SYSTEMATIC REVIEW

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Noninvasive objective skin measurement methods for rosacea assessment: a systematic review*

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Summary

Background Rosacea assessment and therapy monitoring can be challenging to standardize, as most clinical evaluation systems are prone to interobserver variability and not always validated. Therefore, objective, reliable and preferably noninvasive measurement tools are needed.

Objectives To give insight into available noninvasive imaging techniques and biophysical methods in rosacea by performing a systematic review.

Methods PubMed, Embase, Cochrane and Web of Science databases were searched until 1 September 2018 in accordance with PRISMA guidelines, to identify studies providing original data about objective noninvasive imaging and/or biophysical skin measurement techniques for diagnosis, assessing severity or therapy monitoring of adult patients with cutaneous facial rosacea. Risk of bias of included articles was assessed with the Cochrane Risk of Bias tool, Quality in Prognosis Studies tool, and the Newcastle–Ottawa Scale.

Results A total of 78 studies were included, describing 14 imaging and biophysical methods. Widespread information about (sub)surface cutaneous morphology and functionality was obtained. Methodological study quality was relatively low and interstudy outcome variability was large. Several tools show promising value in research settings: for treatment follow-up *Demodex* mites are countable with reflectance confocal microscopy, spectrometry can quantify erythema, and rosacea severity could be objectified with skin hydration- and transepidermal water loss measurements.

Conclusions This systematic review describes the spectrum of noninvasive imaging and biophysical methods in rosacea assessment, giving multifaceted information about structure and properties of rosacea skin, especially useful for research purposes. Larger studies with good methodological quality are needed to create validated protocols for further implementation into research.

What's already known about this topic?

- Rosacea is a chronic inflammatory skin disease with a variety of clinical manifestations.
- Most clinical evaluation systems are subjective, not always validated, and subsurface skin processes remain unnoticed.
- Currently, different types of noninvasive measurement tools are available for rosacea assessment and therapy monitoring, but a comprehensive overview is lacking.

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What does this study add?

- Seventy-eight publications were included, describing 14 imaging and biophysical tools, providing a wide range of information about rosacea skin morphology and functionality.
- Reflectance confocal microscopy and spectrometry are especially promising in therapy monitoring and skin barrier measurements for rosacea severity assessment.
- Larger studies with better methodological quality are needed to create validated protocols for implementation into research.

Rosacea is a chronic inflammatory skin disease of uncertain pathophysiology; many factors may play a role in disease development.[1–9] Initially, four rosacea subtypes were described: erythematotelangiectatic, papulopustular, phymatous and ocular. Recently, the classification system was changed from subtype-based to phenotype-based to increase diagnostic and presentation accuracy, but as many trials predate the updated phenotype approach, the subtype-based system still dominates rosacea literature.[8,10–12] To achieve optimal results, rosacea treatment is preferably adjusted to clinical symptoms and disease severity.[3,13,14] However, the variety of clinical manifestations among individual patients and presence of various classification systems make standardization and quantification of rosacea measurements challenging.[11,15] Currently, clinical features represent the gold standard to establish the diagnosis.[8,11] Various numerical scales exist to assess erythema, telangiectasia, papules, pustules and global rosacea score for research purposes.[16,17] These scales are subjective and often not validated, decreasing confidence in the validity of reported outcomes.[7,16–19] Moreover, visual evaluation alone cannot appreciate processes unfolding below the skin surface. Histopathological findings are nonspecific,[1] but experienced dermatopathologists are generally able to diagnose rosacea based on characteristic histological and immunohistochemical features,[20] which can overlap among subtypes.[1,15] Recently, a study showed that high *Demodex* densities [measured by two consecutive standardized skin surface biopsies (SSSBs)] were associated with papulopustular rosacea;[21] however, this sampling method can cause slight ephemeral irritation and the test has yet to be confirmed by other independent studies and for other clinical features of rosacea.

Due to these complexities standardized, validated, objective, reliable and preferably noninvasive measurement tools are needed. The advantage of noninvasive over invasive techniques is the ability to monitor the same facial skin location over time without causing irritation, damage or alteration, including inflammatory responses, which may interfere with diagnosis and evaluation. A variety of noninvasive objective skin measurements exist.[22–25] These techniques are widely used in rosacea, but a comprehensive overview is lacking. This systematic review elucidates the spectrum of available noninvasive objective skin measurement techniques for rosacea.

