPL treated patients whereas no significant differences were observed in skin pigmentation at any time.

We found that three IPL treatments at 1 month intervals had no efficacy on rhytides. Treatment outcomes might have changed with the use of other treatment parameters and an increased number of treatments. However, Goldberg et Cutler showed improvements of rhytides in 25 of 30 patients after 1–4 IPL treatments [20] whereas only 4 of 14 patients obtained improvements of rhytides after five IPL treatments in a study by Carruthers et Carruthers [21]. Most physicians today do from three to six

TABLE 2. Rhytide Scores on Fitzpatrick Wrinkle Assessment Scale (Score 1–9)

<table>
<thead>
<tr>
<th>Time</th>
<th>Preoperative</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dermatologist 1</td>
<td>Dermatologist 2</td>
<td>Dermatologist 1</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Preoperative</td>
<td>5 (4–6)</td>
<td>4.5 (4–6)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>1 month</td>
<td>3 (2.5–4)**</td>
<td>4.5 (4–6)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>3 months</td>
<td>3 (2–4)**</td>
<td>4.5 (4–6)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>6 months</td>
<td>3 (2–3.5)**</td>
<td>4.8 (4–5)</td>
<td>5 (4–6)</td>
</tr>
<tr>
<td>12 months</td>
<td>3 (2.5–4)**</td>
<td>4.5 (4–6)</td>
<td>5 (4–6)</td>
</tr>
</tbody>
</table>

Stars illustrate significant differences between CO₂ laser treated and IPL treated patients (**P < 0.01, *P < 0.05). Rhytide scores were significantly reduced (postoperative minus preoperative values) in CO₂ laser treated patients (P < 0.01). No significant differences were found among IPL treated patients. Abbreviation: IQR, interquartile range, 25% to 75%.
treatments but still a clear and reproducible treatment strategy needs to be defined.

Non-invasive measurements showed a long-term increase in skin echogenicity after CO₂ laser resurfacing which is most likely caused by changes in the amount and alignment of collagen fibers [22–24]. These results are supported in a study by Moody et al. showing an increased reflection of echogenic signals 1 and 3 months after a single treatment with a 585 nm pulsed dye laser [25]. Moreover, a few previous studies have demonstrated a significant increase in skin elasticity (measured as elastic recovery) after treatment with CO₂ laser as well as IPL [26, 27]. Thus, in a methodological study a significant increase in the perioral skin elasticity was found 6 months after CO₂ laser resurfacing [26] and just recently a multicenter study showed a significant increase in skin elasticity that was related to a clinical rhytide reduction 6 months

<table>
<thead>
<tr>
<th>Side effects</th>
<th>CO₂ laser number of patients (months)</th>
<th>IPL</th>
<th>CO₂ laser number of patients (months)</th>
<th>IPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>12 (1 m)(^b)</td>
<td>0</td>
<td>5 (3 m)(^a)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>2 (6 m)(^a)</td>
<td>0</td>
<td>2 (6 m + 12 m)(^a)</td>
<td>0</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>3 (6 m + 12 m)(^a)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Milia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scarring</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Mild degree.  
\(^b\)Mild–moderate degree.  
\(^c\)1, 3, 6, and 12 months.
after IPL rejuvenation [27]. As expected the present study showed an increase in TEWL after CO2 laser resurfacing whereas IPL rejuvenation did not seem to affect the overlying epidermis.

The present study compares efficacy and side effects of CO2 laser resurfacing and IPL rejuvenation in a randomized controlled design. The randomization process was performed by concealed allocation and it was intended that the efficacy outcome should be evaluated by blinded evaluations. However, the CO2 laser treatment could not be completely masked, because of postoperative erythema which was especially pronounced 1 month after CO2 laser resurfacing. Moreover, patients who failed to start the allocated treatment might compromise the effect of random allocation. However, none of the treated patients were lost to follow-up and statistical analysis therefore included all patients who received the treatment they were randomly assigned for.

In the last decade, reduction of rhytides with lasers and Intense Pulsed Light (IPL) sources has been the subject of intense research. Non-ablative approaches that cause dermal wounding without harming the epidermis have been introduced and suggested as alternative treatment methods in preference to the well-established ablative skin rejuvenation modalities. Several treatment techniques have been used to obtain non-ablative remodeling. However, differences in wavelengths, treatment settings, number of treatments, duration of treatments intervals, treatment areas, and rhytides severity makes it difficult to compare and draw conclusions about the efficacy of the different non-ablative devices available for treatment of
facial rhytides. Nevertheless, from six randomized controlled trials and four non-randomized controlled trials it seems that non-ablative skin rejuvenation induces a mild to moderate improvement of rhytides lasting up to 6 months after end treatment [4,9,10,21,28–33]. However, blinded evaluations as well as statistical analysis were not performed in all studies.

To our knowledge this is the first study that directly compares efficacy and side effects of IPL rejuvenation and ablative laser resurfacing for treatment of facial rhytides in a homogeneous group of patients. The present results shows that CO₂ laser resurfacing induces a significantly higher degree of clinical rhytide reduction followed by considerably more side effects compared to IPL rejuvenation.

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REFERENCES

The influence of a humectant-rich mixture on normalz skin barrier function and on once- and twice-daily treatment of foot xerosis. A prospective, randomized, evaluator-blind, bilateral and untreated-control study

Marie Lodén¹, Johan von Scheele¹ and Sophie Michelson²

¹Epiderm Institute AB, Solna, Sweden and ²Engelbrektshosspitalen, Stockholm, Sweden

Background: Moisturizers are often used to overcome dry skin conditions. However, cosmetic moisturizers may lack in efficiency and may also deteriorate skin barrier function. The objective of this study was to generate data on a new humectant-rich formulation (15% alfa hydroxy acids and 15% urea) in the treatment of normal skin as well as in dry feet with hyperkeratosis and cracked skin with fissures. Changes in permeability and effectiveness of the product after once- and twice-daily applications to the feet will be monitored.

Methods: The study was randomized, bilateral, controlled and evaluator-blind. The first part of the study included 12 healthy volunteers and the second part 50 patients with hyperkeratotic feet. The changes in the skin was evaluated by an expert, the patients and using non-invasive biophysical measurements of skin barrier function (transepidermal water loss, TEWL), erythema, thickness (ultrasound) and hydration (conductance).

Results: The humectant-rich formulation increased skin hydration, removed scales and reduced thickness of hyperkeratotic skin. Skin barrier function was improved in normal skin, but no changes in TEWL were noted in the feet. No difference between once and twice-daily applications was found. Some smarting and stinging was noted.

Conclusion: The humectant-rich formulation efficiently relieved the xerosis on the feet without inducing any weakening of the skin barrier function. Instead the normal skin became more resistant to external insults by the treatment.

Key words: hyperkeratosis – AHA – lactic acid – urea – pedal skin – TEWL – ultrasound – medical device

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Hyperkeratotic and xerosis are clinical manifestations of a number of dermatological diseases, such as e.g. atopic dermatitis, ichthyosis and psoriasis. Xerosis and cracking of the skin on the feet are also common in patients with diabetes (1).

Moisturizers are often used to overcome dry skin conditions. The majority of products available for treatment of dryness are conventional moisturizers (cosmetics). However, cosmetic moisturizers may lack in efficiency and are not allowed to be marketed on hyperkeratotic skin with injured and broken surface, or on xerotic skin connected to diseases (2), whereas more efficient and 'stronger' moisturizers (topical pharmaceuticals and medical devices) are more valuable tools in the treatment of hyperkeratosis.

Urea and alfahydroxy acids (AHA), especially glycolic and lactic acid are found to be beneficial for treatment of hyperkeratotic skin, such as ichthyosis, where the number of stratum corneum layers is reduced after treatment with 10% urea in combination with 5% lactic acid (3-5). The severity of foot xerosis has also been found to improve by treatment with 10% urea and 5% salicylic acid ointment to a similar extent as with 12% lactic acid/lactate (6). A more rapid and pronounced improvement of plantar xerosis was found after treatment with 40% urea cream in comparison with 12% ammonium lactate (7).
However, a thinner and more hydrated stratum corneum may lead to changes in its permeability and susceptibility to environmental stimuli. Both increased (8-13) and decreased susceptibility (12, 14, 15) to topically applied substances have been found after treatment with certain products. A urea formulation (11) and some lactic acid formulations have been shown to worsen skin barrier function in hyperkeratotic skin (16, 17).

The objective of this study is to generate data on a new humectant-rich formulation (15%, AHA, and 15% urea) in the treatment of normal skin as well as in dry feet with hyperkeratosis and cracked skin with fissures. Changes in permeability and effectiveness of the product after once- and twice-daily applications to the feet will be monitored.

Methods
The study was randomized, bilateral, controlled and evaluator-blind. The first part of the study included healthy volunteers and the second part patients with hyperkeratotic feet. The study was approved by the regional ethics committee (Karolinska Institute, Sweden) and the competent authority also approved the second part on patients with hyperkeratotic feet. Written informed consent was obtained from all volunteers.

Test subjects
The study on normal skin comprised 12 healthy volunteers (7 females and 5 males, mean age 31 years, standard deviation (SD) 17).

The study on patients included 50 patients (25 men and 25 women), median age 64 years, range 21–86 years, mean 60 ± 15 years.

The following were excluded:

1. Known hypersensitivity or contact allergy to the ingredients in the test products.
2. Any serious current medical condition which, in the opinion of the Investigator, may interfere with the evaluation of the results or may be contraindicated by the use of the test product (e.g. deep or widely spread foot ulcers in the patient study).
3. Use of any concomitant medication that may interfere with the study related activities or assessment of efficacy, as judged by the Investigator.
4. Female patient who, according to the patient, is pregnant or breast-feeding, or plans to become pregnant during the course of the study.
5. Any patient-related factor suggesting potential poor compliance with study procedures (e.g. psychiatric disorders, history of alcohol or substance abuse), as judged by the Investigator.

The following concomitant treatments were not allowed:

1. Peroral glucocorticoids for treatment of inflammatory disorders. Inhaled glucocorticoids for treatment of asthma were allowed.
2. Peroral anti-fungal medication.
3. Topical immunomodulators or anti-fungal creams.
4. Moisturizers or other topical products on the study areas.

Treatments
The humectant-rich formulation (Footmender®, Auxilum Cura Innovatio, Dublin, Ireland) contained 15% AHA and 15% urea in a lipid cream base (aqua, sodium lactate, lactic acid, glycolic acid, tartaric acid, panthenol, glycercin, PEG-20 Methyl Glucose Sesquisteareate, Methyl Glucose Sesquisteareate, Butyroperumum Parkii Butter, Ocylidodecanol, Behenyl Alcohol, Simmondsia Chinensis Seed Oil, Caprylyl Glycol, Menthol Polyacrylate-1 Crosspolymer, Sodium Gluconate, Retinyl Palmitate).

In the first part of the study the healthy subjects treated the volar aspect of their forearms twice daily for 20 days with the test product. After treatment for 10 and 20 days the volunteers attended the clinic for evaluations. The subjects were asked to wash their forearms in the morning prior to the visit to ensure that no cream residue was left on the surface which to influence the readings. During the study period, the subjects were allowed to wash normally but not to use any other skin care products on their arms.

In the second part of the study the patients were asked to apply the cream once or twice daily on one of their feet (randomized). All patients were asked to apply the cream in the

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evening and half of the group also in the morning. After treatment for 1 and 2 weeks the degree of dryness and cracks were measured by expert evaluation, by self-grading of degree of dryness and using non-invasive measurements of skin characteristics. The patients were instructed not to treat their foot in the morning prior to the clinic visit. Compliance was recorded by notes in the patient diary and weighing of the jars after the 2 weeks treatment period.

Evaluations
All evaluations were made without knowledge of treatment and previous readings. A trained expert made all clinical scorings and another expert made all instrumental measurements.

The influence of the test product on the forearm on healthy individuals was investigated by biophysical measurement of skin color, skin hydration and transepidermal water loss (TEWL) days 10 and 20. On day 20 the skin susceptibility was further characterized by exposing the skin to an aqueous solution of 1% sodium lauryl sulfate (SLS) purity 99%, Sigma-Aldrich). 50 µl of the SLS-solution was pipetted onto one layer of filter paper placed in aluminium chambers (Ø 12 mm, Finn chambers, Vita-flo Scandinavia AB, Göteborg, Sweden). The chambers were fixed to the skin for 24 h with adhesive tape (Scanpor, Actavis, and Oslo, Norway). The degree of irritation was scored on a scale from 0 to 5 (18) and instrumentally on day 22.

The instrumental measurements of the xerotic feet were made on the proximal side of the heel and on the plantar area. From administrative reasons 38 of the 50 included patients were measured. Some readings were also lost due to technical failure.

Expert scoring of the dryness severity (xerosis and fissuring) was made of the treated and untreated foot scored according to the scale in Table 1.

Patient evaluation
The judgment of the dryness of the feet by the patient was marked on a Visual Analogue Scale (VAS) in the patient diary, where the left end corresponded to extreme dryness and right end to normal skin.

Table 1: Grading of the degree of severity of xerosis and fissuring

<table>
<thead>
<tr>
<th>Rating</th>
<th>Severity</th>
<th>Xerosis</th>
<th>Fissures, cracks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No dryness, soft skin</td>
<td>No fissures, soft skin no dryness</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>Few minute fl akes, dusty appearance</td>
<td>Xerosis (≥ 1 according to above) and hardened skin</td>
</tr>
<tr>
<td>2</td>
<td>Many undifferentiated skin flakes, generalized dusty appearance</td>
<td>Fissuring between scales, shallow fissures, no redness</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Some polygonal scales, defined scaling with flat borders</td>
<td>In-between 2 and 4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>Moderate number of polygonal scales, well-defined heavy scaling with raised borders</td>
<td>Moderate deep fissuring between scales, potential redness</td>
</tr>
<tr>
<td>5</td>
<td>Large number of polygonal scales, and hardened skin</td>
<td>Severe deep fissuring, potential redness</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Severe</td>
<td>Score 5 and fissuring between scales</td>
<td>Deep erythematous fissuring, several fissures</td>
</tr>
</tbody>
</table>

Instrumental evaluation
All measurements were performed with a DermaLab® Combo (Cortex Technology, Hadsund, Denmark) equipped with probes for skin color, conductance, ultra-sound and TEWL. The probes are placed on the skin and used in accordance with instructions given by the manufacturer.

Skin thickness was measured using ultrasound with a rotating X-tal, frequency 20 MHz, band-width 5-35 MHz. The traveled distance over the skin 17.6 mm with a maximum penetration into the skin 3.7 mm. To be able to penetrate the hyperkeratotic tissue maximum gain was used during the measurements.

Measurement of TEWL is made with an open-chamber with two combined humidity/temperature sensors mounted in a cylindrical diffusion chamber (10 mm diameter). After application of the probe onto the skin, the TEWL value is recorded into the computer until the SD of the values is < 0.2, where after the measurements stops (typically 30-45 s). This value is used for further calculations.

Skin hydration is measured as conductance (alternating voltage) using a spring loaded probe which triggers and stops the measurements. The probe has eight pins to minimize moisture accumulation under the probe. The value is expressed as µSiemens (µS).

Skin color measurement is based on an active color detecting chip where illumination is
provided by white LED’s and the measure of erythema corresponds to the redness (hemoglobin) of the skin. Target area for measurement is 7 mm diameter.

Safety, skin reactions and adverse events
Safety endpoint was the rate of AEs including assessment of local skin reactions, such as smarting. The degree of uncomfortable skin reactions are evaluated by the patient and marked on a 5-point category scale in the patient diary. Other possible adverse events were registered by the Investigator.

Calculation and statistics
The results are presented using box plots. The bottom line of the box is the first quartile (Q1), and the top is at the third quartile (Q3) value. A line is drawn across the box at the median. The whiskers are the lines that extend from the top and bottom of the box to the lowest and highest observation.

Wilcoxon signed rank test on paired data was used to test the differences between the treatments using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. P < 0.05 was considered as significant.

Results
All included subjects participated in the study of the forearms, while seven patients dropped out from the study of the feet; five dropped out during the first week and another two dropped out during the second week. No patients were withdrawn. Two of the patients reported disagreeable skin reactions (itching, stinging), one had back-pain and four others reported lack of time. The majority of patients were treated for a number of different diseases, such as thyreosis (13), high blood pressure (9), diabetes (8), high cholesterol (5), fibromyalgia (1), anemia (1), asthma/lung diseases (2), stomach (2), kidney (1), and psoriasis (1).

The patient diaries showed proper compliance in the treatment of the feet. The weighing of 35 returned pump jars showed that the patients using the creams once daily had applied 1.7 ± 0.7 g in the evening (mean ± SD, n = 17) and those using the creams twice daily had applied 3.1 ± 1.3 g daily (n = 18) on one of their feet. The median use was 1.6 g in the once-daily group and 2.8 g in the twice-daily group.

In the normal forearm skin, conductance increased and TEWL decreased significantly by the treatment, Fig. 1 and 2. Furthermore, skin susceptibility to the irritant decreased by the treatment, measured by lower degree of irritation (measurement of TEWL and erythema, and visual assessment) on the area treated with the cream, Fig. 3.

Treatment of the xerotic and hyperkeratotic feet with the cream improved the skin, as judged by the expert. None of the patients scored moderate or more severe degree of dryness and/or cracks after the treatment, whereas at inclusion the majority of the feet was graded to be moderate dry (score 4) and/or to show moderate degree of fissuring (score 4). The successive improvement of the skin by time is shown as decreased mean values in degree of dryness and cracks, Fig. 4. The patients noted a significant improvement in their skin condition on the VAS already after 24 h (P = 0.017),

![Fig. 1. Skin conductance (hydration) after treatment with the cream and in corresponding untreated area. The grey boxes denote treated skin and the white boxes untreated control skin (n = 12). Significant increased values after 10 and 20 days.](image1)

![Fig. 2. Transpidermal water loss (TEWL) after treatment with the cream and after challenge of the skin with sodium laureyl sulfate (SLS). The grey boxes denote treated skin and the white boxes untreated control skin (n = 12). Significant lower TEWL after 20 days and after challenge with SLS in treated skin.](image2)
which improved further during the subsequent 2 weeks, data not shown.

Treatment of the foot once or twice daily for 2 weeks did not provide any significant differences in the degree of improvement between the two frequencies of applications, as judged by the expert and the patients, Table 2, Fig. 5.

The thickness of stratum corneum on the proximal and plantar area of the heel decreased, Fig. 6. The proximal area had a significant reduction in thickness already after 1 week, Fig. 6. There was no evidence that the reduction in thickness was more pronounced after 2 weeks in the feet treated twice daily compared to once daily, Fig. 7.

Skin conductance varied between 10 and 50 μ Siemens on the control areas on the feet throughout the study (data not shown). Treatment with the cream increased significantly the conductance on the proximal side of the feet after 1 and 2 weeks (P < 0.003, data not shown). In the plantar area the increase was significant after 2 weeks (P = 0.008) and almost significant after 1 week (P = 0.053, data not shown). There were no significant differences in skin hydration between
once- and twice-daily treatment for 1 week of the proximal and plantar area of feet. $P = 0.27$ and $P = 0.07$, respectively. Neither were there any significant differences between once and twice daily treatment for 2 weeks of the proximal and plantar areas, $P = 0.31$ and $P = 0.40$.