The current literature was reviewed for the following purposes: (i) to provide an overview of available noninvasive objective skin measurement techniques for assessing diagnosis, severity and therapy monitoring of rosacea; (ii) to assess displayed skin features of these tools, including technique advantages and limitations; and (iii) to provide recommendations for future use of these tools in an investigational setting.

Methods

The study protocol was registered in PROSPERO (registration number: CRD42018108401).[26] A systematic literature search following PRISMA guidelines was performed in four electronic databases:[27] PubMed, Embase, Cochrane Library and Web of Science. The search was based on studies using objective noninvasive imaging and/or biophysical skin measurement techniques for diagnosis, assessing severity or therapy follow-up of rosacea. Skin measurement tools were extracted by literature search and by exploring their PubMed MeSH-terms.[4,22–25,28] We defined 'noninvasive' as every method that theoretically cannot lead to skin irritation, bleeding or scarring; this excluded biopsies, epilation of eyelashes/hairs, application of tape or glue onto the skin, and collection of skin scrapings or excretions from sebaceous follicles. Only studies involving adult patients with cutaneous facial rosacea were included (Table S1; see Supporting Information).

All databases were searched to include published studies from date of inception until 1 September 2018. Full details on the search strategy are available in Table S2 (see Supporting Information). Titles and abstracts were screened for relevance by two independent reviewers (J.G.M.L. and F.M.C.d.V.). Next, full texts were critically assessed for eligibility by the same independent reviewers. Missing full texts were requested via e-mail from study authors and Radboud University Medical Library. In both phases, any differences regarding inclusion between the reviewers were resolved by discussion. Excluded were papers involving patients aged < 18 years; ocular, extrafacial and drug-induced rosacea; therapeutic techniques; subjective measurements; *in vitro* and animal studies; studies in languages other than English, German or Dutch; meta-analysis, (systematic) reviews and abstracts of congresses or with