Skin barrier function, measured as TEWL, was not significantly affected by the treatments, Fig. 8.

No serious adverse events occurred during the study. After application of the cream to the forearm one of the subjects reported unpleasant skin reactions (tingling, erythema), which was not visible upon the clinical evaluations. After 1-week treatment of the feet in total 9 patients (20%) reported some kind of sensory skin reaction. Five patients dropped out during the first week and another two dropped out during the second week. Two patients dropped out due to stinging and itching after the first treatment, whereas the other reported reasons not related to the treatment. Two of the patients (5%) scored the degree of smarting and stinging to be ‘moderate’ and 5% to be ‘weak’, whereas the other did not experienced any smarting and stinging. 1 of the patients (2%) reported ‘moderate’ itching and 2 patients (5%) reported very weak itching. Four patients also reported dryness/irritation (very weak to moderate). Another patient mentioned about a transient redness on the heel after the application.

**Discussion**

Non-invasive measurements allow objective characterization of the skin and monitoring of clinical changes during intervention studies of the skin. As expected in this study, the normal skin area on the volar forearm had higher conductance (hydration) and lower TEWL than the xerotic and hyperkeratotic skin on the feet. Treatment with the humectant-rich formulation increased skin conductance in both types of skin and surprisingly also improved skin barrier function in normal skin. Improvement in barrier function was noted as decreased TEWL and reduced skin susceptibility to SLS (measured as TEWL and erythema). Furthermore, treatment of
the feet improved the clinical signs of dryness (xerosis) and cracks (fissures). The patients noted a rapid reduction in skin symptoms and already 24 h after the first treatment the improvement was significant. The instrumental assessments substantiated the subjective improvements, as skin conductance increased in both the proximal and plantar area after treatment for 2 weeks. The abnormal stratum corneum thickness also decreased significantly in the proximal and plantar area. However, the reduced thickness of stratum corneum did not increase TEWL, as have been noted in other studies on hyperkeratotic skin with AHA-treatments. For example, TEWL increased in patients with lamellar ichthyosis after treatment with 5% lactic acid (16), in patients with atopic eczema (12% ammonium lactate) (19), and in xerotic legs in elderly (15% glycolic acid) (17). This result suggests that the present humectant-rich formulation had the ability to improve skin barrier function; clearly shown in the volar forearm skin where TEWL was significantly reduced by the treatment.

Changes in permeability may occur at three different targets in the skin; Cracks is one possible reason to impairment in barrier function in hyperkeratotic and scaly skin (20–28) and consequently a more hydrated stratum corneum is more elastic and resistant to cracking. Another target is the projected size of the corneocytes (29, 30) where larger corneocytes will reduce the tortuous penetration pathway through the stratum corneum (30, 31). Finally, the structure of the barrier-lipids may change. Which one of these targets that is affected by the treatment is not known?

This study also interestingly showed that once-daily application of the humectant-rich formulation was equally effective as the twice-daily applications. Common sense may suggest that more frequent treatment will produce better results. However, our findings are in agreement with the conclusions that twice-daily applications of corticosteroids are not superior to once-daily applications (32, 33). The findings are also compatible with the skin penetration theory and Fick’s law of diffusion, which states that the concentration gradient of the active substance between the outside and the inside of the skin constitutes the driving force for penetration (34). As usually very small fractions of applied actives are absorbed by the skin during the first 24 h, more frequent application of a topical formulation will not necessarily increase the gradient and produce higher concentrations of the active substance deeper in the skin. Thus, the dosage of the humectants on the skin can be seen as infinite, giving a fairly constant driving force for penetration throughout the day independent of application frequencies. Furthermore, studies show that 50% of the applied cream remains on the surface after 8 h (35).

The study also showed that the humectant-rich formulation showed good skin compatibility as the majority of the patients did not report any adverse events. No irritation linked to barrier damage was found, but instead only transient sensory skin reactions, such as smarting and stinging were noted. These adverse reactions are commonly encountered when sensitive skin is exposed to products with low pH and certain ingredients, such as lactic acid (36, 37), urea (38, 39) and menthol.

In conclusion, the present humectant-rich formulation increases skin hydration, removes scales and reduce hyperkeratotic skin thickness. Furthermore, skin barrier function is not weakened, and instead the healthy skin becomes more resistant to external insults by the treatment. Once-daily is equally effective as twice-daily applications.

Acknowledgment

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Address: Marie Loden Euderm Institute Bergshamra Alle 9 SE-17077, Solna Sweden Tel: +46 708285832 e-mail: marie.loden@euderm.se

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Assessment of Aging of the Human Skin by In Vivo Ultrasonic Imaging

Jean de Riga, Ph.D., Catherine Escoffier, M.Pharm., Bernard Querleux, Ph.D., Brigitte Faivre, M.D., Pierre Agache, M.D., and Jean-Luc Lévéque, Ph.D.

Advanced Research Laboratories of L’Oréal, Aulnay-Sous-Bois, (JR, CE, BQ, J-LL), and Department of Dermatology, CHU Saint-Jacques Besançon, France (BF, PA)

The ultrasonic imaging technique that we have developed provides cross-sectional images of human skin in vivo with a resolution of about 80 μm axially (i.e., deep into the skin) and 250 μm lateral (parallel to the surface). In order to study aging skin, we obtained ultrasonic images from the mid-forearm (volar and dorsal sides) of 142 women. Ultrasonically, on the images, the dermis appears composed of two bands: a dark superficial one where the ultrasonic waves are propagated in a relatively homogeneous or non-echogenic medium, and a deeper one, which is lighter in color, suggesting a heterogeneous medium. Our results show that skin is thicker on the dorsal than on the volar forearm. In contrast to previously published results, skin thickness remains constant until the seventh decade of life, diminishing thereafter. The relative thicknesses of the two bands show marked variations with age: a progressive thickening of the dark band, from zero in infants to approximately 75% of total skin thickness in aged subjects, while the light band shows the inverse trend. Comparing the amplitude of the bands on the volar and dorsal forearm, the relative thickness of the dark band is larger on the dorsal (exposed) side and increases with age. These findings and the analysis of variously stained biopsies taken in some of our patients lead us to assign this dark band to a zone in the upper dermis where the collagen network is delicate, dense, and well organized. This is supported by some data in the literature. The thickness of this subepidermal non-echogenic band appears to be a far more sensitive marker of skin aging at the dermal level than is the measurement of skin thickness. J Invest Dermatol 93:621 – 625, 1989

human skin aging is accompanied by many clinical signs, the most evident of which are dryness, color changes (yellowing, uneven pigmentation), wrinkles, and a loss of firmness. These modifications play an important role in our perception and estimation of age. Signs of skin aging appear first in the exposed areas (face, hands, chest) where certain clinical anomalies such as actinic keratosis or solar elastosis, directly due to exposure to UV radiation, can also appear. These clinical manifestations parallel morphologic and structural changes in the skin and are likely related to functional declines. The quantitative description of the biochemical modifications in the main constituents of the skin, together with the disturbances that occur in their organization, have been the purpose of numerous studies. Similarly, the functional alterations in the skin with age have been extensively studied, often by means of non-invasive biophysical techniques. Without going into the details of these numerous publications, we would like to underline some general features that explain why, despite this abundant literature, we still remain unable to clearly explain the various phenomena occurring during the skin aging process. First, the studies undertaken have too often been dealing with the effects of environmental factors rather than the physiologic process of aging. Second, the extreme diversity in the techniques used has frequently led to contradictory results [1].

With regard to studies dealing with the skin structure, too little attention has been paid to the gross changes in the skin structures, which, we believe, is essential for understanding the properties of the skin, while there has been much work on the microscopic organization of the skin or on the ultrastructure of the collagenous component. Finally, it is well known that individual variability increases with age; there is therefore a statistical aspect involved which, no doubt, has contributed to the discrepancies observed in some results. The present study describes a new investigation of the skin as a function of age and attempts to avoid some of the pitfalls listed above. It uses a non-invasive biophysical method, B-scan ultrasonic echography, which is a simple and relatively recent technique [2] for producing cross-sectional images of the human skin. Our imaging prototype produces images representing a cross-section of the skin: 2 cm long over 4 mm deep into the skin with a resolution of approximately 80 μm in depthness. A number of structural elements can be identified and studied on the images [3]. The results are extremely consistent from one observer to another. In order to evaluate the possible influence of the environment on the natural process of skin aging, we compared the images of the volar (protected) and dorsal (exposed) sides of the forearm of 142 women.

MATERIALS AND METHODS

Equipment The use of pulsed ultrasound in dermatology is now well known and has been extensively used since 1982 [4]. The incident ultrasonic energy, partially transmitted and partially reflected at boundary between adjacent structures, generates echos, the amplitude of which is characteristic of the nature of the two
The A-scan signal, obtained at one point, is made of a series of echoes of various amplitude, characteristic of the interfaces encountered.

The acquisition of successive A-scan lines and the conversion of the amplitudes of the rectified signal into grey levels, allows us to form a cross-sectional image of the skin. A heterogeneous medium generates numerous echoes and appears light on the picture. On the contrary, a homogeneous medium does not generate echoes and appears dark. The main feature of our prototype ultrasonic imaging apparatus [5] lies in the large improvement in axial (i.e., deep into the skin) and lateral (i.e., parallel to the surface of the skin) resolution over the commercially available ultrasound echographs used, up to now, in medical research. Our prototype digitizes 100 radio-frequency signal lines produced by a transducer with a central frequency of 25 MHz, focused at 25.4 millimeters, giving an axial resolution of approximately 80 μm and a lateral resolution on the order of 250 μm. Taking into account this latter parameter, the probe is set to move by 0.2 mm steps, giving an effective range of 20 mm. The transducer is housed in a perspex tip filled with an aqueous coupling gel.

All the acquisitions are carried out in a standardized way (same gain and image processing), allowing subject to subject comparison.

**Measurement Protocol** Each image obtained on the video monitor is photographed in black and white using a standardized procedure. The thickness of the various visible “bands” is measured directly in millimeters on the photograph, taking into account the velocity of ultrasonic waves through the skin (1605 m/s) [6]. Each value represents the mean of six determinations regularly spaced.

**Figure 1.** High resolution ultrasonic images of the human skin from (a) a child (6 years), (b) a young adult (31 years), (c) an older adult (49 years), and (d) an aged woman (78 years). Vertical bar: 5 mm; Horizontal bar: 1 mm; S: SENE; D: DEB.

**Subjects** The study concerned the volar and dorsal sides of the mid-region of the forearm of 142 women, with 10 to 20 (mean 15) subjects in each decade of life (0–10 years up to 80–90 years).

**Biopsies** Punch biopsies (3 mm) were taken on the mid-dorsal forearm of three subjects after informed consent. The histologic sections were stained using Eosin/Hematoxylin and Orcein and Luna technique for Elastin.

**Statistics** All the results are expressed as mean ± standard error of the mean for each decade and each side studied. Linear regression analysis was performed using the least-square method on the overall experimental data. Analysis of variance was carried out on the experimental data taking into account the age distribution, in decades.

**RESULTS** Figure 1a–d shows typical ultrasonic skin images obtained on the volar forearm of persons aged 6 years (a), 31 years (b), 49 years (c), and 85 years (d). The skin clearly appears located between the white line produced by the interface between the coupling gel and the stratum corneum (SC) and the more-or-less uniform black area representing the subcutaneous tissue. The junction between the dermis and the underlying fatty tissue is less regular and well-defined than the gel-SC interface. These images show the general trend in skin thickness with age: relatively thin in both children and aged subjects and somewhat thicker in adults. In addition, one can immediately observe below the white line, corresponding to the entry echo, a black zone, previously described [3], corresponding in these conditions to a relatively homogeneous, non-echogenic structure that we refer to as the Sub-Epidermal Non-Echogenic Band (SENB). It has
been previously checked that the thickness of this band is not influenced by the amplitude of the first major echo, generated by the interface between the gel and the Stratum Corneum.

This band, which is not observed in the young, increases with age and represents in the aged almost the whole thickness of the skin (Fig 1d). In contrast, the echogenic band, characteristic of the reticular dermis [3], the Dermal Echogenic Band (DEB), diminishes with age.

**Skin Thickness** The changes in skin thickness as a function of age in the volar and dorsal forearm are shown in Fig 2. There is a highly significant ($p < 0.001$) difference between these sides. The dorsal skin is approximately 17% thicker than the ventral one; however, both are not different beyond 70 years of age.

On the volar forearm, skin thickness does not vary significantly between the first and seventh decade of life ($p > 0.001$), but atrophy appears ($p < 0.05$) after the eighth decade. Trend of dorsal skin thickness with age is somewhat different. A phase of maturation is observed up to 15 years of age ($p > 0.05$), and atrophy begins after the seventh decade ($p < 0.05$). Analysis of variance detects an age-side interaction ($F = 3.07, p < 0.003$) confirming the different behaviors of the two sides (volar and dorsal forearm) with age.

**Thicknesses of the Different Bands** The age relationship of the thickness of the skin, the SENEB, and the DEB versus age are shown in Fig 3a (volar forearm) and 3b (dorsal forearm).

On the volar forearm, the variation of the thickness of the SENEB follows a linear equation ($E_p = 0.03 + 0.0048 \times \text{Age}$) ($R = 0.844, p < 0.0001$). The same holds true for the DEB ($R = -0.454, p < 0.001$). With regard to the dorsal forearm, here again, the SENEB is better correlated with age ($E_p = 0.03 + 0.0063 \times \text{Age}$) ($R = 0.851, p < 0.0001$) than DEB ($R = -0.653, p < 0.001$).

Figure 4 shows that, as a whole, the relative thickness of the SENEB is higher in the dorsal than in the volar forearm ($E_p = 23.3, p < 0.001$). However, the class-by-class differences are only significant in the last 3 decades ($p < 0.05$). Moreover, relative thickness of the SENEB increases more rapidly in dorsal than in volar forearm ($E_p = 4.82, p < 0.0001$). In addition, standard error in the last 2 decades are obviously larger than in the preceding ones.

**DISCUSSION**

Though our results confirm the difference in skin thickness between the dorsal and the volar forearm, they differ from those previously published by Tan et al [7] and Escorifer et al [8] concerning skin thickness as a function of age. These authors both carried out A-scan ultrasound measurement on the forearm. Our results show a skin thickness 15% greater on average than that found in these two studies. By obtaining images of the skin, it can be seen that the skin is not limited by two well defined lines. Although the gel-stratum corneum interface is well characterized, the limit of the dermis is difficult to delineate. In the echographic A-scan technique, it is therefore difficult to determine which echo exactly corresponds to the dermis-hypodermis interface. In the B-scan technique, this interface is more precisely determined directly on the picture where the doubt on one line is removed by the preceding or the following one. In addition, skin thickness determination by A-scan technique is based on the selection of the last major echo

![Figure 2. Variation of skin thickness (forearm) with age. Dorsal side: solid line; ventral side: dashed line.](image)

![Figure 3. Variation with age of the thicknesses of SENEB, DEB, and total skin. a: Ventrail side; b: dorsal side.](image)

![Figure 4. Variation with age in the relative contribution (%) of the SENEB to the total skin thickness. Ventrail side: dashed line; dorsal side: solid line.](image)
induced by the dermis-hypodermis interface. In B-scan, the interface is delineated by the last of all the echoes, related to the skin structure. Differences in the population cannot explain these discrepancies because the results obtained by these two authors are indeed superimposable, although the populations studied were different.

The problem concerning the progressive reduction in skin thickness with age has been discussed elsewhere [8,9]. Is this reduction continuous after 30 years of age [7], or is skin thickness relatively constant until approximately 65 years, becoming thinner thereafter [8]? A comparative study of these results favors the second hypothesis [9].

The most striking result of the present study is the marked variation with age of the two structural elements that this new technology is able to distinguish. As can be seen in Figs 3a,b, these two structural elements inversely change with age. The SENEB, hardly visible in the child, represents nearly 75% of total skin thickness in the aged subject, whereas the thickness of the DEB decreases almost continuously. The interindividual variations of the percentage of the SENEB in the skin are larger in the old groups than in the young groups, a frequent phenomenon observed in studies on skin aging. These large and continuous age-related changes raise the question of the actual anatomic identities of these two bands.

In the ultrasonic technique, the signal received by the detector and converted into grey levels corresponds to echoes produced by partial reflection of ultrasonic waves at the interfaces of media with different acoustic properties. A black zone therefore corresponds to a homogeneous or near-homogeneous medium composed of structural elements whose spacial periodicity is greatly inferior to the wavelength used (60 μm under our experimental conditions). A white or grey zone corresponds to medium composed of more heterogeneous structures forming a multitude of interfaces at distances superior or of the same order as the wavelength used. In a previous work, Querleux et al [3], studying an adult population interpreted the SENEB as image of the adventitial dermis. The nature of this upper or papillary dermis, a well-vascularized area composed of thin collagen bundles, corresponds to the ultrasonic criteria of a homogeneous and therefore non-echogenic medium. In contrast, the reticular dermis, composed of large collagen bundles, would correspond to the DEB. It is logical to interpret the ultrasonic images that reveal gross structural elements in terms of the density and organization of the collagen [11], the principal component of the dermis (approximately 60% of the dry weight). Recent work has shown that the size distribution of the collagen bundles varies with their location within the dermis [11,12]. In the upper dermis, they appear thin, forming a “feltwork” composed of thin bundles closely interwoven, while the reticular dermis, composed of larger wavy bundles, loosely interwoven, contains numerous voids filled by hydrated proteoglycans or glycosaminoglycans.

This can be observed in Fig 5, which shows a cross-section of the skin of a 37-year-old subject: the histometric differences in the bundles clearly appear according to their location within the dermis (superficial (Fig 5a), central, or deep (Fig 5b)). The progressive increase in the amplitude of the SENEB with age could therefore reflect a relative increase in thin collagen bundles with regard to larger ones. This is confirmed by optical microscopic examination of histologic cross-sections in agreement with the findings of Lovell [12]. Other authors, including Lavker [11], reported that in the child the papillary dermis was hardly distinguishable from the reticular dermis. This finding fits with the absence of SENEB in the skin images of children. However, a more precise interpretation of this SENEB needs deeper structural investigations.

In Fig 4, it can be clearly seen that the SENEB thickness is related to light exposure. It has been recently shown that solar damaged skin displays a characteristic low dermal echo amplitude, as observed by A-scan ultrasound echography [13]. This would corre-

Figure 5. Histology of the skin forearm of a 37-year-old woman (Hematoxylin/Eosin staining). a: Epidermis and upper part of the dermis; b: lower part of the dermis.
spond to the presence of the SENEB in the B-scan technique. To check this hypothesis, histologic examinations were carried out on three subjects having a significant SENEB (30% to 70% of the total skin thickness). Both volar and dorsal forearm show that elastic material is only detectable in the form of thin fractionated fibers. We therefore consider that elastic material is not the unique cause of the reduction in the echo amplitude leading to the SENEB. This can also be due to collagen bundles too thin and too dense to be detected by the ultrasonic waves with a resolution of approximately 80 μm.

The skin has often been described by various authors as a highly resistant organ whose fundamental properties remain intact throughout most of the life span. This view is supported by results such as those concerning skin thickness and extensibility [8]. However, recent measurements of mechanical properties as a function of age have shown a relatively rapid and progressive decline in the ability of the skin to compensate the deformation [8,14]. The present study also highlights important changes in the structure of the skin which in turn might also explain the results obtained concerning its elasticity. Thus, in terms of elasticity and ultrasonic imaging, the skin appears to be an organ whose structure, composition, and some functions begin to change immediately following maturity. This is in agreement with the opinion that some specialists have repeatedly stated [15]. Clearly, the relative thickness of the SENEB appears to be a more sensitive parameter for skin aging than the total skin thickness.

REFERENCES


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Preliminary study on the development of an antistretch marks water-in-oil cream: ultrasound assessment, texture analysis, and sensory analysis

Cătălina Bogdan¹
Mirela L Moldovan¹
Ioana Manuela Man²
Maria Crişan²

¹Department of Dermopharmacy and Cosmetics, Faculty of Pharmacy, 
²Department of Histology, Faculty of Medicine, University of Medicine and Pharmacy “Iuliu Hațieganu”, Cluj-Napoca, Romania

Purpose: Striae distensae represent the result of the failure of the dermis to sustain intrinsic mechanical forces. Intensive moisturization of the lesions and use of emollient oils have been recommended for the prevention and treatment of striae distensae rubra. The aim of this research was to formulate an emollient water-in-oil cosmetic cream containing argan oil, which may be helpful in the prevention or early treatment of striae distensae.

Patients and methods: Sensory evaluation of the consistency, firmness, adhesiveness, oiliness, spreadability, and rapidity of penetration into the skin was evaluated by 22 volunteers using 10-point scales for each descriptor. The instrumental characterization of the cream was performed using Brookfield® CT3 Texture Analyzer. The cutaneous changes induced by the topical use of the cream were evaluated by assessing the thickness of the epidermis, hydration, and elasticity of the skin using DermaLab® Combo scanner.

Results: Ultrasound measurements showed an improvement in the elasticity of the epidermis following the application of cream. The product was well tolerated and appreciated by the consumers in terms of its spreadability, penetration ability, and lack of stickiness. The values recorded for texture analysis were firmness 10.16±0.15 mJ, adhesiveness 30.94±6.87 g, consistency 1229.50±119.78 g, spreadability 481.50±39 g, and stringiness 0.56±0.09 mJ.

Conclusion: A water-in-oil cream containing argan oil and emollient ingredients with appropriate physical characteristics was obtained. In vivo study of clinical efficacy revealed a positive effect on increasing the skin elasticity, suggesting that the cream may be helpful in the prevention or early treatment of striae distensae.

Keywords: striae distensae, cosmetic cream, sensory properties, cream evaluation

Introduction

Striae distensae, also known as stretch marks, are the result of the failure of the dermis to sustain intrinsic mechanical forces. They are depressed lines or bands of thin, reddened skin, which later become white, smooth, and shiny, affecting almost half of adolescents and young adults, especially pregnant women. They occur most commonly on the abdomen during and after pregnancy (striae gravidarum) and on the breasts after lactation.¹ They also occur on the buttocks and thighs, the inguinal areas, the posterior zone of the arm, and over the knees and elbows in children during the growth spurt of puberty. The shape of the lesions is linear or fusiform, with variable length. Their surface is often smooth and tense when the striae are recent. Older lesions tend to become crumpled and atrophic, giving the sensation of vacuity at palpation. They are hairless and no sweat or sebum excretion seems to be present. Striae distensae are a reflection of “breaks” in the connective tissue. Skin distension may lead to excessive...
mast cell degranulation and subsequent damage of collagen and elastin fibers.\(^2\)

In striae distensae, both the mechanical functions and the structure of the dermal fibrous networks are modified and the epidermis also becomes thinner. Striae result from ruptures in the direction where the tissue is the weakest to sustain the mechanical stress. As a result, the axis of striae is oriented along the extension lines and the alterations in the matrix structure occur in the direction of the long axis of the striae. The causes responsible for this process are represented by factors distending the skin, such as fat expansion when gaining weight, visceral pressure during pregnancy, muscular hypertrophy, and movement-related skin extension. Compared to normal skin, striae distensae have diverse colors. Recent lesions look reddish at first and finally become white, but sometimes the color palette is broader. Blue striae are characteristic in case of patients with endogenous or exogenous hypercorticism.\(^1\)

During the early stage of striae distensae (striae rubra), there are a few options to improve the appearance of stretch marks, such as pharmacologic and nonpharmacologic treatment and also procedures such as peeling, microdermabrasion, laser therapy, and surgical methods. For the treatment of striae distensae rubra, intensive moisturization of the lesions and use of vitamin C, fruit acids, and retinoids show a positive effect. When stretch marks become white (striae alba), they become difficult to treat and only few treatment modalities exist.\(^1\) Overall, in the management of striae distensae, prevention is a priority, with emphasis on topical formulations that maintain the elasticity and hydration of the skin.

In order to improve the skin condition predisposed to stretch marks, an emollient water-in-oil (W/O) cream containing argan oil was formulated and tested. Formulation of a cosmetic product represents a challenging work, especially in terms of stability and textural and sensorial properties of the final product.\(^4\) Rheological properties of the emulsions offer useful information about the colloidal structure of the systems and long-term stability. Besides, sensory characteristics of the emulsions are related to rheological properties. A combined approach using texture analysis for evaluation of the mechanical characteristics of emulsions associated with the sensory profile could be helpful in the cosmetic emulsion formulation process.\(^5\)

Evaluation of efficacy of a cosmetic formulation requires an objective measurement tool. For this purpose, high-frequency ultrasound can be a useful tool to evaluate the skin improvements during the clinical trial. Ultrasonography is widely used in clinical medicine as a noninvasive method of diagnosis. During the past decade, diagnostic ultrasonography has been used in clinical dermatology as well because of the multiple benefits. High-resolution ultrasound systems with probes of at least 20 MHz can provide useful details regarding skin lesions such as tumor extension and inflammatory infiltrate. High-frequency ultrasound is also an appropriate tool for monitoring the evolution and therapeutic efficacy of diseases associated with skin sclerosis (eg, morphea, systemic scleroderma, and scleroderma-like diseases).\(^6\)–\(^10\)

Ultrasonography represents a valuable tool that can be used to evaluate the normal skin in a rapid and noninvasive way through cross-sectional images, especially for the measurement of skin thickness. Skin thickness is considered an objective physiological parameter for monitoring the influence of endogenous or environmental factors on skin structure. It also reflects changes in the cutaneous structure during studies that assess the effects of topical and systemic drugs or studies on efficacy of cosmetic creams. Currently, many techniques are used for assessing skin thickness such as pulsed ultrasound, conventional ultrasound, and skin-fold measurements.\(^8\)–\(^14\)

The main objectives of the present study were:

- Preparation of the emollient cream containing argan oil and the most suitable substances selected as ingredients for the cosmetic cream base.
- Assessment of sensory properties of the cosmetic cream using volunteers’ evaluation as an innovative tool for predicting skinfeel properties.
- Assessment of firmness, consistency, adhesiveness, and stringiness of the cream performed using texture analysis.
- Ultrasound assessment of the cutaneous changes induced by the topical use of the antistretch marks cream.

**Patients and methods**

**Cream preparation**

Argan oil (Transvital Cosmetics, Cluj-Napoca, Romania) was selected as active ingredient of the W/O cream. The ingredients used were glyceryl stearate (Elemental, Ora-dea, Romania), Rapithix A 60 (sodium polyacrylate [and] hydrogenated polydecene [and] trideceth-6; Ashland Inc., Covington, KY, USA), Montane 481 VG (sorbitan oleate [and] beeswax [and] hydrogenated castor oil [and] stearic acid; Seppic, Paris, France), Estasan GT8-60 (caprylic/capric triglycerides; Croda, Snaith, UK), Euxyl PE 9010 (phenoxyethanol [and] ethylhexylglycerin; Schülke & Mayr, Norderstedt, Germany), silicone oil (Elemental), and butylated hydroxyanisole (Sigma-Aldrich Co., St. Louis,
MO, USA). The cocoa butter, carbopol 940, glycerol, and magnesium sulfate were supplied by Vitamar, Bucharest, Romania. The following other materials were used: paraffin oil (Remed Prodimpex, Bucharest, Romania), cetaceum (Cognis, Monheim, Germany), cera alba (Mosselman, Ghlin, Belgium), cetylstearyl alcohol (Sabo, Levate, Italy), and distilled water (European Pharmacopoeia). All substances and reactants used were of pharmaceutical purity.

The W/O cream was prepared by heating separately the aqueous phase and the oily phase containing the lipophilic surfactants and the active ingredient. The aqueous phase was added to the oily phase under agitation at high temperature at 50°C ± 2°C, for different time intervals.

**Evaluation of sensory properties**

Sensory analysis represents a valuable tool in qualifying consumer perception, regarding a cosmetic product. Sensory evaluation provides helpful input to formulators and supports them to improve the texture properties of the cosmetic product. The sensory panel consisted of 22 volunteers aged from 22 years to 34 years. The volunteers were asked to fill in a questionnaire evaluating the sensory properties of the tested product from their point of view. They received the cosmetic formulation and the analysis form containing instructions of the sensory evaluation for the firmness, stickiness, consistency, spreadability, oiliness, and penetration degree into the skin, following a 1 to 10 scale for each descriptor (1 minimum and 10 maximum of a characteristic). In order to facilitate the evaluation process, reference standards of the scale (values 1 and 10) were made available to the volunteers.

Sensory attributes were evaluated between two fingers or when rubbed into the skin on the dorsal side of the hand. Thus, firmness was evaluated as the force necessary to press the surface of the sample (0.2 g) between two fingers, while the adhesiveness of the cosmetic product was appreciated as the work necessary to overcome the attractive forces between the surfaces of the two fingers joined together by a layer of cosmetic cream. The assessors evaluated consistency as the perceived amount of sample (0.2 g) between the two fingers. Each sample was characterized also regarding spreadability (the ease of spreading the cosmetic emulsion over a given distance), oiliness (the greasy feel perceived after cosmetic product application), and the penetration degree (the moment when the product is no longer felt at the skin surface).

**Texture analysis**

Texture profile analysis was performed using CT3 Texture Analyzer (Brookfield Engineering Laboratories, Middleboro, MA, USA). The following parameters were calculated: firmness, consistency, adhesiveness, stringiness, and spreadability.

The assessment of firmness, consistency, adhesiveness, and stringiness of the cream was performed using fixture base table (TA-BT-KIT) and back extrusion cell (TA-DEC), while the probe penetrated into the sample containers, to a depth of 25 mm at a rate of 2 mm/s. The force exerted to the probe was recorded using Texture ProCT Software 1.5 (Brookfield Engineering Laboratories, Middleboro MA, USA). The spreadability test was performed using fixture base table (TA-BT-KIT) and spreadability accessory (TA-SF). A conical shape sample holder was filled evenly with the sample while the cone analytical probe was forced down into each sample at a defined test speed (2 mm/s) and to a defined depth (15 mm). The samples were analyzed in triplicate, and the average values were calculated.

**In vivo study design**

A pilot study was performed on 12 female volunteers with age between 22 years and 60 years, who used the tested cream during 7 days. Every subject was informed about the nature and the purpose of the study and signed an informed consent before enrolling into the study. The study was carried out according to Declaration of Helsinki, regarding Ethical Principles for Medical Research Involving Human Subjects and has been approved by the Research Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy (registration number: 534 and date of approval: December 23, 2015).

The cosmetic product was applied twice daily, by massage, at the upper arms level on the area predisposed to stretch marks occurrence. All measurements were made in the same area in controlled temperature and humidity conditions (T = 22°C, relative humidity = 50% ± 5%). The volunteers have been preconditioned in the test room for at least 15 minutes before the measurements.

The instrumental assessments were carried out at the beginning of the study (t0) and at the end of the study (t1). For every subject, the following parameters were measured: thickness of the epidermis, the hydration level of the stratum corneum, and the elasticity of the upper skin layer.

**Volunteer selection**

**Inclusion criteria**

The target population was composed by the patients predisposed to stretch marks occurrence due to important variation in weight, glucocorticoid treatment, genetic influence, or after giving birth.

The volunteers included in the study accomplished the following criteria: absence of cutaneous diseases and absence
of any type of lesion on the interest area that could interfere with evaluation study.

Exclusion criteria
The study excluded patients with known allergies to one of the cream components, with known skin diseases and those who used topical treatment for increasing the elasticity of the skin in the last 2 months.

Ultrasonographic evaluation
The cutaneous changes induced by the topical use of the cream in the sites predisposed to stretch marks at the arms level were assessed with DermaLab® Combo (Cortex Technology, Hadsund, Denmark), a computer-supported skin diagnostics system equipped with a rotating high-resolution ultrasound sensor probe (20 MHz).

DermaLab® Combo represents a complex instrument for skin analysis, which combines ultrasound assessment with hydration and elasticity measurements and may be used in order to assess the efficacy of topical applied therapies or cosmetic creams. Previous studies have shown that the thickness of the epidermis and dermis, as well as the dermal density represents important parameters that assess the cutaneous regeneration process, hydration is important for all skin functions and also to improve skin appearance, and elasticity is important to prevent stretch marks.16

The thickness of the epidermis was obtained by calculating the mean of three measurements performed at three different sites of each image (the two extremities of the analyzed image and the center of the image). For the skin hydration status and elasticity, measurements data collection from the volunteers enrolled in the study consisted of quantitative assessment of hydration level (μS) and retraction time (ms) as an indicator for the elasticity of the skin.

Statistical analysis
The analysis was performed by relating the data of the cosmetic product-treated sites to the corresponding starting value. Data were collected in a Microsoft® Excel file and classified by study code, code of the volunteer subject, and day of the study.

The obtained data were analyzed, calculating the mean and standard deviation for the quantitative variables of every group and the proportions for the qualitative variables. The difference in mean values before and after treatment was tested using a Student’s t-test for paired samples. A P-value <0.05 was considered significant.

In order to evaluate the correlation between the parameters of the sensory analysis, the Pearson’s correlation coefficients were determined. The Pearson’s correlation coefficient is a measure of the linear correlation between two variables. The range of values for the coefficient is between −1 (total negative correlation) and +1 (total positive correlation), where zero values would mean no correlation at all. The dependent variable was considered to be the consistency of the cosmetic product. The variables were also tested for linearity by creating scatter plots. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 19.0 (IBM Corporation, Armonk, NY, USA).

Results
The product was very well tolerated by all the volunteers, without evoking any adverse effects (erythema and pruritus). Thus, this product may be considered as nonirritant, regarding its primary skin tolerance. Subjectively, an increase in skin firmness was noticed by the volunteers enrolled into the study.

Our study revealed significant reduction in the retraction time (time required for the raised skin to return to flat, in ms) from 720.42±108.08 to 569.33±146.30 \( (P=0.019) \). Shorter retraction time in elasticity measurements reveals an improvement in skin elasticity. Although the causes of striae distensae are not elucidated, the condition is known to relate to changes in the structures that provide skin elasticity.17–19

Regarding the hydration level of the stratum corneum, the statistic analysis showed no significant increase during the study. The mean thickness of the epidermis before the application of the cosmetic cream was 893.91 μm, while the thickness increased up to 955.25 μm \( (P>0.05) \).

The general variation pattern of the quantifiable ultrasonographic parameters after cream application is illustrated in Table 1 and Figure 1.

Figure 2 presents medium values of the assessors’ appreciation for each established characteristic of the tested product during the sensory analysis. As we can observe, all volunteers considered that the tested product has a good spreadability, despite the high consistency of the cosmetic cream formulation. The volunteers also appreciated that the product was not sticky and the degree of oiliness felt after

Table 1 Cutaneous parameters quantified by high-frequency ultrasound before and after cream application

<table>
<thead>
<tr>
<th>Parameter tested</th>
<th>Before study, mean±SD</th>
<th>After study, mean±SD</th>
<th>P-value, ( \alpha=0.05 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention time (ms)</td>
<td>720.42±108.08</td>
<td>569.33±146.30</td>
<td>0.019</td>
</tr>
<tr>
<td>Hydration of stratum corneum (μS)</td>
<td>251.75±29.06</td>
<td>257.25±22.53</td>
<td>0.61</td>
</tr>
<tr>
<td>Thickness of epidermis (μm)</td>
<td>893.91±222.73</td>
<td>955.25±93.11</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
application was acceptable. The tested product revealed good penetration ability into the skin.

The Pearson’s coefficient shows that there is a positive correlation between consistency and oiliness of the cream and also between adhesiveness and oiliness. A negative correlation is perceived between penetration degree and consistency values. The correlations between these variables are not very strong, but the results show that there is significance between the coefficients of the sensory analysis (Table 2).

The values recorded for texture analysis were firmness 10.16 ± 0.15 mJ, adhesiveness 30.94 ± 6.87 g, consistency 1229.50 ± 119.78 g, spreadability 481.50 ± 39 g, and stringiness 0.56 ± 0.09 mJ.

**Discussion**

So far, a great number of topical antistretch marks formulations containing herbal extracts have been claimed for their efficacy in the treatment of striae distensae. The present study investigated the potential effect of an emollient W/O formulation containing argan oil on preventing stretch marks. Argan oil is obtained from the fruits of argan trees (*Argania spinosa*) following a multistep process. The acylglycerols constitute 99% of the argan oil including 95% triacylglycerols and the remaining 4% are composed of monoacylglycerols (0.27%–0.65%), diacylglycerols (0.68%–1.53%) and free fatty acids (1.1%–2%). Unsaponifiable fraction constitutes 1% of argan oil and it is represented by carotenes (37%), tocopherols (8%), triterpene alcohols (20%), sterols (29%), and xanthophylls (5%). In extra virgin argan oil, the level of tocopherols varies between 600 mg/kg and 900 mg/kg. Other phenols that may act as antioxidants have been identified by mass spectroscopy. The chemical
composition justifies the use of argan oil in antistretch marks creams for benefits in restoration of the skin water–lipid layer, neutralization of free radical agents, and protection of the conjunctive tissue.20,21

The other ingredients of the cosmetic cream were chosen for the most suitable properties in patients with striae, because in case of antistretch marks cosmetic formulations, the efficacy is given by the actives incorporated in the moisturizing formula and also by the emollient ingredients, whose role is to maintain skin elasticity.

In a previous study on early striae distensae, Sheu et al22 found that sequential changes in elastolysis accompanied by mast cell degeneration occur in the very early stage of striae distensae. Elastic fiber is the primary target of the pathological process and the abnormalities extend as far as 3 cm beyond the lesion into the normal skin.22,23 There are suggestions that deficiencies in elastic properties, endocrine imbalances, and toxins may be factors in the cause of striae distensae.24–27 Hence, an increase in the elasticity of the connective tissue presents an important aspect in the prevention of striae distensae.