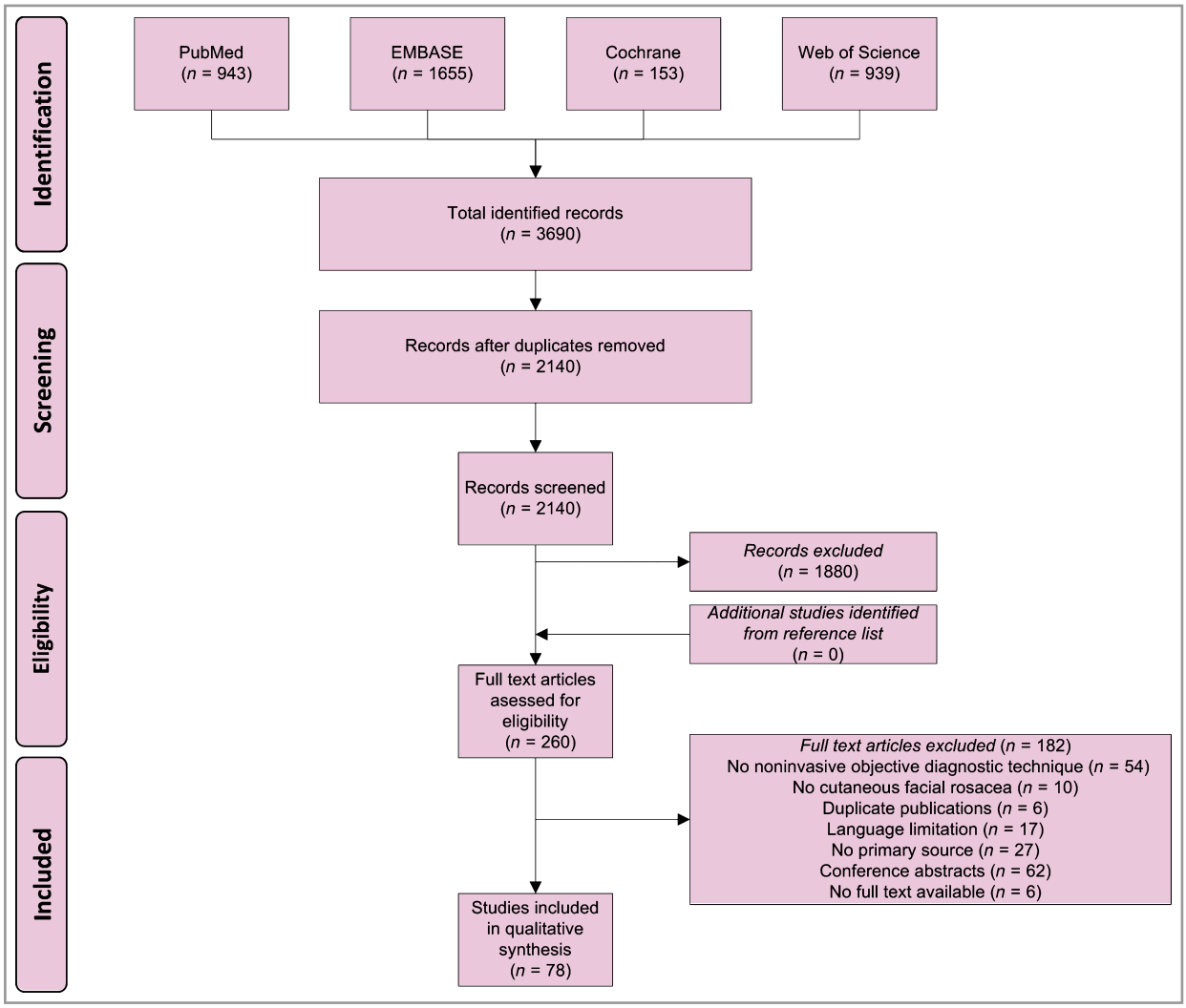

Fig 1. Flowchart: article selection process.

unavailable full texts. The reference lists of all included articles were checked for relevant articles not identified by the initial search.

Extracted study characteristics included study design, number of participants, rosacea type, assessed skin parameters, measurement locations, method type/aim/findings and use of reference test. A narrative synthesis was conducted for imaging techniques and biophysical methods separately. Risk of bias was assessed by two reviewers (J.G.M.L. and F.M.C.d.V.), with disagreements resolved by discussion. The Cochrane Risk of Bias tool was used for assessment of risk of bias in randomized controlled trials (RCTs), with studies graded as having low, high, or unclear risk of bias.[29] For case–control studies, the Newcastle–Ottawa Scale was used.[30] For prognostic cohort studies without a control group (including case reports and case series), the Quality in Prognosis Studies (QUIPS) tool was used.[31] For the QUIPS, overall risk of bias for each of the studies was judged as: (i) low, if there was a low risk of bias in all key domains; (ii) unclear, if there was an unclear risk of bias for one or more key domains; and (3) high, if there was a high risk of bias for one or more key domains.[32]

Results

A total of 3690 articles were identified (Fig. 1). After removal of duplicates, 2140 articles were assessed for screening. This resulted in inclusion of 260 abstracts, eligible for full-text screening. Finally, 78 articles were included for this systematic review: 36 articles concerned skin imaging techniques and 79 articles were about noninvasive biophysical measurements. Several studies were included in multiple categories, because more than one method was used (Table S3; see Supporting Information). Most of the included studies in this review were cohort studies (n = 31) and case–control studies (n = 24), followed by RCTs (n = 14), case reports (n = 8) and case series (n = 1). Below and in Table S4 (see Supporting Information), all imaging techniques and biophysical skin measurement methods included in this review are presented. Advantages and limitations of each technique are presented in Table 1.

Table 1 Summary of imaging and biophysical noninvasive methods used in assessing severity and therapy monitoring of rosacea