Based on these observations, argan oil was incorporated in a W/O formula containing several emollients as mineral oil, silicone oil, cocoa butter, caprylic/capric triglycerides, cetaceum, glycerol stearate, beeswax, and cetylstearylic alcohol. In this formulation, triethanolamine was used to neutralize carbopol in order to achieve maximum viscosity. Glycerin was incorporated in the cream formula as moisturizer to increase stratum corneum hydration. Usually, when it is used as a humectant agent or moisturizer, it is associated with occlusive compounds, in our case glycerol stearate, beeswax, cocoa butter, and caprylic/capric triglycerides.28 Besides, occlusion and moisturizing agents are known to improve the signs and symptoms of scarring. The moisturizing agents reduce excessive scarring through a suppressive effect on collagen production in fibroblasts, while the occlusion regulates epidermal cytokine production and reduces the formation of hypertrophic scars.29 As striae have been suggested to be anatomically similar to scars, it is expected that the occlusive and moisturizing ingredients reduce the signs and symptoms of striae.30

Sensory analysis of the cosmetic cream revealed that the product was well tolerated and appreciated by the consumers regarding its spreadability, penetration ability, and lack of stickiness, mainly due to the emollients with textural qualities. Decreasing the consistency is recommended in order to increase the ease of pick up the cream from the container and to facilitate the cream application because antistretch marks products are indicated to be used for a long period on large body surfaces. Increasing the content of silicone oil and decreasing the cetylstearylic alcohol and beeswax would improve the consistency characteristics and also will ameliorate the oily feel after cream application and the adhesiveness of the cosmetic product.

Table 2 Pearson’s correlation coefficients between the parameters of the sensory analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Consistency</th>
<th>Firmness</th>
<th>Adhesiveness</th>
<th>Spreadability</th>
<th>Oiliness</th>
<th>Penetration degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>1.000</td>
<td>−0.356</td>
<td>0.286</td>
<td>−0.279</td>
<td>0.632</td>
<td>−0.531</td>
</tr>
<tr>
<td>Firmness</td>
<td>−0.356</td>
<td>1.000</td>
<td>0.158</td>
<td>0.073</td>
<td>0.173</td>
<td>0.151</td>
</tr>
<tr>
<td>Adhesiveness</td>
<td>0.286</td>
<td>0.158</td>
<td>1.000</td>
<td>−0.036</td>
<td>0.544</td>
<td>−0.130</td>
</tr>
<tr>
<td>Spreadability</td>
<td>−0.279</td>
<td>0.073</td>
<td>−0.036</td>
<td>1.000</td>
<td>−0.174</td>
<td>0.119</td>
</tr>
<tr>
<td>Oiliness</td>
<td>0.632</td>
<td>0.173</td>
<td>0.544</td>
<td>−0.174</td>
<td>1.000</td>
<td>−0.413</td>
</tr>
<tr>
<td>Penetration degree</td>
<td>−0.531</td>
<td>0.151</td>
<td>−0.130</td>
<td>0.119</td>
<td>−0.413</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Texture analysis and sensory analysis are complementary methods used in order to characterize the sensorial properties of the cream. Sensory evaluation provides useful information about perceptual attributes of the creams and consumer perception regarding cosmetic product, as these contribute to the improvements in the texture properties of the final product. Moreover, the different texturizing excipients reveal different texture properties and show the importance of the choice of excipients in order to obtain an appropriate cosmetic product.15,31

Our study revealed statistically significant changes in the skin elasticity, but no significant changes in the hydration and thickness of the epidermis, probably due to the short period of application of the cosmetic product. In the same time, the preliminary results offer an encouraging perspective for the continuation of the study for a longer time frame and reveal that the ultrasonographic assessment may be an appropriate tool in order to observe the variation in the skin parameters.

**Conclusion**

An emollient W/O cream containing argan oil was formulated. The study of clinical efficacy showed an increase in the skin elasticity; therefore, the formulation may be useful in the prevention and early treatment of striae distensae. For this purpose, the effect should be proven by follow-up, by observing the dynamics of the ultrasonographic parameters for a longer period of time.
Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

References


A systematic review of objective burn scar measurements

Kwang Chear Lee1,4*, Janine Dretzke2, Liam Grover3, Ann Logan4 and Naiem Moiemen1

Abstract

Background: Problematic scarring remains a challenging aspect to address in the treatment of burns and can significantly affect the quality of life of the burn survivor. At present, there are few treatments available in the clinic to control adverse scarring, but experimental pharmacological anti-scarring strategies are now beginning to emerge. Their comparative success must be based on objective measurements of scarring, yet currently the clinical assessment of scars is not carried out systematically and is mostly based on subjective review of patients. However, several techniques and devices are being introduced that allow objective analysis of the burn scar. The aim of this article is to evaluate various objective measurement tools currently available and recommend a useful panel that is suitable for use in clinical trials of anti-scarring therapies.

Methods: A systematic literature search was done using the Web of Science, PubMed and Cochrane databases. The identified devices were then classified and grouped according to the parameters they measured. The tools were then compared and assessed in terms of inter- and intra-rater reproducibility, ease of use and cost.

Results: After duplicates were removed, 5062 articles were obtained in the search. After further screening, 157 articles which utilised objective burn scar measurement systems or tools were obtained. The scar measurement devices can be broadly classified into those measuring colour, metric variables, texture, biomechanical properties and pathophysiological disturbances.

Conclusions: Objective scar measurement tools allow the accurate and reproducible evaluation of scars, which is important for both clinical and scientific use. However, studies to evaluate their relative performance and merits of these tools are scarce, and there remain factors, such as itch and pain, which cannot be measured objectively. On reviewing the available evidence, a panel of devices for objective scar measurement is recommended consisting of the 3D cameras (Eykona/Lifeviz/Vectra H1) for surface area and volume, DSM II colorimeter for colour, Dermascan high-frequency ultrasound for scar thickness and Cutometer for skin elasticity and pliability.

Keywords: Scar measurement, Burn, Objective measurement, 3D camera, Laser imaging, High-frequency ultrasound image, Colorimeter, Cutometer

Background

Burn injury is one of the most common type of traumatic injuries in the world with an estimated incidence of 1.1 per 100,000 population [1] and remains one of the leading causes of deaths, accounting for 5.2% of 5.1 million deaths due to injuries and violence in 2012 [2]. In the last few decades, major advances in burn care have greatly improved survival rates [3] and an increased number of patients are surviving large burns. Non-fatal burns however is a leading cause of morbidity, as many of these patients develop hypertrophic scars that may lead to significant disfigurement and disability (e.g. contractures).

In order to assess and track the evolution of scars over time, subjective rating scales have been introduced into clinical practice. These scales in general are free or low cost and require minimal training to utilise. Several such scar scales have been developed and are used widely, including the commonly used Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS) [4]. However, these scar scales are considered to be subjective and the resulting scores can vary between different assessors (inter-assessor variation) [5], different scar severities [6] and age of the scar [7], and some studies have suggested
that more than one rater (sometimes as many as five), and utilising the average, is required in order to produce reliable ratings [7, 8]. The POSAS attempts to improve the method of rating scars by including the patients’ perspective; however, patients’ perception and subjective evaluation of their scars have been shown to be influenced by depressive symptoms [9]. The physical characteristics of scars further add to the complexity of rating as changes in both the vascularity and pigmentation can occur simultaneously, and scars are also rarely homogenous in both colour and texture, which makes estimation of mean values difficult and inaccurate for a human observer.

Standardised, quantifiable, reliable (reproducible) and valid assessment tools that provide a more objective evaluation of scars are essential for monitoring the changes in scar quality over time and also to determine the effectiveness of scar treatments.

The various objective measures that relate to scar severity can be divided into the following categories:

- **Colour**: erythema and pigmentation contribute significantly to the appearance of a scar.
- **Dimensions**: it includes planimetry (surface area), thickness and volume.
- **Texture**: surface texture or scar roughness has a significant effect on the patient’s and observer’s opinion of the scar.
- **Biomechanical properties**: it includes pliability and elasticity. Stiffness and hardening of scars are due to increased collagen synthesis and lack of elastin in the dermal layer and can lead to impairment of skin function, especially when the scar is located around joints.
- **Pathophysiological disturbances**: it includes transcutaneous oxygen tension and transepidermal water loss and moisture content.
- **Tissue microstructure**: new non-invasive in vivo imaging techniques analyse the morphological tissue architecture of the scar, providing measurements previously only possible by histopathological analysis of biopsy samples.
- **Pain/sensation**: pain is a commonly measured parameter in many subjective scales however objective methods to measure it are yet to be available. However the measurement of altered sensation may be useful.

In this article, we describe and compare the underlying principles and performance of various currently available objective measurement devices in order to inform clinicians and researchers about their clinical utility for scar assessment. In addition, we discuss innovative technologies that may be applicable to burn scar assessment in the near future.

**Methods**

**Criteria for considering articles for inclusion**

Published articles that describe non-invasive burn scar measurements were included in this systematic review. Studies that used scar scales which utilise subjective scoring systems were excluded, as studies that made histopathological evaluations of scars via biopsies had no potential to be used in vivo (i.e. requiring the use of ex vivo processing and staining). We chose to include studies comparing the outcomes of wound or scar treatments as well as animal studies and in some cases non-burn scars if appropriate, as excluding these studies may prevent us from identifying new or emerging technologies.

**Search methods**

A computerised literature search (until October 2015) was performed using the web-based Web of Science (http://wok.mimas.ac.uk/; years 1900–2015) and PubMed services (www.ncbi.nlm.nih.gov/pubmed/; years 1950–2015) and utilising the Web of Science Core collection and Medline databases. No language limit was set.

The following search strategies were used:

1) (Skin OR derma* OR dermis OR epidermis OR epiderma*) AND (scar OR cicatrix OR fibrosis) AND (objective OR quantitative) AND (burn OR burn$ OR hypertrophic).
2) (Skin OR derma* OR dermis OR epidermis OR epiderma*) AND (scar OR cicatrix OR fibrosis) AND (evaluation OR assessment) AND scale
3) ((burn$ OR burn) and hypertrophy)
4) ((burn$ OR burn) and (scar or cicatrix))
5) ((scar or cicatrix or fibrosis) and hypertrophy)
6) ((Objective assess* or objective evaluat* or objective measure* or assess$ instrument or assess$ tool or device or measurement system or objective) adj3 assess$)
7) (objective evaluat* or objective measur* or assess$ instrument or assess$ tool or (device or scale or measurement system))
8) NOT (uterus or cardio* or neoplasm or cancer or metastas$ or malignancy)

Web of Science core collection results were further refined by the following terms: surgery or dermatology or critical care medicine or emergency medicine or medicine research experimental or computer science interdisciplinary applications or computer science artificial intelligence or imaging science photographic technology or rehabilitation or medical laboratory technology or engineering biomedical or medicine legal or medical informatics or biophysics or anatomy morphology.
This search produced 5062 articles after duplicates (n = 2334) were removed. After filtering by review of titles and abstracts, 151 suitable articles were chosen.

A separate search was also conducted using the PubMed database (www.ncbi.nlm.nih.gov/pubmed) using the following keywords/terms (including MeSH [Medical Subject Headings] terms): skin AND (scar OR cicatrix OR fibrosis) AND (evaluation OR assessment OR assess OR measure OR measurement) AND (objective OR quantitative) AND (burn OR burns OR hypertrophic). A further broader search was conducted using the following keywords and MeSH terms: skin AND (scar OR cicatrix OR fibrosis) AND (evaluation OR assessment) AND scale. No language limit was set. This search retrieved 613 articles, and after filtering by review of titles and abstracts and removal of duplicates, a further 27 articles were included. The reference lists of the selected articles were also searched for suitable studies, and an additional 12 articles were included.

A search of the Cochrane database retrieved no suitable articles.

A grey literature search was performed using the Bielefeld Academic Search Engine (BASE) database with the term “objective measurement of scarring”. This search included books, reports, papers, lectures, theses, reviews, and primary data document types and excluded article, journals, audio, videos, images, maps, software and sheet music document types. This search produced 180 hits (after 50 duplicates removed), and after review, 6 articles were deemed suitable for inclusion into the review.

Full text articles were obtained for the articles where possible, and a further 28 records were removed after evaluating the full text. Articles which were only available in abstract form and had no extractable data were also excluded.

Thus, the total number of articles selected for review was 157. This includes 9 review articles.

The selection process for the eligible articles is outlined in Fig. 1 below.

**Quality assessment**

The validity and reproducibility of the devices were evaluated when statistical data were available especially in terms of reproducibility of the assessments. Where available, the additional value of the device compared with subjective scar scales and/or other tools is discussed.

In terms of interpreting the intra-class correlation coefficients (ICC), some guidelines have been provided by Landis and Koch [10] for Kappa coefficients (which are also reasonable for the ICC) suggesting that:

- Kappa of <0.00 indicates “poor” agreement
- Kappas from 0.00 to 0.20 indicate “slight” agreement
- Kappas from 0.21 to 0.40 indicate “fair” agreement
- Kappas from 0.41 to 0.60 indicate “moderate” agreement
- Kappas from 0.61 to 0.80 indicate “substantial” agreement
- Kappas from 0.81 to 1.00 indicate “almost prefect” agreement

However, it should be noted that these guidelines are subjective.

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**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart
Feasibility of devices was assessed via the commercial availability, portability and cost of the devices. An economical assessment of the devices based on the literature was not possible due to the lack of such data in the articles; however, several of the companies with commercially available devices were contacted to provide quotes, and although it was not possible to publish the exact prices due to confidentiality issues, the devices are categorised into price ranges (<£5000, £5000–10,000, >£10,000, >£30,000).

Results
Articles, reviews and editorials that described objective burn scar assessments were retained. These were then classified into six categories based on the assessed variables: (1) colour, (2) scar dimensions (e.g. thickness or height, surface area), (3) texture, (4) biomechanical properties (e.g. elasticity, pliability), (5) physiological disturbances (e.g. hydration) and (6) non-invasive morphological imaging techniques.

Colour
Colour is a major factor that affects the aesthetics of a scar and is mainly composed of two components: melanin (the brown pigment made by activated cutaneous melanocytes) and erythema (the redness that is caused by haemoglobin in the dilated/congested remodelled cutaneous vasculature). Other pigments that localise in scars, such as bile and carotene, may also contribute to the overall appearance of the scar. Colour measurements can be used to gauge the effectiveness of anti-scarring treatments since they reflect abnormal skin architecture/composition [11]. Measurement of the scar colour can be complicated by several factors, such as skin layer thickness, reflection from the skin surface and environmental factors including light and temperature. The measurement of erythema is further influenced by patient-related factors such as activity and positioning of affected areas as such movements may affect the blood circulation and hence the erythema of the skin.

Although visual assessment of colour has been incorporated into various scar scales, it is a subjective evaluation method that provides relative rating systems. Even in normal circumstances, the human brain cannot accurately quantify colour or its intensity. A famous recent example of this is the “blue and black dress” which shows that human colour discrimination may be affected by the illuminant colours, level of ambient illumination and the background colours of a visual display terminal [12, 13]. Neuropsychiatric conditions have also been shown to affect colour discrimination [14]. In scars, changes in vascularity and pigmentation occur simultaneously and overlap each other which make colour observation and reporting even more difficult for a human observer, e.g. it is difficult to assess the pigmentation of a scar in a highly vascularised scar as the erythema would obscure the increase or lack of pigment. Additionally, as scars often have an uneven colour distribution, human observers cannot easily or accurately provide a mean value for a certain area.

More recently, several objective and reproducible methods of colour evaluation have been developed and they can be broadly classified as follows:

- Reflectance spectroscopy: tristimulus reflectance colorimetry and narrow-band spectrophotometry
- Laser imaging: it measures the microcirculation in the scar which influences the erythema of the scar.
- Computerised analysis of digital photographs: it can include two-dimensional (2D) and three-dimensional (3D) images which are then digitally analysed to quantify colour values.

Reflectance spectroscopy
Reflectance spectroscopy is a well-established technique of more than 50 years [7] and currently one of the most commonly used methods for measuring colour. Techniques that utilise reflectance spectroscopy quantitatively measure the colour and intensity of reflected light. For example in Fig. 2, when light consisting of red, blue and green is shone upon a surface, if the material absorbs red and green light, then only the blue light is reflected which will make us perceive the material as blue. A biological example is the detection of the oxygenation of haemoglobin. When haemoglobin is illuminated with white light, oxygenated haemoglobin will absorb a higher proportion of blue light and reflect back red light whereas de-oxygenated haemoglobin absorbs more red light and thus appears bluer. In reality, the process is more complicated as the light that is shone (termed incident light) onto biological tissues can be reflected in many different trajectories, and this scattering also influences our perception of the colour of an object.

![Fig. 2 Graphical illustration of the concept of reflectance spectroscopy.](http://commons.wikimedia.org/wiki/File:Simple_reflectance.svg)
Tristimulus reflectance colorimetry and narrow-band simple reflectance (or spectrophotometry) are both based on the principle of reflectance spectroscopy.

Tristimulus reflectance colorimetry [15] describes colour by three values: L* (clarity, lightness or brightness); a*, the amount of red or green (erythema); and b*, the amount of yellow or blue (pigmentation) (see Fig. 3). For example, a white coloured object would have a higher L* value compared to a darker coloured object and a scar that it is redder than normal skin would give a higher a* value than normal skin. Additionally, another approach to quantify colour is by using the saturation or chroma of colour (C*) which is a vector magnitude in the chromatic plane calculated from a* and b* values [16, 17].

There are currently several spectrophotometer devices that utilise the principle of tristimulus reflectance colorimetry, including the Minolta Chromameter [15, 18, 19] (Minolta Camera Co., Osaka, Japan), the Labscan XE [17] (Hunter Associates Laboratory, Inc., Reston, VA), DSM II Colormeter [20], NF-333 [21] (Nippon Denshoku Co. Ltd, Japan), Micro Color (Dr. Bruno Lange GmbBH, Dusseldorf, Germany) [22], X-Rite SP64 Spectrophotometer (X-rite Inc, Michigan, USA) [23] and the Visi-Chroma VC-100 (Bio-photonics, Belgium) [22, 24]. Camera systems such as the Eykona 3D camera can also be calibrated to report colour values using the L*a*b* system [25]. However, a drawback of the Eykona 3D camera is that although it is cost is low, it currently requires consumables in the form of one-use targets (about £70 for 25 targets) that have to be placed next to the area of interest when taking an image, although there are plans to introduce reusable targets in the coming months according to the company.

A study by Li-Tsang et al. [17] showed that the intra- and inter-rater reliability for the Labscan XE device for hypertrophic scars was satisfactory, with an intra-class correlation coefficient (ICC) ranging from 0.95 to 0.99 for intra-rater reliability, and 0.50 to 0.99 for inter-rater reliability in all the three colour parameters (L*, a* and b*). A strong positive correlation was also found between VSS scores and the readings obtained from the Labscan XE device. The device that was utilised in the literature was not portable; however, newer portable versions are currently available. A study by Draaijers et al. showed that the overall evaluations of scar colour with both the Dermaspectrometer and the Minolta Chromameter are more reliable than the visual evaluation and scoring of scar colour carried out by observers using a 10-step score, whereby a score of 1 reflects normal skin and a score of 10 reflects the worst scar imaginable [15]. However, devices that rely solely on tristimulus colorimetry have been shown to have poor correlation scores with patient scar scales when measuring pigmented or hypo-pigmented scars due to the scar scales scoring hyper- and hypo-pigmented scars higher as deviations from normal skin.

Narrow-band spectrophotometry [15] devices on the other hand measures the vascularisation and pigmentation of the scar based on differences in red and green light absorption by haemoglobin and melanin, respectively. The Dermatospectrometer (or the newer version, DSM II Colormeter) [20, 26, 27] (Cortex Technology, Hadsund, Denmark) and Mexameter [20, 28] (Courage + Khazaka, Germany) are examples of a device that uses this principle. In comparison with the Minolta Chromameter and Labscan XE, the Dermaspectrometer is a smaller and hence a more portable device and the use of the erythema and melanin indexes is less complicated to understand and analyse compared to the L*, a* and b* of the Minolta Chromameter. It has also been shown to have a slightly better correlation with clinical scores when compared with the Chromameter [29]. Unfortunately, the Dermatospectrometer has been withdrawn from the market but it has been replaced with a newer model, the DSM II Colormeter. The DSM II Colormeter [20] (Cortex Technology, Denmark) is a small, fully hand-held device that utilises both tristimulus colorimetry and narrow-band spectrophotometry technology and produces reliable readings [20]. It has an improved utility, in terms of cost and assessment time as it utilises one instrument instead of two to obtain both tristimulus colorimetry readings as well as narrow-band spectroscopy readings. The Mexameter also has good intra-observer and inter-observer reliability in scar assessments [20].

Caution however must be used when using erythema to grade the severity of scars. This is because scars can often be very vascular initially but this does not mean that they will become hypertrophic, e.g. in the study by Nedelec et al. [30], the Mexameter was unable to differentiate hypertrophic scars from normal scars as donor...
sites were very erythematous, but we know that donor sites rarely progress to become hypertrophic scars.

A common disadvantage of all of the aforementioned devices is that they employ a small measuring area, e.g. the measuring area for the Minolta Chromameter is only 3 mm [18] and the other devices range from 5 to 8 mm [7]. Therefore, multiple measurements, especially in larger scars, need to be performed to provide accurate scores, but these increase the risk of observational bias. Additionally, these devices also require contact with the skin which can change the colour if too much pressure is applied. Environmental lighting may also affect the readings obtained, although many of the companies of these devices (e.g. DSM II Colormeter) claim that the flash that is utilised by these devices is strong enough to overcome and compensate for any differences in colour caused by indoor lighting.

**Large area spectrophotometry**

Some investigators have attempted to overcome the problem of small measurement areas by utilising camera systems to allow the imaging of larger areas. Cheon et al. utilised digital photographs taken with a digital camera (Nikon D70s, Tokyo, Japan) under the same light source and obtained L*a*b* values for the regions of interest (whole scar lesions when possible) using Adobe Photoshop (Adobe systems Incorporated, San Jose, CA). The test–retest consistency (or intra-rater reliability) of the L*a*b* as determined by the intra-class coefficient ranged from 0.95 to 0.99 and the inter-rater reliability was also good with values ranging from 0.94 to 0.98 [31, 32].

Another method of spectral modelling developed by Kaartinen et al. utilises standardised digital imaging (SDI) with computer controlled lighting to quantify colour changes [7, 8, 33]. This system allows a larger area of the skin to be analysed with an only slightly weaker accuracy compared to the previously mentioned spectroscopy-based systems [33]. This method, however, is yet to become commercially available, but a similar system, Scanoskin (Leniomed Ltd, London, UK), is available. The Scanoskin system utilises polarised light, which has the advantage of blocking the reflectance from the skin which allows better analysis of the epidermal and superficial dermal layers [34]. The system is currently used only to assess burn depth via the imaging of haemoglobin (erythema/vascularisation) and haemosiderin or melanin. Images which are taken (with a modified SLR camera with polarised lenses) are processed by the provided software which splits them into separate erythema and melanin components. Quantification of erythema and pigmentation (melanin) has to be performed on the exported images using software such as ImageJ [35–37].

The evidence for using objective measures in measuring colour is encouraging and is based on a relatively small number of studies, and more research is needed [38].

**Spectrophotometric intra-cutaneous analysis (SIA)**

Analysis of colour information purely in the visible spectrum is insufficient to provide information relating to a lesion’s deeper structures, and it was this realisation that prompted research at the University of Birmingham to extend the spectrum of light used into the infrared region (700–1000 nm). Spectrophotometric intra-cutaneous analysis via the clinical device, SIA Scope, utilises a probe (12 × 12 mm or 24 × 24 mm) that utilises radiation ranging from 400–1000 nm and produces 8 narrow-band spectrally filtered images of the skin which are then processed by software algorithms and allows the visualisation and quantification of melanin, collagen and blood [39]. Although developed for diagnosing skin cancers, it can and has been used to monitor the changes in scar tissue in response to treatment [40].

**Computerised analysis of digital photographs**

Digital photographs can be taken with any standard digital camera, e.g. the Nikon 8400 [19]. Photos are then downloaded for analysis by proprietary software packages such as KS400 (Kontron Electronic GMB, Carl Zeiss Micro-Imaging, Inc., Thornwood, NY, USA) [41] or the freely available ImageJ. One study utilised an artificial neural network to perform chromatic analysis of the digital image of a burn scar [42]. Colour measurements using ImageJ have been shown to be equivalent to those obtained using a colorimeter (Chromameter, Konica-Minolta) [19]. Several studies have attempted to improve the objectivity of photograph analysis of scars by standardising factors such as distance and lighting [19] or using computerised image capturing systems [43–45]. However, even this method fails to allow scars to be compared objectively as humans vary in terms of how we set the measurement criteria for and analyse colour [29, 46] and the photographs have been shown to have limited utility when assessed using computer-based subjective scales [47]. Improved computer programmes may overcome the limitations of the human brain and provide objective analysis of the digital photographs. However, computer programmes cannot properly “see” colour and thus have to convert colour information into digital data, thereby losing valuable information.

Computer programmes utilise two methods to analyse colour. The hue-saturation-value (HSV) method analyses colour by separating it into three main components: hue (dominant wavelength), saturation (amount of white) and value (amount of black). The other method utilises colour models of which there are two main ones: the Red, Green and Blue (RGB) model and the Cyan, Magenta, Yellow and Black (CMYK) model. Measurement techniques using other systems such as the L*a*b* system have also been described [48].
To remove the influence of light and camera settings, generally a card carrying standard colours (e.g. Pantone colour chart [Pantone Inc, USA] [16], Macbeth Digital Colorchecker SG colour chart [Munsell Colour services Laboratory, X-Rite Inc, Michigan, USA] [25, 44]) is recommended to be placed beside the scar being photographed so that every photo taken would include areas of known colour properties, allowing an objective colour evaluation [16].

Table 1 summarises the colour measurement devices in terms of parameter measured, reliability, correlation with clinical score and cost.

**Laser imaging**

The amount of haemoglobin or erythema present in a scar can be measured indirectly via laser imaging [49, 50] that measures the blood flow in a scar. Immature scars show a significantly increased blood flow due to their higher vascularity compared to mature scars. Increased microcirculatory blood flow (as measured by Laser Doppler Flowmetry (LDF)) has also been shown to be a potential indicator for the occurrence of hypertrophic scarring [51]. Hypertrophic scars will typically generate readings that are two to three times greater than that made in normal skin [50, 52, 53] and four times greater than that in a non-hypertrophic scar [50]. Laser-based methods have the advantage of being fast, reproducible and having a good correlation with the VSS; however, they are subject to structural changes in the skin and environmental and body temperature fluctuations [54–56].

Laser-based methods can be divided into three techniques: LDF, Laser Doppler Imaging (LDI) and Laser Speckle Imaging (LSI)/Laser Speckle Perfusion Imaging (LSPI). With the older Laser Doppler Flowmeter, the fibre optic probe is in contact with the tissue surface and is a single-point measure [49, 57]. Laser Doppler Flowmeter [29, 52, 55, 56] systems, such as the DRT4 [53] (Moor instruments, Devon, UK) or the LaserfloBPM [58] (Vasamedics Corp, St Paul, Minnesota, USA), the fibre optic probe is in contact with the tissue surface and provides a single-point measure of an indirect evaluation of scar colour by measuring the cutaneous bloodflow present in a scar [49, 57]. LDF systems are more limited compared to the other laser-based methods (see below) as they measure flow within a small area and, thus, are unsuitable for use with larger, heterogeneous scars.

In contrast, Laser Doppler Imaging (LDI) devices, such as the Lisca PIM1.0 imager (Lisca Development AB, Linköpen, Sweden) and The Moor LDI (Moor Instruments, Devon, UK) [49], utilise a laser beam to scan several points across a tissue surface and generates a 2D colour-coded image that is correlated to the blood flow [49]. They are primarily used for burn depth assessment but have been utilised for scar evaluation [49, 59]. The method is, however, hampered by long measurement times and low resolution [57]. LSI and LSPI are alternative perfusion monitoring techniques that generate rapid, high-resolution images of tissue. As red blood cells move during circulation, dynamic interference patterns that change with time are created. Blood flow maps can then be created from the coherent light that is reflected from stationary tissue, generating a high contrasted speckle pattern that remains static in time. As indicated previously, high measurements reflect high blood flow and immature/hypertrophic scars. LSI devices compare favourably with the more established LDI instruments, but offer advantages in terms of a faster scan time, higher resolutions and the ability to zoom in with increased resolution of a smaller field of view, a feature that is not possible with LDI [57, 60].

A major disadvantage common to all laser imaging systems are that they are not very portable (with the exception of a new commercially available laser speckle imaging device developed by Moor instruments [61]) due to their size and are often very expensive, with costs of >£30,000.

Table 2 summarises the comparison of laser devices in terms of parameter measured, reliability, correlation with clinical score and cost.

**Thermographic analysis of burn scars**

Thermographic cameras detect radiation in the long-infrared range of the electromagnetic spectrum (9–14 μm) and can be used to produce images or videos of that radiation. Thermography can be divided into passive (where the object can be imaged directly as it has a higher or lower temperature than the background) and active thermography (where an energy source is required to produce a thermal contrast between the imaged object and the background). Several studies have looked at using thermography to assess the depth of burn wounds [37, 62–64].

Our literature search however has only been able to identify one small study done in 1985 (n = 12) which utilised thermographic analysis of the scar temperature in an attempt to differentiate hypertrophic and non-hypertrophic scars [65]. No relationship between scar temperature and hypertrophic scar formation was found.

A more recent case report by Horta et al. [66] which utilised a thermography camera (FLIR SC7000 thermography camera; FLIR Systems, Wilsonville, OR, USA) showed that factors such as muscle activity or the lack of mucosa, cartilage and bone can influence the thermographic reading of scars rather than the degree of hypertrophy itself. This further complicates the use of thermography to objectively quantify scars.
<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater Reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computerised colour analysis</td>
<td>Sony Hi-8 Handycam CCD-TR 705E video camera recorder and Adobe Photoshop</td>
<td>Hue, saturation, value</td>
<td>No data</td>
<td>No data</td>
<td>VSS Vascularity score significantly correlated with hue ($r = 0.311$) and saturation ($r = 0.35$) ($p &lt; 0.051$), index with hue and saturation combined correlated even better ($r = 0.42$).</td>
<td>£5000–10,000</td>
<td>Yes</td>
<td>Davey et al. 1999 [16].</td>
</tr>
<tr>
<td>Computerised colour analysis</td>
<td>Nikon D70 camera and Adobe photoshop</td>
<td>Tristimulus colorimetry (L<em>a</em>b*)</td>
<td>0.95–0.99</td>
<td>0.94–0.95</td>
<td>L* and a* values are more important than b* values in distinguishing colour features between normal skin and scars.</td>
<td>No data</td>
<td>Yes</td>
<td>Cheon et al. 2010 [32].</td>
</tr>
<tr>
<td>Labscan XE (non-portable version)</td>
<td>Hunterlab</td>
<td>Tristimulus colorimetry (L<em>a</em>b*), chroma and hue.</td>
<td>Good (0.95–0.99)</td>
<td>Acceptable to good (0.90–0.99, outlier low value of 0.50 for a* [ranged from 0.01 to 0.77])</td>
<td>L*, a*, b* and hue had moderate to strong correlation with VSS pigmentation and vascularity scores. Chroma had low correlation with pigmentation and vascularity ($r = −0.40$ and $−0.17$).</td>
<td>£10,000</td>
<td>Poor</td>
<td>Li-Tsang et al. 2003 [17].</td>
</tr>
<tr>
<td>Labscan XE (portable version)</td>
<td>Hunterlab</td>
<td>Tristimulus colorimetry (L<em>a</em>b*)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>£5000–10,000</td>
<td>Yes</td>
<td>Li-Tsang et al. 2005 [102].</td>
</tr>
<tr>
<td>Chromameter</td>
<td>Konica-Minolta</td>
<td>Tristimulus colorimetry (L<em>a</em>b*)</td>
<td>Acceptable (0.73–0.89)</td>
<td>Good (0.91–0.97)</td>
<td>Unable to differentiate between hypo- and hyperpigmented scars and normal and ‘red’ skin (On Seattle, Hamilton and Vancouver scar scales)</td>
<td>£5000–10,000</td>
<td>Yes</td>
<td>Draaijers et al. 2004 [15], Oliveira et al. 2005 [29].</td>
</tr>
<tr>
<td>Eykona 3D camera</td>
<td>Fuel 3D</td>
<td>Tristimulus colorimetry (L<em>a</em>b*)</td>
<td>No data</td>
<td>No data</td>
<td>Good correlation (Manchester scar scale)</td>
<td>£5000 (not including targets)</td>
<td>Yes</td>
<td>Hallam et al 2013 [25].</td>
</tr>
<tr>
<td>Colorimeter</td>
<td>Courage + Khazaka</td>
<td>Tristimulus colorimetry (L<em>a</em>b*) and ITA (Individual Typology Angle)</td>
<td>No data</td>
<td>No data</td>
<td>Good (0.91–0.97)</td>
<td>£5000–10,000 (including cost of hub)</td>
<td>Yes</td>
<td>van der Wal et al. 2013 [20].</td>
</tr>
<tr>
<td>Mexameter</td>
<td>Courage + Khazaka</td>
<td>Narrow-band spectrophotometry (melanin and erythema)</td>
<td>Good for melanin (0.89–0.97) and acceptable for erythema (0.74–0.90)</td>
<td>Good for melanin (0.95) and erythema (0.82–0.85)</td>
<td>No data</td>
<td>&lt;£5000</td>
<td>Yes</td>
<td>Nedelec et al. 2008 (I) [30], Nedelec et al. 2008 (II) [106], van der Wal et al. 2013 [20].</td>
</tr>
<tr>
<td>Dermaspectrometer/DSM II Colorimeter</td>
<td>Cortex</td>
<td>Both tristimulus colorimetry and narrow-band spectrophotometry</td>
<td>Erythema: 0.29–0.94 Melanin: 0.72–0.87 L<em>a</em>b*: no data.</td>
<td>Erythema: 0.68–0.91 Melanin: 0.91–0.94 L<em>a</em>b*: no data.</td>
<td>Erythema: Moderate but significant $r = 0.50$ (&lt;0.001) Melanin: weak but significant $r = 0.32$ (0.02–0.63) (&lt;0.001)</td>
<td>&lt;£5000</td>
<td>Yes</td>
<td>Gankande et al. 2014 [6], Gankande et al. 2015 [248], van der Wal et al. 2013 [20], Oliveira et al. 2005 [29].</td>
</tr>
<tr>
<td>Standardised digital imaging (SDI) + Spectral modelling (SpM)</td>
<td>Custom made</td>
<td>Estimated concentration change of haemoglobin and melanin</td>
<td>Good for haemoglobin (0.875) and melanin (0.886)</td>
<td>Good for haemoglobin (0.955) and melanin (0.959)</td>
<td>Acceptable correlation with POSAS (0.63 for haemoglobin; 0.60 for melanin) and VSS (0.74 for haemoglobin, 0.53 for melanin)</td>
<td>£5000 (but not commercially available)</td>
<td>Yes</td>
<td>Kaartinen et al. 2011 [7, 8].</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
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</tr>
<tr>
<td>Dermoscopy</td>
<td>Hong Kong Productivity Council</td>
<td>RGB values: lightness and redness</td>
<td>Redness: 0.980 Lightness: 0.965</td>
<td>Redness: 0.93 Lightness: 0.871</td>
<td>Strong correlation between the VSS scores of vascularity and the RGB values of redness obtained from the dermoscope ($r = 0.625$, $p &lt; 0.01$). Strong correlation also found between transformed VSS scores of pigmentation and the lightness of the dermoscope pictures when vascularity was blanched out (i.e. when measuring pure pigmentation) ($r = 0.783$, $p &lt; 0.01$).</td>
<td>No data</td>
<td>Yes</td>
<td>Wei et al. 2015 [238].</td>
</tr>
</tbody>
</table>

$\text{RGB} = \text{red, green and blue}$
Scar dimensions

Surface area and volume

Planimetry is the measure of the surface area of a scar and, when done over time, can be used to assess the contraction or expansion of a scar.

The most basic method of planimetry, that does not require specialist equipment or trained personnel, is the linear method where the maximum length and width of the wound is measured directly on the patient and the surface area is then calculated by multiplying the maximum length and width. As can be expected, this technique is inaccurate as scars are rarely rectangular or square in shape and will produce results that are significantly different from those obtained with tracing and photography methods [67].

The second method involves the tracing of scar margins either on sheets of paper, clear plastic film or any transparent non-stretchable material [27, 46]. The surface area traced on these sheets can then be calculated by outlining wound margin with the tip of a planimeter (Koizuni Sokk Manufacturing Ltd., Nagoaka-shi, Japan) [67] or by digitising the tracings on these sheets and using software such as NIS-Elements (Nikon, Amstelveen, The Netherlands) [27], ImageJ [68] or Digitimizer software [69] to calculate the surface area. Dedicated systems have also been developed such as the Visitrak (Smith & Nephew) which have been shown to have high intra- and inter-rater reliability and high validity in the measurement of the surface area of ulcers [70] although the maximum size of the area that can be measured at a time is limited by the disposable tracing grid used (14 cm × 14 cm).

The third method uses digital photography combined with image analysing programmes such as ImageJ, Image Tool (C.D. Wilcox and colleagues, San Antonio, TX, USA) [29] or Adobe Photoshop (Adobe Systems Inc., San Jose, California, USA) [71] to measure the surface area. A significant problem with 2D photography is that it is subject to parallax errors and projecting a threedimensional object onto a two-dimensional image. Due to this, the 2D surface area (or planimetric area) calculated does not take into account the wound surface topography and will nearly always underestimate the true three-dimensional surface area (see Fig. 4).