	Technique	Measurement principle	Skin features displayed	Advantages	Limitations
Imaging	RCM[33–38]	*En face* imaging of epidermis and superficial dermis at cellular resolution with 830-diode laser	*Demodex* mites (structure; number; optimal visualization depth 10–90 μm)	Rapid (10 min); painless; easy protocol; real time; resolution comparable with histology; medium-sized probes for imaging of recessed body parts; portable (VivaScope 3000)	Expensive; limited penetration depth (up to 250 μm); no *z*-axis imaging; training needed for image interpretation; large device; imaging challenges at anatomical surface irregularities (VivaScope 1500); mm-level motion artefact; no mite species/viability/life stages distinction
	Dermoscopy[40–48]	Optical magnified (usually 10-fold) visualization of colours and microstructures in epidermis and papillary dermis	Background erythema; vascular polygons; *Demodex* tails/follicular openings; rosette sign	Rapid; painless; cheap; real-time; easily applicable. *Polarized light*: deeper structures visible (erythema, hair follicle contents, haemoglobin) so possibly better to evaluate vascular changes; reduced surface shining; avoidance of pressure artefacts (no fluid immersions needed. *Videodermoscopy*: digital image storage; colour calibration; monitoring	Training needed for image interpretation; interobserver variability; pressure artefacts; no quantitative analysis; rosette sign unspecific; *Demodex* not distinguishable from similar structures (e.g. trichostasis, follicular hyperkeratosis. *Polarized light*: lower illumination and resolution
	Capillaroscopy[50,51]	Optical magnified visualization of skin microcirculation until deep dermis	Skin capillary shape and diameter	Rapid, easily repeatable; painless; cheap	Vessel irregularities difficult to quantify (subjective); pressure artefacts
	Computer-aided imaging analysis[46,48,57–67,69,70]	VISIA® system; multispectral imaging with digital analysis	Erythema; telangiectasias; haemoglobin	Quantification; non-skin contact; portable; facial distribution enabling mapping (detailing concentration and location of chromophores with 50–100-μm resolution)	Expensive; limited resolution; lack of imaging in *z*-axis and information on depth; not real-time; influenced by intrinsic factors (melanin content, physiological blood supply)
	Optical coherence tomography[52,53]	Reflections of infrared light source detected based on low-coherence interferometry until reticular dermis	*Demodex* mites (number); (epi)dermal reflectivity	Rapid (2–5 min); real time; cross-sectional/*en face* imaging comparable with histology; high spatial resolution (3–10 μm^2); compared with RCM deeper penetration depth (up to 1·5 mm) and wider field of view	Expensive; lower contrast and axial resolution than RCM (15 μm); no cellular and subcellular details visible; only architectural changes; decreasing resolution at level of reticular dermis; image localization depends on contact gel amount; reduced image quality in uneven skin (papular eruptions)
	Ultrasonography[72]	Detection of reflected sound waves	Oedema; nodules	Real-time; painless; widely available; portable; inexpensive; clear visualization of dermis and subcutis	Training needed; low resolution; no visualization of epidermis; no distinction between inflammatory infiltrates/oedema/tumour/scar tissue (similar echo-poor areas); image difficulties in recessed body parts

(continued)

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Table 1 (continued)

	Technique	Measurement principle	Skin features displayed	Advantages	Limitations
	Infrared photography[71]	Infrared light	Skin vasculature pattern	Painless; rapid; inexpensive	No differentiation between arterial and venous structures; no quantification
Biophysical	Corneometry[62,66,68,73–85]	Electrical capacitance of skin surface	Hydration of SC and upper part of epidermis	Easy to use; rapid; small probes for measurement in recessed body parts; relatively inexpensive	Influenced by intrinsic and extrinsic factors; small facial area covered
	Evaporimetry[66,73–77,80,81,83–90]	Flux density of water vapour	Transepidermal water loss	Easy to use; rapid; small probes for measurement in recessed body parts	Influenced by intrinsic and extrinsic factors (especially open measurement chambers); small facial area covered
	Sebumetry[38,68,82,84,85,92–97]	Photometric quantification of sebum transparency on skin tapes	Skin sebum levels	Easy to use; rapid; inexpensive; extremely accurate quantification of skin oils	Influenced by intrinsic and extrinsic factors; no 1 : 1 correlation between value and skin oil level; value is oily material dependent; small facial area covered; reference values scarce
	pH meter[82,83,85]	H^+-ion activity with glass H^+ ion-sensitive electrode	Skin pH	Easy to use; rapid (3 s); no skin occlusion effect	Reference values scarce; small facial area covered; reliability questioned (SC is relatively dry, lipid environment); possible overestimation of values due to too short a measurement time
	Spectrometry[48,64,68,78–80,82,83,90,96,103–114]	Reflectance spectrophotometry; tristimulus colorimetry; diffuse reflectance spectroscopy	Skin erythema	Easy to use; rapid; small probes for measurement in recessed body parts; relatively inexpensive	Influenced by intrinsic and extrinsic factors; small facial area covered; method of calibration often not described
	Laser Doppler velocimetry[57,89,115–120]	Doppler shift of moving erythrocytes by laser light; electrical signal processed proportional to blood perfusion (average penetration depth: 0·2 mm)	Relative changes in skin blood flow	Noncontact; inexpensive; portable; dataset comparisons on computer	Small facial area covered; influenced by intrinsic and extrinsic factors; no information about depth; no z-axis imaging
	Infrared thermography[115,121,122]	Detection of radiation in long-infrared range of electromagnetic spectrum	Skin temperature	Real-time	Influenced by intrinsic and extrinsic factors; less accurate than contact methods

SC, stratum corneum; RCM, reflectance confocal microscopy.

Imaging techniques

Reflectance confocal microscopy

Six studies described use of reflectance confocal microscopy (RCM; also called confocal laser scanning microscopy) in diagnostics and therapy monitoring of rosacea.[33–38] Imaging items of interest were *Demodex* mites, inhabiting human facial sebaceous follicles.[39]

Demodex manifested as roundish/elongated cone-shaped grey structures, surrounded by a bright ring.[33–35,37] All case–control studies showed significantly higher *Demodex* numbers in patients compared with controls.[33,34,37,38] There was evidence that patients with papulopustular rosacea (PPR) had significantly higher mite numbers than those with erythematotelangiectatic rosacea (ETR),[37] and that RCM measures higher *Demodex* densities compared with only one SSSB (when two consecutive SSSBs were not taken).[34] Moreover, a significant reduction in *Demodex* mites after topical treatment was seen, correlating with clinical improvement.[35,36] Treatment also resulted in qualitative changes of residual mite appearance.[36] In contrast, Harmelin *et al.* reported *Demodex* disappearance in six of eight treated patients, while complete clinical resolution (not further specified) was established in only three from the six patients with *Demodex* disappearance; the other three showed clinical improvement, but did not resolve completely.[33] No correlation between clinical severity and mite density was found by Falay Gur *et al.*[38] It was not possible to distinguish mite species, viability or life stages.[35,37,38]

Dermoscopy

In total, eight studies used dermoscopy[40–47] (of which two studies used polarized light[40,41]), and one article used video dermoscopy for diagnostic and monitoring purposes.[48] ETR was the most studied rosacea subtype.[42,43,46–48]

Lallas *et al.* showed a 100% presence of vascular polygons in patients with ETR.[42,43] Vascular polygons were also seen in granulomatous rosacea,[45] together with a rosette sign.[41] Unfortunately, rosette signs are nonspecific optical effects of polarized light interacting with keratin-filled adnexal openings, observable in a wide range of skin neoplasms.[41,49] Two studies showed a reduction of background erythema after laser treatment.[44,46] Vascular changes were described in three studies: decrease of vascular network,[47] vessel density[44] and capillary diameter.[48] However, Lallas *et al.* showed that polygonal vessels only disappeared in four of 12 patients after treatment with topical metronidazole, while clinical improvement (not further specified) was seen in eight patients;[43] Micali *et al.* noticed persistence of telangiectasias after brimonidine application while clinical improvement was substantial.[46] Segal *et al.* noticed *Demodex* tails and follicular openings, and reticular dilated vessels in patients with microscopically proven demodicosis using skin scrapings.[40]

Capillaroscopy

Two case–control studies involving capillaroscopy were performed in patients with rosacea.[50,51] Fonseca *et al.* examined the nail-fold capillary beds in eight patients and controls with a stereomicroscope.[51] No specific capillaroscopic patterns in rosacea were found. Rosina *et al.* performed videocapillaroscopy on the cheek and nail folds in patients with ETR, seborrhoeic dermatitis and healthy controls.[50] In the nail folds, this study too did not show any differences between all three mentioned cohorts. On the cheek, patients with ETR had significantly larger polygons, more prominent telangiectases, larger mean vessel diameter and neoangiogenesis. Moreover, they showed a reddish background due to subpapillary vessel dilation.