With smaller scars, this error would be small but will increase as the size increases. A study by van Zuijlen et al. compared the direct and indirect (through 2D photography) tracing methods [71]. It found that both techniques were reliable ($r \geq 0.82$, $p < .001$) for surface lesions with a scar surface area of 25 cm$^2$, but planimetry by photography was superior to planimetry by direct tracing in respect to inter-observer reliability for surface lesions of 50 and 75 cm$^2$, with increasing scar size resulting in decreasing inter-observer reliability. However, planimetry by direct tracing was more accurate on curved surfaces (e.g. forearm), with a statistically significant reduction of the surface area obtained when compared to results with planimetry after photography. The use of photography [29, 43] to measure surface area, although useful, is subject to variance caused by lighting conditions, distance and camera settings and does not provide any information on volume.

Three-dimensional (3D) measurement systems can overcome the limitation of 2D photograph, and in addition to

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Doppler Flowmeter</td>
<td>Moor</td>
<td>Blood flow</td>
<td>No data</td>
<td>No data</td>
<td>LDF showed significant difference in blood flow within hypertrophic and keloid scars and normal skin (2.6–2.8-fold higher).</td>
<td>&gt;£30,000</td>
<td>Poor</td>
<td>Clark et al. 1996 [56], Timar-Banu et al. 2001 [53].</td>
</tr>
<tr>
<td>Laser Doppler Imaging</td>
<td>Lisca, Moor</td>
<td>Blood flow (red and near infrared wavelengths)</td>
<td>No data</td>
<td>No data</td>
<td>Correlations with clinically assessed grades (VSS) of pigment, vascularity, pliability, and height ranged from $r^2 = 0.63$ to 0.95.</td>
<td>&gt;£30,000</td>
<td>Poor</td>
<td>Stewart et al. 2005 [60], Bray et al. 2003 [49].</td>
</tr>
<tr>
<td>Laser Speckle Perfusion Imaging</td>
<td>Moor</td>
<td>Blood flow</td>
<td>No data</td>
<td>No data</td>
<td>Correlations with clinically assessed grades (VSS) of pigment, vascularity, pliability, and height ranged from $r^2 = 0.73$ to 0.94.</td>
<td>&gt;£30,000</td>
<td>Poor</td>
<td>Stewart et al. 2005 [60].</td>
</tr>
</tbody>
</table>

LDF = Laser Doppler Flowmetry; VSS = Vancouver Scar Scale

Fig. 4 The 2D or planimetric area (in pink) is always smaller than the 3D area (in blue). (Source: Kwang Chear Lee)
surface area measurements, the 3D camera systems are also able to measure the volume of scars much more quickly and easily compared to traditional moulage and moulding [72] methods.

A 3D image can be achieved via various methods. A method that is commonly used in the medical is stereophotogrammetry. These systems are non-contact and involve taking two or more pictures using either one or multiple cameras which can be on the same device (e.g. Eykona wound measurement system, Fuel 3D, UK [25]) or separate devices (e.g. 3D MD static systems, 3dMD, USA [73]). Some authors have even developed their own systems with standard cameras (e.g. Stereogage optical topometer (Korea University, Seoul, South Korea) with PC vision plus (AES, Sydney, Australia)) [74]. Other devices utilise mirrors to achieve a similar effect for, e.g. LifeViz I, II, Mini or Micro (Quantificare S.A., Sophia Antipolis, France) [75, 76] and Vectra H1 3D imaging system (Canfield Scientific Inc, Fairfield, NJ, USA) [77–80]. Other systems utilise the projection of a complex speckled pattern in combination with a colour camera to produce the 3D images [81].

These software are able to provide information about the surface area [82] and tissue volume above the skin [83] (including correction for curved surfaces) as well as geometry, texture and, as mentioned above, the colour of scars for which the performance of the Eykona device has been shown to compare favourably with the subjective Manchester Scar Scale (MSS) [25]. These devices share a few common drawbacks. Firstly, none of them have been validated in scar studies, but their ability to measure the area [83–85] and volume of wounds and tissue (e.g. breasts [82]) has been shown in other non-scar related studies. Additionally, the maximum area that can be imaged is limited to the size of about an A4 size sheet of paper which is not ideal for large burns scars. Furthermore, although stitching of images is possible, this really only applies to the face as it is easy to identify anchor points such as the eyes and nose, but to do so for other highly curved surfaces such as the forearm or the whole body would be technically challenging and time consuming and requires high-end hardware and thus a true 360° view would not be easily possible [80]. Hairy areas of the body can also pose a problem [80].

The LifeViz and Vectra H1 systems have an advantage over the Eykona in that they have adjustable light-beam pointers to aid positioning and do not require one-use disposable targets which the Eykona system does but they are also significantly more expensive. Furthermore, the Eykona is no longer being developed by the company and has not been updated recently, thus its resolution is significantly lower (250 micron sampling via two 5 MP sensors) [86] compared to the Lifeviz Mini (13.5–24 MP, 0.5–2 mm geometry resolution) [87] or Vectra H1 cameras (18 MP, 0.8 mm geometry resolution) [88].

More recently, light field or plenoptic technology has been introduced. Cameras utilising this technology (Raytrix 3D camera systems, Raytrix, Germany [89]) capture information about the intensity and also direction of the light rays utilising an array of micro-lenses [89]. The images or data are then processed and merged using dedicated image analysis software into a single 3D image. Additionally, other commonly used 3D imaging techniques include structured light scanner systems (or coherence scanning interferometery) such as the Artec [90] (Artec Group,USA/Luxemborg/Russia) and ATOS series of scanners [91], and laser scanning devices such as the Minolta Vivid 900 or 910 3D linear laser scanner (Konica-Minolta, Osaka, Japan) [92, 93]. Whole body scanners such as the Cyberware Whole Body Color 3D Scanner (Model WBX, Cyberware Inc, Monterey, California) [94] are also available. These other systems have the ability to scan much larger areas (up to the size of a car with some systems) compared to the Eykona, Lifeviz and Vectra; however, they have not been specifically manufactured or optimised for medical use. For example with the Artec Eva system, the software supplied is able to calculate the surface area and volume of an object on a flat surface but not on curved surfaces. Specialised 3D analysis software such as Rapidform (Inus technology, Seoul, South Korea) [93] is required to measure and quantify surface area and volume information obtained from these scans. The authors are not aware of any published studies that have validated the surface area and volume measurements produced by these devices or software.

A different approach to calculating the surface area of scars is through the use of a combination of 2D photography and 3D models. The Burncase 3D (RISC Software GmbH, Austria) software has been developed for the estimation of burn surface areas primarily but it theoretically can be adapted to measure the surface area of scars. With the Burncase 3D programme, 2D photographs of the lesions are superimposed onto a 3D model that can be adjusted according to the height, weight, age and gender of the patient. The outline of the lesion is then traced onto the 3D model from the photographs (which can be multiple and is aided by an automated alignment algorithm that uses corresponding landmarks to allow quick matching [95]) and the software then estimates the surface area. The areas can also be classified into different categories if needed (e.g. normal and hypertrophic scar areas) and thus useful to track the progression of the wounds from time of burn through to scar formation. As it uses standardised 3D models to estimate surface area, much work is still required to validate the accuracy and precision especially in small children (currently in
progress [96, 97]) and obese patients [95]. In a study which utilised mannequins, the inter-class correlation between the single raters of the mean percentage of artificially created burn areas was 0.988 with relative underestimations of burn wound areas of 0.4 % in the child mannequin, and overestimations of 2.8 and 1.5 % for the female and male mannequins when compared to areas as measured with 2D planimetry imaging [97].

Table 3 below summarises the comparison of 3D measurement devices in terms of parameter measured, reliability, correlation with clinical score and cost.

### Thickness
The accuracy of subjective estimation of scar thickness has been shown to be quite low, 67 % (when measured against ultrasound measured thickness) [98] and thus unreliable.

Objective thickness or height of a scar can be evaluated by measurement by 3D photography (see above) or the use of negative–positive moulage [99]. A negative–positive moulage is performed by firstly making a negative impression cast (negative moulage) of the scar using materials such as alginate, silicon, siloxane [58, 72], dental impression material [100] or plaster of paris. A positive impression cast (positive moulage) is then made by pouring a material that will harden (e.g. plaster of paris, wax) into the negative moulage. Once hardened, this positive moulage can then be measured. These techniques have some limitations and are inaccurate as the portion of the scar below the surface of the skin is not included in the measurement [101].

This limitation can be overcome by using high-frequency (5–20 MHz) ultrasound systems such as the Tissue Ultrasound Palpation System (TUPS; Biomedical Ultrasonic Solutions, Hong Kong) [102–105], the Dermascan C [30, 53, 106, 107] (Cortex, Hadsund, Denmark) devices, Acuson Sequoia 512 [108] (Siemens, Germany; highest frequency probe available is 10 MHz), HDI 5000 (Philips, Amsterdam, Netherlands) [109], and the Dermcup 2020 (Atys Medica, Soucieu-en-Jarret, France) [110]. High-frequency ultrasound systems have previously been used in many dermatological applications [111].

Ultrasound skin imaging is performed by firing an acoustic pulse into the skin and measuring the acoustic response from the skin which is picked up by an ultrasound transducer. The signals are then processed, and a cross-sectional image is produced which represents an intensity/amplitude analysis of these returned signals. Areas with small changes in density between structures such as scar tissue and fat will produce a low reflection and be visualised as dark colours, whereas areas with significant changes in density between structures (e.g. healthy dermis) will be visualised as bright areas (Fig. 5).

An advantage of ultrasound systems are that they allow real-time measurement on changes of scar thickness upon pressure loading [112]. Additionally, high-frequency ultrasound systems will also allow the identification of aberrant structures within the scars which may affect treatment [113].

The frequency of the ultrasound determines the resolution and penetrance of the measurement. A low frequency will allow deeper penetration but lower resolution images, whereas a higher frequency will have a shallower penetration but produce higher resolution images (Fig. 6). High-frequency ultrasound systems utilise a frequency above 18 MHz to obtain images of the skin structure with acceptable resolution. In earlier studies, 7.5-MHz probes have been used to measure and track the change in thickness of healing burn scars [101, 114]. These lower frequency systems allow evaluation of deeper tissues (penetration of >15 mm) but have a low resolution of 2–3 mm which may not be sufficient for the evaluation of superficial skin structures [115]. More recently, higher frequency ultrasound probes (20 MHz) have been used to allow more detailed images of the structures of the skin to be visualised, producing higher resolutions of at least 50 μm [115–117]. Probes with frequencies below 50 MHz are advised as systems with higher frequencies and will not be able to penetrate to the average depth of hypertrophic scars which is around 4–5 mm.

It is advisable to always check with the manufacturer the actual penetrance of the systems as cheaper portable ultrasound systems (e.g. Dermalab USB Ultrasound, Cortex, Hadsund, Denmark) only penetrate a maximum of 3.4 mm despite being a 20-MHz system [6].

These high-frequency ultrasound devices both show good inter-observer reliability and moderately correlate with the modified VSS [118] (modified version of the Vancouver Scar Scale by Nedelec et al.), with the Dermascan C system having the better correlation of the two (0.41–0.50 versus 0.34). It has to be noted that the VSS measures clinical scar thickness (i.e. the thickness of the scar that is above the surface of the skin), whereas the two ultrasound systems measure histological thickness (i.e. the whole thickness of the scar above and below the surface of the skin). The Dermascan system would thus be preferred, although it is more expensive than the TUPS (however at the time of writing, there was no method to purchase the TUPS from their website). Other ultrasound systems that are commercially available include the Acuson Sequoia 512 (Siemens, Germany) [119], Episcan (Longport, USA) [120, 121] and the DUB®SkinScanner (EOTech, France) [122], although at present there are no published studies that have utilised these for scar measurement.

Ultrasound systems that can capture a 3D image of a scar have now become commercially available, albeit
<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater Reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eykona 3D camera</td>
<td>Fuel 3D</td>
<td>Surface area and volume</td>
<td>Intra-operator variability: area: 0.9 %; volume: 4.0 %</td>
<td>No data</td>
<td>Surface area: ICC = 0.99 (Coefficient of variation 5.9–6.8 %)</td>
<td>No data</td>
<td>£10,000–£15,000</td>
<td>Paterson et al. (Eykona Medical Imaging FAQ) [86].</td>
</tr>
<tr>
<td>Lifeviz I, II, Micro</td>
<td>Quantificare</td>
<td>Surface area and volume</td>
<td>No data</td>
<td>No data</td>
<td>Surface area: Excellent level of agreement with Vistrak (ICC 0.96, 95 % CI 0.93, 0.97); however greater level of variability in larger wounds especially circumferential wounds. Volume: $r^2 = 0.9678$ when correlated with actual volumes of model scars</td>
<td>No data</td>
<td>£10,000–£15,000</td>
<td>Yes</td>
</tr>
<tr>
<td>Vectra H1</td>
<td>Canfield Imaging Systems Inc.</td>
<td>Surface area and volume</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>£10,000–£15,000</td>
<td>Yes</td>
<td>Tzou et al. 2014 [256], Urbanova et al. 2015 [80].</td>
</tr>
<tr>
<td>Artec Eva</td>
<td>Artec</td>
<td>Surface area and volume</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>&lt;£10,000 (depends on package)</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Minolta Vivid 910 3D linear laser scanner</td>
<td>Konica-Minolta</td>
<td>Surface area and volume</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>&gt;£15,000</td>
<td>Yes</td>
<td>Taylor et al. 2007 [93].</td>
</tr>
<tr>
<td>Moulding (positive–negative moulage)</td>
<td>N/a</td>
<td>Volume</td>
<td>ICC = 0.921–0.995</td>
<td>ICC = 0.759–0.977</td>
<td>No data</td>
<td>Dependent on moulding material and measurement techniques used</td>
<td>Yes</td>
<td>Berman et al. 2015 [72].</td>
</tr>
</tbody>
</table>
Fig. 5 High-frequency ultrasound image of normal skin (top left, site: forearm). High-frequency ultrasound image of hypertrophic scar (top right, site: shoulder). High-frequency ultrasound image of normal skin (top) and adjacent scar tissue (bottom) (site: shoulder). Note that the scars appear more hypo-echoic as it is more homogenic and thus appears darker. Colours represent the intensity of the acoustic signal with bright colours (yellow) representing high-intensity and darker colours (e.g. green, black) representing low-intensity areas. (Source: Kwang Chear Lee, taken with Dermascan C)

Fig. 6 Different frequencies of ultrasounds and their penetrance into the skin. (Source: Kwang Chear Lee, adapted from image from http://www.eotech.fr/Fiches/produits/107_DUB_Brochure_English_DB10_2012_O.pdf)
only from one company (Cortex, Hadsund, Denmark). However, this system has not been trialled on scars, is limited to a small measurement area \((22 \times 22 \text{ mm})\) and costs significantly more compared to the 2D system (Table 4).

A summary of the different ultrasound systems is given in Table 4.

**Texture**

**Skin topography**

Scar roughness has a significant effect on the patient’s and observer’s opinion of the scar [4]. Indirect methods of measuring skin topography that involve creating a negative replica of the skin using materials such as polymers (e.g. Silflo silicon polymer; Flexico Developments Ltd., Hertfordshire, UK [123]) and then further analysing this with devices (e.g. mechanical, optical, laser or interference fringe projection profilometry [123–125]), although accurate can be very time consuming and not appropriate for clinical use [126]. Transparency profilometry (using the Visiometer; Courage + Khazaka, Germany) uses the Silflo silicon polymer but analysis is much easier and quicker [127, 128]. However, these indirect measurement techniques have been clinimetrically evaluated [123].

The Phaseshift Rapid In Vivo Measurement Of the Skin [129] (PRIMOS; Omniscan, GFMesstechnik GmbH; Germany) and the Visioscan VC 98 (Courage + Khazaka, Germany) are the only devices currently on the market that can be used to measure skin topography directly, but only the PRIMOS system has published studies in scars.

Three parameters were used for the evaluation of the PRIMOS system by Bloemen et al [129]. These were the peak count (PC, number of peaks per unit length), arithmetic mean of surface area roughness (Sa, in micrometers) and the mean of five highest peaks and five deepest valleys form entire measurement (Sz, in millimeters).

The PRIMOS has been shown to have excellent intra-observer and inter-observer reliability on both normal skin and scars and a high correlation with the relief score of the Patient and Observer Scar Assessment Scale (POSAS) on scar (The relief score in the POSAS questionnaire is the rating given by patients and clinicians on the surface irregularity of their scar compared to normal skin).

An added advantage of the PRIMOS system is that it can also be used to measure scar height [130].

The Visioscan VC 98 is a UVA-light video camera with high resolution that utilises the Surface Evaluation for Living Skin (SELS) method to evaluate the roughness of skin [131]. This method analyses the grey level distribution of the image captures and allows the calculation of four clinical parameters to quantitatively and qualitatively describe the skin surface as an index: skin smoothness (Sesm), skin roughness (Ser), scaliness (Sesc), wrinkles (Sew). As mentioned previously, this system has not been used to evaluate scars but has shown a high reliability for the measure of in vivo skin roughness in normal skin [131]. However, the Visioscan only measures an area of \(6 \times 8 \text{ mm}\) at a time which is probably too small for the analysis of the irregularity of a burn scar.

The aforementioned 3D camera systems can potentially also be used for skin topography analysis. However, these systems are already becoming the preferred devices in the clinic for scar surface area measurement as they are significantly more portable than the PRIMOS system although portable versions of the PRIMOS system are now commercially available (PRIMOS lite, GFMesstechnik GmbH; Germany). Lumenta et al. showed that the Lievez Micro 3D camera system (Quantificare S.A., Sophia Antipolis, France) was able to detect surface irregularities (SI) much better than subjective visual assessment which failed to detect at least half of the broader changes in SI of \(\geq 34 \%\) [76]. Kim et al. utilised a self-developed 3D camera system (Steroimage Optical Topometer, Korea University, Seoul, Korea) to calculate the mean surface area roughness (Sa) and root mean square roughness (Sq) for acne scars which were found to have a positive correlation with visual gradings (Spearman correlation coefficient \(ρ = 0.463\) and 0.438 respectively, \(p < 0.001\)). Table 5 below summarises the surface topography devices.

**Biomechanical properties**

**Pliability, elasticity or stiffness**

The biomechanical properties of skin can be measured with a variety of methods including suction, tonometry, torsion, adherence and reviscometry. Other methods include elastometry, ballistometry, quantitative electrical methods (dielectric measurements and bio-impedance) [132] as well as ultrasound and MRI techniques [133].

**Non-suction extension methods** Older methods of measuring skin elasticity relied on extension methods (i.e. physical stretching) to measure the viscoelastic properties of skin tissue using ex vivo [134] or in vivo extensometers [135–140] or elastometers [58], which utilises a constant-tension spring and a strain gauge to distract two points on the skin [58, 141]. The majority of these devices suffer from an unwanted peripheral force contribution due to the deformation of surrounding tissues during measurement which can lead to reduced accuracy and reproducibility of results, although newer designs have sought to improve their accuracy [137].

**Suction extension methods** Extension of the skin by suction is the method used by devices such as the Cutometer [18, 28, 106, 142–153] (Courage + Khazaka, Germany) and the DermaLab elasticity probe [144, 154].
### Table 4  Comparison of ultrasound devices in terms of parameter measured, reliability, correlation with clinical score and cost

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermascan C (2D)</td>
<td>Cortex</td>
<td>Thickness (2D)</td>
<td>ICC = 0.91–0.93</td>
<td>ICC = 0.90–0.91</td>
<td>Modified VSS and ultrasound thickness: Spearman’s $r = 0.41–0.50$</td>
<td>£15,000–20,000</td>
<td>Yes</td>
<td>Nedelec et al.  2008 [30, 106].</td>
</tr>
<tr>
<td>Dermalab USB (2D)</td>
<td>Cortex</td>
<td>Thickness (2D)</td>
<td>ICC = 0.92–0.97</td>
<td>ICC = 0.86–0.98</td>
<td>No data</td>
<td>&lt;£10,000</td>
<td>Yes</td>
<td>Gankande et al. 2014 [6].</td>
</tr>
<tr>
<td>Dermascan C (3D)</td>
<td>Cortex</td>
<td>Thickness (3D)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>£30,000–40,000</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Tissue ultrasound palpation system</td>
<td>Biomedical Ultrasonic Solutions</td>
<td>Thickness (2D)</td>
<td>ICC = 0.98</td>
<td>ICC = 0.84</td>
<td>Spearman Correlation of 0.42 between VSS thickness score and TUPS measurement ($p &lt; 0.01$), and $r = 0.34$ ($p &lt; 0.01$) between VSS total score and TUPS.</td>
<td>Not currently commercially available.</td>
<td>Yes</td>
<td>Lau et al. 2005 [103].</td>
</tr>
</tbody>
</table>

2D = two-dimensional; 3D = three-dimensional; ICC = intra-class correlation coefficient; VSS = Vancouver Scar Scale; TUPS = Tissue Ultrasound Palpation System
<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMOS</td>
<td>GFMesstechnik</td>
<td>Surface roughness (PC, Sa, Sz)</td>
<td>ICC of PC = 0.97, Sa = 0.99, Sz = 0.98</td>
<td>ICC of PC = 0.9, Sa = 0.96, Sz = 0.94</td>
<td>Correlation with POSAS: $r = 0.617$ ($p &lt; 0.001$)</td>
<td>£17,000–£14,000</td>
<td>Yes</td>
<td>Bloemen et al. 2011 [129]</td>
</tr>
<tr>
<td>Visioscan VC 9B</td>
<td>Courage + Khazaka</td>
<td>Skin parameters (Sesm, Ser, Sesc, Sew)</td>
<td>Not been used in scars</td>
<td>Not been used in scars</td>
<td>Not been used in scars</td>
<td>£5000–£10,000</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Eykona 3D camera</td>
<td>Fuel 3D</td>
<td>Not been used in scars</td>
<td>Not been used in scars</td>
<td>Not been used in scars</td>
<td>Not been used in scars</td>
<td>£5000</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Lifeviz Micro</td>
<td>Quantificare</td>
<td>Surface Irregularity</td>
<td>No data</td>
<td>No data</td>
<td>Performed better than subjective visual assessment</td>
<td>£10,000–£15,000</td>
<td>Yes</td>
<td>Lumenta et al. 2011 [76]</td>
</tr>
</tbody>
</table>

PRIMOS = Phaseshift Rapid In Vivo Measurement Of the Skin; ICC = intra-class correlation coefficient; PC = peak count; Sa = mean surface area roughness; Sz = mean of five highest peaks and five deepest valleys; POSAS = Patient and Observer Scar Assessment Scale.
(Cortex Technology, Hadsund, Denmark). With the Cutometer, negative pressure is created in the device by vacuum and the skin is drawn into the aperture of the probe and after a defined time is released again. Inside the probe, height of skin that is drawn up is determined by a non-contact optical measuring system which consists of a light source and a light receptor, as well as two prisms facing each other, which project the light from transmitter to receptor (Fig. 7). The resistance of the skin to the negative pressure (firmness) and its ability to return into its original position (elasticity) are displayed as curves (penetration depth in mm/time) in real time during the measurement (Fig. 8). This measurement principle allows getting information about the elastic and mechanical properties of the skin surface.

The Cutometer is reliable for measurement of the elastic and mechanical properties in scars and normal skin; however, its measurements only have a weak to moderate correlation with the pliability score of the POSAS and the subjective pliability assessment of the VSS [142]. Rennekampff et al. also suggested that the Cutometer may not be sensitive enough to pick up small changes in pliability as he found no correlation was found between subscale VSS pliability rating and Cutometer readings [155].

It was also found to be unreliable for severe scars due to a ceiling effect when rigid tissue is encountered [106]. However, the low ICC values have more to do with difficulty in relocating device to same measurement spot and the high sensitivity of the device [30, 106].

The mechanical parameters of the skin can be divided into absolute and relative parameters:

- **Absolute (in milimeters):** $U_e$ (immediate deformation), $U_v$ (delayed deformation), $U_f$ (maximal deformation), $U_{f_1}$ (immediate retraction), $R$ (residual deformation), $R_8$ (visco part).
- **Relative (in percentage):** $U_a/U_f$ (gross elasticity), $U_r/U_f$ (biological elasticity), $U_r/U_e$ (net elasticity), $U_v/U_e$ (viscoelastic to elastic ratio), $H$ (hysteresis).

Absolute parameters are likely to be influenced by skin thickness which in turn is dependent on various factors such as age, gender, anatomical region thus to compare values you will need to standardise them for skin thickness using an ultrasound and this is not always possible thus the relative parameters are more useful as it can be assumed to be independent of skin thickness which allows the values in different subjects, anatomical regions and times to be compared.

Various different opinions regarding the value that should be used (Table 6); however, Draaijers et al. concluded that either $U_e$ or $U_f$ is sufficient for the evaluation.
of scar as they found a high correlation between the parameters $U_a$, $U_e$, $U_f$, $U_r$, and $U_v$, and that $U_e$ and $U_f$ were found to have the highest reliability. Nedelec et al. agreed with this and also found $U_f$ to have a higher reliability (but not for severe scars) but concluded that as $U_f$ is more convenient to record (automatically calculated by computer software, whereas $U_e$ requires manual calculations), it should be used instead.

Other studies have also utilised the $R$ (dimensionless parameters derived from the $U$ values) and $Q$ (maximum recovery, elastic recovery and viscous recovery areas) values [143].

The Dermalab elasticity probe [6, 156] consists of a light plastic probe that is much smaller than that of the Cutometer (Fig. 5). This probe is attached to the skin using double-sided adhesive rings to form a closed chamber. Within this chamber, two narrow beams of light run at different heights parallel to the skin surface and serve as elevation detectors [154] (Fig. 5). A computer controlled vacuum pump connected to the probe is then used to increase the suction within this closed chamber over 30–60 s. In contrast to the Cutometer where a set pressure is applied and the skin deformation is measured, the Dermalab elasticity probe measures the amount of suction (in kilopascals, kPa) that is required to lift the skin to pass the height of the two light beams. This may cause problems when the measured skin is too stiff to be stretched enough to reach the level of the detectors [154]. The stiffness of the skin (or Young’s modulus, $E$) is then calculated and expressed in millimeter per kilopascal. Skin that is firm, e.g. scar tissue will have a higher stiffness index compared to normal skin.

A study by Gankande et al. with the Dermalab elasticity probe showed that the test–retest reliability for pliability was “excellent” (ICC 0.76–0.91) in scar areas but only “good” (ICC 0.45, 95 % CI 0.30–0.76) in contralateral normal skin areas [6]. It should be noted that significant difficulties were encountered by the researchers in the study in obtaining elasticity measurements and they failed to obtain matched measurements for test–retest analysis in 31–52 % of the subjects [6].

Both devices have the advantage of being a “hub” to which other measuring devices can be attached. For example, the Dermalab combo device provides additional probes that can be fitted to provide spectrophotometry data (melanin and erythema) and ultrasound measurement of dermal thickness [6].

**Tonometry**

Tonometry measures the firmness and flexibility of skin and scars by exerting pressure either via an airflow

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**Table 6** Comparison of used and recommended parameters for the cutometer in different papers

<table>
<thead>
<tr>
<th>Authors and papers</th>
<th>Parameter used/recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fong et al. 1997 [146].</td>
<td>$U_f$, $U_r/U_f$, $U_v/U_e$, $R_8$</td>
</tr>
<tr>
<td>Draaijers et al. 2004 [147].</td>
<td>Recommends $U_e$ or $U_f$</td>
</tr>
<tr>
<td>Dobrev et al. 2005. [257]</td>
<td>Recommends $U_e$ and $U_f$ (distensibility), $U_a/U_f$ and $U_r/U_f$ (elasticity) and $U_v$ and $U_v/U_e$ (viscoelasticity)</td>
</tr>
<tr>
<td>Nedelec et al. 2008 [30, 106].</td>
<td>Recommends using only $U_f$</td>
</tr>
<tr>
<td>Rennekampff et al. 2002 [155] and 2006 [142].</td>
<td>$U_f$, $U_a$, $U_r$, $U_e$, $U_r/U_e$ and $U_r/U_f$</td>
</tr>
</tbody>
</table>

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**Fig. 8** Example of skin deformation curve obtained with the Cutometer. (Source: Courage + Khazaka Electronic GmbH, reprinted with permission)
system that is blocked at a certain pressure (e.g. Pneumatometer [157] (Medtronic Solan Model 30 Classic, Jacksonville, FL, USA), Cicatrometer [114], Tissue Tonometer [158] (Flinders Medical Centre Biomedical Engineering, Australia) or an indentation load in a vertical direction, e.g. durometer [114, 158–161] (Rex model H 1000, Rex Gauge company, IL, USA), Schiotz tonometer [162], and Tissue Compliance Meter [163] (Model and company not stated by author). In the study by Lye et al., the Tissue Tonometer showed good intra-observer reliability and a moderate correlation with the pliability score of the VSS scale, but the measure is a relative one as it requires a contralateral reference point [158]. A study by Corica et al. [164], utilising a modified Tissue Tonometer, showed that the intra-class correlation coefficient for averaged measures between measurers (inter-rater reliability) was 0.957, and the standard error of measurement was 0.025 mm. A significant difference ($p = .0000$) between scar (2.64 ± 0.5 mm) and normal tissue (3.23 ± 0.46 mm) measurements was also demonstrated in the study. Tonometry devices are, however, less suitable for skin locations with hard bony structures underneath—as the hard underlying structures limit the degree in which the skin can be compressed. At the time of writing, the mechanical tonometer is no longer commercially available but a digital version is in the experimental phase. Other shortcomings with the mechanical design include the need to place the device accurately (must be within 5° of upright to measure correctly).

The durometer also showed good reliability and validity in one study but this was performed on sclerodermal skin [160] which demonstrates symmetrical skin thickening compared to scars where thickening can vary from area to area depending on the initial injury.

**Torsional force and adherence measurement methods**

Torsional force can be used to measure the elasticity of skin (Dermal Torque Meter; Dia-Stron, UK) [165] and the device is able to differentiate between native skin, autographs and cultured skin substitutes; however, rigorous clinical appraisals of the device have not yet been performed.

**Acoustic methods**

The Shear Velocity Device (SVD) is a portable tool that can be used to analyse soft biologic tissue by measuring the propagation of an auditory shear wave through the skin surface [166, 167]. The device works on the principal that an acoustic shear wave will have a higher velocity in a hard material (e.g. scar tissue) compared to softer material (e.g. normal skin). Experimental validation of the SVD by McHugh et al. claims that it provides similar results to the Shore Type A durometer; however, this data has yet to be published [166]. The coefficient of variation (CV) for the device in measurements of 254 hypertrophic scar locations was ±4.8 % whilst on 210 normal skin sites this was ±4.4 %. Unfortunately, the authors have not been able to locate any subsequent publications on this device and it is not currently commercially available.

Revisometry [168] (Revisometer; Dermaviduals and Courage + Khazaka, Germany) is another portable tool that measures the elastic and viscoelastic features of skin and scars by utilising an acoustic shock wave and reports this as resonance running time (RRT). Scars have a significantly lower mean RRT compared with normal skin (52.3 versus 91.6). It has been shown to be reliable with inter-rater observer reliability of more than 0.86 on scars but more studies are required to establish its validity and comparative performance.

**Electrical of bio-impedance methods**

Utilising an impedance device, the capacitance of scar tissue has been shown to be stronger than that of normal skin and the resistance of scar tissue is lower than that of normal skin. The impedance of scar tissue however varies according to the depth and density of scar tissue [132]. This electrical property of scar tissue could be utilised to quantify scars; however, no method has been developed as of yet.

**Modelling and other techniques**

All of the methods that have been discussed thus far rely on measurements in a small area of the scar which may not be representative of the scar as a whole.

The Adheremeter [169] (Fondazione Salvatore Maugeri, Italy) uses an entirely different approach and measures the restriction of scar mobility with respect to the underlying tissue at the worst adherent point when stretched in 4 orthogonal directions using a transparent film print-out of 9 concentric rings with varying radii. It is a relatively new device and has only been tested in one study [169] but it showed an adequate level of reliability and validity when compared to the VSS. However, it has a degree of subjectivity in operation as the measurement is based on the rater’s evaluation of the force required to stretch the skin and on the patient’s judgement of comfort. It is also not suitable for use on highly concave surfaces.

A different approach to measuring the elasticity of skin is to use computerised models of skin motion analysis [170, 171]. These experimental methods are able to detect and measure the differences in elasticity between normal and scar tissue by comparing images taken at two time instances before and after deformation. Regular 2D images, combined with 3D data, can offer a method of estimating scar pliability in a more global manner [94]. In simple terms, these methods utilise a grid painted onto the skin which will then deform according to the elasticity
of the skin. Grid portions that are less pliable (scar tissue) will deform less than areas which are more pliable (normal skin). A technique called Finite element modelling (FEM) can then be used to analyse this information [170–173]. This technique is still experimental and yet to be commercially available. Some devices that may be commercially available soon that utilise this technique include CutiScan CS 100 (Courage + Khazaka, Germany) which is still under development.

Other methods include the measurement of ranges of movement to determine the severity of burn contractures and thus indirectly the viscoelasticity of the scars. The current standard involves the measurement of the passive and active range of motion of an extremity in a single plane or functional movements (which are better related to activities of daily living) [174] using conventional measurements [175] (e.g. goniometry, tape measures, inclinometer) or 3D motion analysis [174, 176, 177]. The Faciometer (University of Vienna) measures the ranges of mimic movements, e.g. the distance between the tragus and the mouth using calipers and an electronic display [178]. A survey by Parry et al. however showed that there is a lack of consensus in the methods and tools used clinically for the measurement of burn contracture and these methods are also rarely checked for reliability or performance competency [175].

Table 7 gives a summary of the comparison of viscoelasticity devices in terms of parameter measured, reliability, correlation with clinical score and cost.

Comparing the devices that measure biomechanical properties of scars, the Cutometer seems to be the best choice at present as it is reliable (in normal, non-hypertrophic scars), shows a reasonable validity and can be used over bony areas. Additionally, the Cutometer is the most often used device for skin viscoelasticity measurements with more publications than most of the other devices reviewed in this paper.

Pathophysiological disturbances
Pathophysiological disturbances are defined as functional changes in the skin associated with, or resulting from, disease or injury, with measurable parameters including gas perfusion and moisture content.

Transcutaneous oxygen tension
Transcutaneous oxygen tension (tcpO₂) is perturbed in injured tissues and can be used as an index of maturity in hypertrophic scars. The tcpO₂ in scar tissue is lower compared to healthy skin, and an increase in tcpO₂ is correlated with a reduction in scar thickness assessed both clinically and by ultrasound [179]. This is thought to be due to low oxygen diffusibility through scar tissue. A study by Ichioka et al. [180] has also shown in animal and human tissues that immature repairing tissues consumed more oxygen than mature tissues and that the oxygen consumption rate in keloid and hypertrophic scars were significantly higher when compared to mature scars which may also explain the lower tcpO₂ in scar tissues. The method for measuring transcutaneous oxygen tension exploits the redox reactions that occur in a modified Clark electrode that measures the oxygen (tcpO₂) and carbon dioxide (tcpCO₂) tension on the surface of the skin. The tcpCO₂ is considered non-specific and highly dependent of external factors, whilst the tcpO₂ is a much more precise indicator of local perfusion [181]. This technique seems to have been recently abandoned from clinical practice.

Transepidermal water loss and moisture content
The water content of the skin is an important factor that influences the softness and smoothness of the skin, and transepidermal water loss and skin hydration are key indicators of skin function. Transepidermal water loss (TEWL) and moisture content can be measured by open and closed chamber systems. Open systems such as the Dermalab TEWL module [182] and Tewameter [183] (Courage + Khazaka, Germany) are the most frequently used (Fig 9). Closed systems such as the Vapometer (Delphin Technologies, Finland) are also available, but one study has shown that the Tewameter is able to detect significantly smaller differences in TEWL when compared to the Vapometer [184]. Anthonissen et al. showed a significant difference in mean TEWL values between normal skin and spontaneously healed scars \((p = 0.036)\) and a significant negative relation between mean TEWL values and time after burn \((p = 0.008)\); however, high SEM values were reported [156, 185].

The hydration of the skin layers, specifically the stratum corneum, can also be measured using electrical methods, such as the conductance method (for example, the Skicon-200 conductance meter [186, 187], IBS Co, Hamamatsu, Japan, Location, and the NOVA Dermal phase Meter [188], Nova, Technology Corp., Gloucester, Mass.) and impedance method (for example, the Corneometer [186], Courage + Khazaka, Germany). One study has shown that the Corneometer is suitable for use in clinical trials, with useful intra-class correlation coefficient (ICC) values (ICC intra = 0.985; ICC inter = 0.984), but only under very strict conditions with a standardised test protocol [189]. Another method for measuring hydration (and protein content) is to measure the dielectric properties of the skin. This is based on the interaction of high-frequency electromagnetic (EM) waves and biological material [190, 191]. The EM waves are generated using a network analyser (HP8753B, Agilent, USA).