Optical coherence tomography

Two studies used optical coherence tomography (OCT) in rosacea for *Demodex* quantification and therapy monitoring.[52,53] Earlier research used OCT to visualize dermal vessels in normal skin.[54–56]

In Maier *et al.*, OCT showed *Demodex* mites in 20 patients with rosacea – *Demodex* folliculitis and *Demodex*-aggravated dermatitis perioralis (Table S4).[52] *Demodex* was visible in all patients as bright, round, grouped dots in the superficial part of dark hair follicles, while skin scraping tests were mite-positive in only 15 patients. Mite number was significantly higher in patients than in controls (positive predictive value 67%, sensitivity 100%, specificity 65%). The case report of Urban *et al.* demonstrated decreased dermal hyporeflectivity of patients with ETR after treatment with brimonidine, suggesting a decrease in dermal oedema.[53] No significant changes in vessel diameter were seen.

Computer-aided imaging analysis

Fifteen articles used computer-aided imaging analysis in rosacea diagnosis, severity assessment and therapy monitoring, mainly in ETR (Table S4).[46,48,57–69] To measure erythema, five studies used the VISIA® Complexion Analysis system (Canfield Scientific, Parsippany, NJ, U.S.A.),[46,62,63,68,69] a commercially available high-resolution facial imaging system with quantitative imaging-analysis software (RBX®; Canfield Scientific), which separates red skin-colour components.[70] In all studies, reduction of concentrated facial dark-red areas after treatment (brimonidine, laser, photodynamic therapy) was seen, corresponding to a reduction in erythema. The remaining 10 articles incorporated a variety of spectral imaging methods (L*a*b* colour space,[60,61,67] red–blue difference index,[61] erythema dose,[61] red–green–blue imaging,[57,59,66] emission of visible and infrared light[48]) to quantify erythema,[57,58,60,61,64–67] telangiectasias[57] and skin haemoglobin distribution.[48,59]

Other techniques

Sonographic imaging and infrared photography are two additional imaging techniques used in rosacea cases.[71,72] Detailed information is summarized in Table 1.

Biophysical methods

Stratum corneum hydration

Skin hydration was assessed in 16 studies by corneometry, mainly for therapy monitoring.[62,66,68,73–85] A corneometer measures electrical capacitance of the skin surface, providing insight into stratum corneum barrier function;[28] its use was motivated by earlier studies implying decreased barrier function in patients with rosacea.[1,3]

In general, a wide range of skin capacitance values was reported (16·5–381·6 a.u.). Case–control studies demonstrated that skin hydration in patients with ETR and PPR was significantly lower than in controls.[81,82,84,85] Moreover, Kim *et al.* found significantly lower values in facial areas with increased erythema (measured with a skin colour imaging system) compared with areas having normal skin colour, and in severe compared with mild/moderate rosacea.[66] Significant skin hydration increases were seen after successful treatment (moisturizers, topical metronidazole, oral tetracyclines).[75,77–80,82,83] In two RCTs where patients with ETR and PPR used creams containing silymarin or glycine/chitosan, the placebo groups using vehicle creams without these ingredients also had significantly higher skin hydration after treatment.[78,79] Others noticed no significant changes in skin hydration, while rosacea severity decreased after treatment (various topical agents, photodynamic therapy).[62,68,73,74,76]

Transepidermal water loss

Transepidermal water loss (TEWL) was assessed in 16 studies.[66,73–77,80,81,83–90] TEWL is widely accepted as a reference parameter to investigate epidermal permeability barrier function.[91] Seven studies used open measurement chambers,[75,77,80,83,86–88] two studies unventilated closed measurement chambers,[66,90] and in seven studies the measurement principle was not specified.[73,74,76,81,84,85,89]

In general, a wide range of TEWL values was reported (11·5–35·8 g m^{-2} h^{-1}). Patients showed higher TEWL values compared with controls.[66,84–86,89] However, some studies showed no differences at the nasolabial fold,[81] lateral chin,[86] forehead[85] and nose.[85] Kim *et al.* found significantly higher values in severe compared with mild/moderate rosacea.[66] Significant decreases after treatment with various topical creams were observed and were associated with reduced rosacea severity.[75,80,83,87,88,90] Others showed no TEWL differences after treatment with topical agents, while rosacea severity score decreased.[73,74,76,77]

Sebum

Eleven studies were interested in quantifying sebum in rosacea.[38,68,82,84,85,92–97] Seven studies used a Sebumeter® (Courage + Khazaka electronic GmbH, Köln, Germany),[38,68,82,84,85,96,97] five studies used other methods (photometric quantification of cigarette paper,[95] gravimetric absorption[92,93] and chromatography[92,94]). It is important to note that a 1 : 1 correlation between Sebumeter score and amount of skin oily material is not present.[98] Moreover, reference values for normal facial sebum levels are scarce.[99]