A study by Suetake et al. found that TEWL was a better parameter for the functional evaluation of scars than
Table 7 Comparison of viscoelasticity devices in terms of parameter measured, reliability, correlation with clinical score and cost

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Parameter</th>
<th>Intra-rater Reliability</th>
<th>Inter-rater reliability</th>
<th>Correlation with clinical score</th>
<th>Cost</th>
<th>Portability</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutometer</td>
<td>Courage + Khazaka</td>
<td>Viscoelastic parameters</td>
<td>Ranges from unacceptable to good (0.12–0.76)*; poor in severe firm scars</td>
<td>Ranges from unacceptable to good (0.11–0.93)*; poor in severe firm scars</td>
<td>Low to moderate, but significant (Spearman’s ( r = -0.29 ) to ( -0.53 )) [30]. Rennekampf et al. could not find any significant correlation between objective viscoelastic measurements and the subjective pliability assessment of the VSS.</td>
<td>£5000–£10,000 (with hub)</td>
<td>Yes</td>
<td>Nedelec et al. 2008 [30, 106], Draaijers et al. 2004 [147], Rennekampf et al. 2006 [142].</td>
</tr>
<tr>
<td>Dermalab Elasticity</td>
<td>Cortex</td>
<td>Viscoelastic parameters</td>
<td>ICC = 0.90–0.93; limited ability to measure rigid scars</td>
<td>ICC = 0.86–0.93; limited ability to measure rigid scars</td>
<td>No data</td>
<td>£5000–£10,000 (with hub)</td>
<td>Yes</td>
<td>Gankande et al. 2014 [6].</td>
</tr>
<tr>
<td>Tonometer</td>
<td>Flinders Medical Centre Biomedical Engineering</td>
<td>Viscoelastic parameters</td>
<td>ICC = 0.90–0.94</td>
<td>ICC = 0.948</td>
<td>No data</td>
<td>No longer commercially available</td>
<td>Yes</td>
<td>Corica et al. 2006 [164], Lye et al. 2006 [158].</td>
</tr>
<tr>
<td>Durometer</td>
<td>Rex Gauge company</td>
<td>Viscoelastic parameters</td>
<td>No data</td>
<td>No data</td>
<td>Good correlation with modified Rodnan skin score (0.70) for sclerodermal skin</td>
<td>&lt;£1000</td>
<td>Yes</td>
<td>Merkel et al. 2008 [160].</td>
</tr>
<tr>
<td>Dermal Torque</td>
<td>Dlas-tron</td>
<td>Viscoelastic parameters</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>N/a</td>
<td>Yes</td>
<td>Boyce et al. 2000 [163].</td>
</tr>
<tr>
<td>Adherometer</td>
<td>Fondazione Salvatore Maugeri</td>
<td>Viscoelastic parameters</td>
<td>Good (0.96)</td>
<td>Good (0.87–0.99)</td>
<td>Moderate correlation with VSS and Pliability subscale of VSS (( r = -0.38 ) to ( -0.66 ))</td>
<td>Free</td>
<td>Yes</td>
<td>Ferriero et al. 2010 [169].</td>
</tr>
<tr>
<td>Reviscometer</td>
<td>Courage + Khazaka</td>
<td>Resonance running time</td>
<td>Good (&gt;0.86)</td>
<td>No data</td>
<td>No data</td>
<td>£10,000–15,000 (with hub)</td>
<td>Yes</td>
<td>Verhaegen et al. 2010 [168].</td>
</tr>
<tr>
<td>Vesimeter</td>
<td>Wave Cyber Co. Ltd.</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>N/a</td>
<td>Yes</td>
<td>Yes</td>
<td>Niyaz et al. 2012 [246].</td>
</tr>
<tr>
<td>Shear Velocity Device</td>
<td>N/a</td>
<td>Shear wave propagation velocity</td>
<td>No data for ICC. (CV for scars is ±4.8 %)</td>
<td>No data</td>
<td>No data</td>
<td>Not commercially available</td>
<td>Yes</td>
<td>McHugh et al. 1997 [166].</td>
</tr>
</tbody>
</table>

*Low ICC values for Cutometer may also be attributed to the difficulty in relocating device to same measurement spot and the high sensitivity of the device \[30\].

ICC = intra-class correlation coefficients; CV = coefficient of variation; VSS = Vancouver Scar Scale
was the hydration state of the skin surface measured by high-frequency conductometry [192].

**Multispectral imaging systems**

A novel polarised multispectral imaging system that combines out-of-plane Stokes polarimetry and Spatial Frequency Domain Imaging has been developed by Ghassemi et al. and allows the colour (haemoglobin, melanin), pathophysiology (blood oxygenation, hydration) as well as structural features (cellularity and roughness) of hypertrophic scars to be analysed in vivo [193, 194]. The results obtained with this multi-modal system showed a good agreement with the VSS and with histological examinations [193]. Although still in experimental stages, it could potentially simplify the scar measuring process due to its multi-modal measurements.

**Non-invasive morphological imaging techniques**

Previously, histopathological analysis of biopsy samples was the only method of morphological investigation of damaged biological tissues. Now, recent advances in imaging techniques have made non-invasive in vivo morphological investigation of tissue microstructure possible.

**Optical coherence tomography**

With the advances in fibre optics and other technologies such as ultra-broadband light sources and frequency domain techniques, optical coherence tomography (OCT) imaging that is capable of generating 3D images of tissue microstructure is now possible. OCT is most frequently used in ophthalmology [195] but can be adapted to be used to analyse the skin [196–203]. OCT can be utilised in various different modes for the assessment of scars [202, 203]. The layered arrangement of normal skin is perturbed in scarred skin so that OCT can be used to provide information about microstructure as well as depth and volume [196]. Scar tissue imaged by OCT appears dense and bright due to the increased collagen content, and this parameter can be used to measure the collagen status of scars [204]. Scar microvasculature density has been quantified using an automated OCT system and found to be increased in hypertrophic scar tissues (38 %) when compared against normal, unscarred skin (22 %) [201]. Vessels in scars have also been shown to be much larger compared to normal skin on OCT [205]. However, due to the strong scattering and absorption of light by skin, current OCT methods are only capable of imaging to a depth of 1 to 2 mm, whereas scar thickness is usually greater than 2 mm (as determined by ultrasound) [6, 103, 206]. Nevertheless, in areas where scar tissue is thinner (e.g. in fingers), OCT (utilising the 1300-nm wavelength region) may still be useful [196]. Another way of differentiating scar tissue from normal tissue using OCT is the use of the attenuation rate, which is defined as the rate at which the OCT signal decreases with depth in the tissue [203]. Lower attenuation coefficients are seen in scarred tissue compared with normal skin tissue [203]. This method bypasses the problem of penetration depth but yields less detailed morphological data when compared to standard OCT methods. A form of OCT (termed "Polarization-sensitive Optical Frequency Domain Imaging") can also be used to image collagen remodelling [207].

OCT imaging has been demonstrated to be feasible for use in the clinical monitoring of scar progression automated quantification of vascularity in cutaneous burn scars [195]. OCT imaging for scarring and fibrosis is currently still in its infancy and further development in the technology is required. In a study by Eraud et al. [208], although OCT was able to detect dermal nodules (which are present in hypertrophic but not keloid scars [209]) in 100 % of the specimens, it was not helpful in identifying hyalinised collagen (which is present in keloids) and cells. The technology however has the potential for tremendous growth [204].
Other in vivo tomography/microscopy techniques

Imaging techniques utilising specialised optical microscopes have been used to image scar tissue. Nonlinear spectral imaging, such as multi-photon tomography based on both two-photon excited fluorescence (TPEF) and second harmonic generation (SHG), can be utilised to demonstrate the morphological structure and spectral characteristics of collagen (with SHG) and elastin fibres (with TPEF) and thus can be used to potentially distinguish hypertrophic scar tissues from normal skin and to evaluate the effects of treatments [210–216]. Information on the orientation of collagen fibres can also be investigated and analysed from these images using fast Fourier transform methods [217, 218]. Advantages these techniques have are that several extracellular matrix components and endogenous biomolecules such as collagen, keratin, melanin and elastin can be visualised in living tissue without the need for specialised processing or staining [219, 220] and high-resolution, high-contrast three-dimensional images can be obtained [220, 221].

These techniques however have similar drawbacks to OCT. The maximum depth of two-photon imaging has been reported to reach up to 1 mm in living brains [222] and thus is comparable to OCT imaging but clinical use in the skin is typically only up to 200 μm, thereby limiting its potential utility for deep scar assessment. In addition, advances in the miniaturisation of spectral imaging apparatus need to be made before it can become of practical use in a clinical setting. The multi-photon technique also has high overall system costs, a long measurement times and the inability to quantify skin redness [223]. Other non-invasive in vivo imaging techniques which currently being developed, such as confocal laser microscopy (CLM) [224, 225], also have a limited imaging depth (~300 μm) due to tissue-related aberrations and light scattering [226].

Other similar microscopy techniques include phase-contrast microtomography with synchrotron radiation technology to detect the 3D structure of dermal tissues [221].

Spectroscopy techniques

Another imaging method that holds future promise is the use of optical spectroscopy methods in the UV-visible-near-infrared wavelength range, including diffuse reflectance (DR) and autofluorescence (AF) spectroscopies. DR spectroscopy is based on the scattering of photons (350–800 nm) inside biological tissues due to the differences in the refractive indices and morphology of the constituents of skin such as collagen fibres. AF spectroscopy, on the other hand, is based on the fluorescence emissions from endogenous fluorophores such as collagen and elastin when excited by light in the 350–459 nm wavelength range. A combination of both spectroscopy methods increases its accuracy [227] and has been used successfully in a rabbit hypertrophic scar model with high sensitivity and specificity [228, 229]. DR spectroscopy on its own has also been shown to be able to differentiate keloids from normal skin in terms of collagen concentration, haemoglobin oxygen saturation and scattering coefficient in an in vivo human study [217] and can potentially be used to evaluate keloid scar severity [230].

High-frequency ultrasound systems

High-frequency ultrasound systems (such as the Dermascan and Dermalab systems [6], Cortex, Denmark) are able to provide a much greater depth of imaging (~8 mm at 20 MHz) but the resolution is inferior to OCT, CLM and MPT [196]. Pathological scars appear as easily identified echo-poor areas that are clearly distinguishable from normal skin and with densitometry analysis with dedicated software, scars are also shown to have significantly reduced densitometric values compared with normal skin (7.6 ± 4.7 versus 31.79 ± 10.8) [231]. More detailed architectural information such as collagen arrangement and cell structure cannot currently be visualised with 2D nor 3D ultrasound techniques.

Intravital video-capillaroscopy

Intravital video-capillaroscopy [232] is a technique that utilises an optic contact probe microscope that is attached to a computerised video microscope (e.g. Microwatcher Model VS-901, Mitsubishi Kasei Corp, Tokyo, Japan [232]) which allows photographic images of skin capillaries to be taken. Scarred skin has a deranged capillary organisation. The pictures are then scored either subjectively and/or objectively. Subjective methods score images according to angiogenic markers [232, 233] such as enlarged or tortuous loops, architectural derangement, neoangiogenesis and quantitative changes of capillary lesions. These scoring systems can be modified to allow objective quantification [234, 235]; for example, the methods used in a study by Hern et al. allowed for both non-stereological measurements (microvessel density and vessel image width) and stereological measurements (image area fraction and microvessel length density) [235]. Intravital capillaroscopic measurement of capillary density (CD) has been shown to be reliable and reproducible with a mean coefficient of intra-observer variation of CD estimate of 5.6 % and the inter-observer correlation coefficient of 0.94 [236].

A similar technique, dermoscopy, and its use in the examination of vascular structures can be a clinically
useful diagnostic tool for differentiating between keloids and hypertrophic scars [237].

The dermoscopy can be used to visualise capillaries and pigmentation in the epidermal and dermal layers of the skin. An added advantage is that since dermascopes have their own light source, it is not likely to be affected by differences in environmental lighting which has been shown by Wei et al. [238].

Wei et al. [238] showed that the L* (or lightness reading) from the Dermoscope (Hong Kong Productivity Council) had a significant correlation (0.448–0.536, p < 0.01) with the readings from the MiniScan XE Plus spectrophotometer (HunterLab, Reston, VA, USA) and VSS scores of pigmentation (when the skin was blanched with pressure; r = 0.783, p < 0.01). The RGB values of redness also showed a strong correlation with the VSS scores of vascularity (r = 0.625, p < 0.01). Both the intra-rater and inter-rater reliability of the dermoscope were found to be excellent (0.965–0.98 and 0.871 to 0.930, respectively).

Measurement of sensory change
A majority of patients with burn scars experience a change in sensation of the scarred skin such as pruritis, pain and hyper- or hypo-sensitivity is common in scars and this can often last for years after the initial injury [239]. However, the objective measurement of such sensory deficits is challenging task and the only gold standard for pain assessment available currently is self-report.

Functional MRI (fMRI) scans have shown promise in assessing pain in the absence of self-report however it is far from ready for regular clinical use [240]. However, skin sensitivity/touch and (indirectly) pain can be examined in an objective manner with the touch pressure threshold method (TPT) using for example Semmes Weinstein monofilaments, which have been shown to have good intra- and inter-rater reliability (ICC = 0.822 and 0.908, respectively) in patients with scars [241].

More recently, an electronic version of the von Frey filaments is also available and showed better reproducibility compared to the traditional von Frey with good to almost perfect intra-observer reliability (ICC ranges from 0.61 to >0.8) (study done on normal skin, not scars) [242, 243].

Discussion
There have been significant advances in many aspects of burn treatment, but hypertrophic scarring remains as one of the major chronic problems after severe burns with few therapeutic options currently available. The accurate assessment of scarring is an important aspect of research into better treatments for this condition. Despite this, scar assessment is still mostly subjective and there is still little consensus regarding the ideal scar measurement tool [244].

Most if not all currently used subjective scales used in evaluating skin scars assume that scar dimensions conform to linear models and thus employ equal appearing interval (EAI) scales. However, a study by Brandt et al. showed that whilst pliability, thickness and surface area were defined well using linear models, the dimensions of vascularity and pigmentation were more accurately described using curvilinear functions [245].

Tools for scar measurement are often modified from tools developed for other industries, e.g. dermatological use in the cosmetic industry, such as the Cutometer; colour probes for measuring the colours of materials in the food and building industries and durometers such as the Vesmeter for testing the hardness of materials in the manufacturing industry [246]. As such, their utility for burns patients is mostly unproven. Accordingly, trials on these tools to evaluate their accuracy and reliability are scarce and few trials have compared the different devices.

The ideal assessment of scars should include the objective and subjective aspects of scars as well as an assessment of the functional limitations that are caused by the scar tissues [94]. The different physical aspects of scars can all change independently of each other during the course of scar evolution and as such a hybrid method of scar assessment which incorporates the most reliable and feasible methods should be used [247]. Combination systems such as the Dermalab combo which incorporate multiple scar measurement tools (e.g. colour, thickness and pliability [6, 248]) are now available [248] to facilitate this although improvement in the clinical interpretation of the measurements is required [247].

A problem with validating objective scar measurement tools is the lack of an ideal gold standard. Biopsies and standard histological analysis whilst proven to be accurate mostly rely on subjective scoring systems [249] unless quantitative measurement techniques are used [43]. Furthermore, Singer et al. showed that histomorphologic scales have been shown to only correlate fairly with gross macroscopic scores [249]. Beausang et al. also found that the clinical scar appearance correlated better with the upper portion of the skin (epidermis and papillary dermis) compared to the deeper parts of the scar [43]. Therefore, the lack of correlation of objective measurement techniques with clinical subjective scores should be considered carefully and not used to dismiss the objective methods.

Future validation studies of pigmentation and vascularity may be possible with standard colour reference cards developed for the cosmetic industry [250].

Objective scar measurement tools are important, especially for interventional clinical studies, as scars and the effect of therapies can be described, analysed and compared more accurately than is possible with
subjective scar scales. Subjective scar scales however should still be incorporated into studies as they can provide a more global assessment of the scar and allow the measurement of variables that are currently not possible with objective measurement devices, such as pain and itch. Indeed, several published studies have incorporated both subjective and objective scar measuring tools [251, 252].

The implementation of objective measurement devices into standard clinical practice still faces many obstacles and there are multiple reasons why potentially great technologies are struggling to get incorporated into the health care system.

As mentioned previously, many new technologies (including all if not most of the devices mentioned in this review) have been developed for non-medical uses and very little if any input has been sought from clinicians or patients during the design process, and thus these devices may have limited practical clinical use. The lack of data security features is also a factor although this issue probably applies more to mobile apps rather than physical devices.

Some clinicians also view the use of new technologies in clinical practice as a crutch to the development of clinical acumen even though many studies have shown that clinical judgement to perform poorer, e.g. in determining surface area [253] or burn depth [254].

Another main issue is the high cost of these devices. Even the simplest of devices, e.g. colour probe, costs at least >£3000 not including annual servicing costs. Without solid research evidence of clinical and patient benefit, it is difficult to justify the costs and use of these devices outside of research.

Despite many of these devices being fairly simple to use, a certain level of technical expertise and additional clinical time to collect and analyse the data generated is still required. To take an example, electronic health records have been used more frequently in hospitals nowadays but it takes longer for an average clinician to input data into the electronic system than onto a paper record for months, even years, after they have started using them [255]. This has been anecdotally quoted as one of the main reasons why some burn clinicians have been slow to adopt new technologies such as LDI in determining burn depth even though there is strong evidence for its accuracy compared to clinical judgement. Staff specially trained in the use of these devices and who are responsible for training of other staff and championing their use in regular clinical practice may be the way forward [255].

Lastly, the scope of this review largely did not include journals or articles in physical sciences or engineering which may have unearthed more potentially useful objective scar measurement devices.

Conclusions
In this review, we aimed to recommend a panel of objective measurement tools for burn scars to be used in conjunction with subjective scar scales, that were reliable, patient friendly, and easy to use (feasibility in terms of cost and portability have now been commented on in the tables in the various sections); generated simple data; and were appropriate for use in a clinical (bedside) environment (i.e. portable). We included in the panel the least number of devices that could measure surface area, colour, thickness, pliability, texture or topography and pathophysiological skin disturbances in order to reduce measurement time and cost. All of the devices considered for inclusion have to be commercially available. As such, the recommended device panel for burn scar assessment is as follows:

- **3D wound measurement camera systems** (Eykona/Lifeviz/Vectra H1): for surface area, texture, volume (including clinical thickness) and colour.
- **Dermascan**: for histological thickness measurements (the TUPS is an alternative but not commercially available).
- **DSM II Colorimeter**: for colour measurements (both Tristimulus reflectance colorimetry and narrow-band simple spectrophotometry).
- **Cutometer system**: for viscoelastic measurements of the skin.
- **Tewameter (optional probe for the Cutometer system)**: for the measurement of transepidermal water loss.

Further studies are needed to validate the performance and utility of this scar panel and to compare them with the commonly used subjective scar scales, such as the POSAS.

It is recommended that new technologies to be utilised in objective measurement should ideally be evaluated in terms of intra- and inter-rater reliability (with at least two observers) before being used in trials; however, this could be time and resource consuming. Collaborations should be established between the industry, clinical research and patient groups to streamline and refine this process and encourage the testing and introduction of improved devices.

Although there is a greater emphasis now compared to previous decades on developing and evaluating devices that measure physical scar parameters, scarce attention has been given to measure the physiological characteristics of scars. It is essential to develop tools that can be used to measure and quantify metabolic and cellular activity in scars so that treatments can be tailored to the individual.
Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

KL conceived and designed the review, collected the data (including searches, screening and extracting data from the papers) and wrote the manuscript. KL and JD designed the search methodology. LG, AL and NM provided general advice on the review and reviewed the manuscript drafts before submission. All authors read and approved the final manuscript.

Author details

1The Healing Foundation Burn Research Centre, University Hospital Birmingham Foundation Trust, Birmingham B15 2TH, UK.  
2Public Health, Epidemiology and Biostatistics, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK.  
3School of Chemical Engineering, University of Birmingham, Birmingham B15 2TT, UK.  
4School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK.

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