Most studies found normal sebum levels and skin surface lipid composition in patients compared with controls,[38,82,93,94,97] and no correlation with disease severity[93,94] or rosacea subtype existed.[68] Two case–control studies found lower than normal skin surface lipids in patients with PPR,[84,95] and another higher oil levels in patients with nasal rosacea.[85] A fourth study showed significant differences in lipid composition on the back of patients (Table S4).[92] Two studies noticed no change in sebum levels after treatment (topical photodynamic therapy, oral tetracyclines);[68,82] two did (other sebum composition, decrease of sebum levels).[92,96]

pH

Skin pH was measured with pH-meters in three studies.[82,83,85] Results were inconclusive: one case–control study found significantly higher centrofacial pH values in patients with PPR vs. controls,[82] while the other did not.[85] No changes in pH were found in patients with PPR after use of oral minocycline,[82] while the RCT did show significant decreases after application of tranexamic acid solution compared with vehicle treatment.[83] However, also for facial pH, reference values are scarcely available.[99–102]

Erythema

Twenty-two studies assessed monitoring of facial skin erythema by spectrometry.[48,64,68,78–80,82,83,90,96,103–114] Three spectrometric methods were applied;[28] reflectance spectrophotometry,[3,64,68,78–80,82,96,104,106–108,110,111,113] tristimulus colorimetry[83,90,103,109,112] and diffuse reflectance spectroscopy.[105,114] One study used an optical densitometer.[48] In all studies, erythema values decreased after treatment, corresponding to clinical improvement. However, erythema index and L*a*b* colour space values varied enormously (16·3–1002·77 and 6·9–20·2 a.u., respectively). Method of colour calibration was often not described.

Skin blood flow

In eight studies, cutaneous blood flow was established by laser Doppler velocimetry. Overall, no significant differences in facial blood flow between patients and controls were seen, nor after flushing-trigger tasks.[89,115,118,119] Only Sibenge *et al.*

found higher blood flow in facial flushing-affected areas in patients compared with controls.[117] Interestingly, flux was greater in patients with severe rosacea than with mild rosacea[118,119] and values at PPR-affected skin were significantly higher than at unaffected skin.[115] Moreover, a decrease of flux was noticed after treatment with intense pulsed light and acupuncture, in line with clinical improvements.[57,120] However, Wilkin found no statistical differences in patients after nadolol treatment.[116]

Skin temperature

Skin temperature was measured in three studies.[115,121,122] This was done with an infrared thermometer,[115] infrared video camera,[122] and iron–constantan thermocouple junctions.[121] No significant differences between ETR- or PPR-affected areas and nonaffected areas or controls were found.[115] Significant skin temperature rises were seen immediately after laser treatment[122] and alcohol ingestion.[121]

Risk of bias

Sample size of most studies was small (and multiple case series/reports). Most RCTs were unblinded or single-blinded (Fig. S1a, b; see Supporting Information). Moreover, the method of random sequence generation and allocation concealment was often not described. For case–control studies, selection of controls, ascertainment of exposure and nonresponse rate were often not described (Table S5; see Supporting Information). For cohort studies, the domain 'Study Confounding' carried the highest risk of bias (Fig. S2a, b; see Supporting Information) due to insufficient description of potential confounders (e.g. comedication). Approximately 50% of studies did not describe or insufficiently described study population characteristics (domain 'Study Population') and reasons for/potential impact of subjects lost to follow-up (domain 'Study Attrition').

Discussion

Noninvasive, objective methods are needed for reliable assessment and therapy monitoring in rosacea. We included a large number of publications describing (sub)surface morphology and functionality of rosacea skin. This is especially useful for research purposes (e.g. follow-up of new treatments), but can possibly also contribute to elucidation of its multifactorial pathogenesis.

Unfortunately, the quality of included studies was relatively low and interstudy outcome variability was large; various rosacea subtypes, measurement locations, treatments and biophysical devices were used. A description of measurement sites (involved or uninvolved skin) was not always given. Method standardization and validation were often lacking. Additionally, most methods can only measure one or a few parameters in the very complex environment of rosacea symptoms. Subsequently, the gained information may not be conclusive with a single modality; more than one instrument may be useful to obtain a more complete picture.

Imaging equipment can have high purchase costs, and require extensive protocols and trained personnel to obtain accurate and reproducible results. Penetration depth and resolution is limited (RCM, OCT and ultrasonography). Vessel irregularities are difficult to quantify (dermoscopy and capillaroscopy), as there is no standard to measure capillary shape.[50,123] *Demodex* could potentially be confused with other similar structures (e.g. trichostasis, follicular hyperkeratosis) by dermoscopy; RCM does not impose this limitation, as the mites are easily recognizable with this imaging technique.

Biophysical parameters are strongly influenced by intrinsic and extrinsic factors like age, sex, race, circadian rhythm, season, exercise and acclimatization period;[22,95,99,100,124–131] therefore data collection is inherently difficult to standardize. For TEWL, open measurement chambers are more vulnerable to environmental influences than are closed chambers;[129,132] condenser closed chambers seem to be the most sensitive TEWL system,[132] but this device type was not used in rosacea. For pH, all three studies used pH900 meters, possibly overestimating true pH due to a small electrode area and short stabilization period of only 3 s.[130] For erythema, skin light absorption by components other than haemoglobin (melanin, bilirubin) may influence outcomes[64,105,114] and application of variable skin pressure can change haemoglobin level and skin colour.[67,82] For laser Doppler, absolute values are meaningless without measuring sympathetic flux changes and blood vessel density, which is impossible with noninvasive techniques.[89,118] Control for these factors was often not described or accounted for in the reviewed articles, and comparisons with normal skin were scarce. Additionally, biophysical tools are probe-related; they only cover a small facial area, questioning representativeness of the entire face. Placing the device on the same area of interest in follow-up visits is therefore challenging.[64,76,113] Computer-aided image analysis does not impose these problems as whole face erythema is mapped. Moreover, redness values are obtained without performing skin contact. However, their analysis methods were often experimental-based, not standardized or validated; therefore results were difficult to interpret.

Due to the strict exclusion criteria we applied in this review, all techniques that could possibly lead to skin irritation were excluded, as well as near-noninvasive tools like SSSBs and tapes. The SSSB (with two consecutive SSSBs) is a standardized, reproducible, cheap and simple sampling method to measure *Demodex* density as accurately as RCM.[21,133] Sebutape® (Clinical and Derm, Dallas, TX, U.S.A.) enables assessment of the seborrhoeic activity of skin pores.[134] Another limitation is that language of published studies was restricted to English, German and Dutch for practical linguistic reasons, which may have resulted in language bias.

Despite the above-mentioned limitations, several tools show promising additional value, especially in research settings; for treatment follow-up, *Demodex* mites can be easily counted by RCM, erythema can be monitored with spectrometry, and

rosacea severity can be objectified with additional skin-hydration and TEWL measurements. Evidence-based and validated protocols are needed for long-term application of these tools. We recommend using standardized study environments and comparison of lesional with nonlesional skin. Furthermore, studies with larger samples sizes are needed.

In conclusion, this systematic review provides an overview of the available noninvasive imaging and biophysical tools for diagnosis, severity assessment and therapy monitoring of rosacea. A selection of these tools are promising and provide valuable additional information about the structure and properties of rosacea skin in a manner well beyond that achievable through naked-eye examination; however, adequate and validated protocols are needed for further implementation of these tools in research.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1a. Review author's judgement about each risk of bias item for each included RCT (n = 14) with Cochrane Risk of Bias tool.

Fig S1b. Review author's judgement about each risk of bias item presented as percentages across all included RCTs (n = 14) with Cochrane Risk of Bias tool.

Fig S2a. Review author's judgement about each risk of bias item for each included cohort study and case report/series (n = 40) with Quality in Prognosis Studies tool.

Fig S2b. Review author's judgement about each risk of bias item presented as percentages across all included cohort studies and case reports/series (n = 40) with Quality in Prognosis Studies tool.

Table S1 Inclusion and exclusion criteria.

Table S2 Search strategy.

Table S3 Overview of categories of included studies.

Table S4 Overview of included studies describing noninvasive objective skin measurement techniques for rosacea assessment.

Table S5 Review author's judgement about each risk of bias item for each included case–control study (n = 24) with Newcastle–Ottawa scale.