

Imaging techniques in the diagnosis and monitoring of psoriasis (Review)

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Abstract. Plaque psoriasis is a chronic, immune-mediated disease, which has a multifactorial etiopathogenesis. Practical non-invasive techniques to monitor plaque psoriasis progression and treatment are necessary. Imaging techniques available for psoriasis assessment may vary in terms of resolution, depth of penetration and visual representation. This review summarizes the current developments in the field of psoriasis non-invasive imaging techniques, such as dermoscopy, conventional ultrasound and high frequency ultrasonography (HFUS), videocapillaroscopy (VC), reflectance confocal microscopy (RCM), optical microangiography (OMAG), laser Doppler imaging (LDI), multiphoton tomography (MPT) and optical coherence tomography (OCT). The aim was to collect and analyze data concerning types, indications, advantages and disadvantages of modern imaging techniques for *in vivo* psoriasis assessment. We focused on two main methods, videodermoscopy and HFUS, which can be included in daily dermatologists' practice and which may assist in establishing diagnosis, as well as monitoring response to topical and/or systemic therapy of psoriasis. Dermoscopy may be useful for a first evaluation and may offer an understanding of the type and distribution of blood vessels, as well as the color of the scale and the background of the lesion. Videodermoscopy allows magnification and offers a detailed evaluation of the vessel type. The utility of HFUS consists mainly in monitoring

therapy response. These methods may be comparable with virtual histopathology.

Contents

1. Introduction
2. Dermoscopy and videodermoscopy as non-invasive techniques in the diagnosis of psoriasis vulgaris
3. High frequency ultrasonography in monitoring therapeutic response in plaques psoriasis
4. Other imaging techniques
5. Conclusions

1. Introduction

Psoriasis represents a chronic immune-mediated systemic disease with multifactorial etiopathogenesis. It has a great impact on the patient's quality of life, affecting the skin and joints and being usually diagnosed according to clinical appearance (1). In ambiguous cases, a biopsy for histopathological examination is required. Taking into account that psoriasis is a chronic disease, more effective *in vivo* techniques are needed, in order to monitor plaque psoriasis progression. Currently, it can be monitored following topical or systemic treatment, using imaging techniques such as dermoscopy, videodermoscopy, conventional ultrasound and high frequency ultrasonography (HFUS), videocapillaroscopy (VC), reflectance confocal microscopy (RCM), laser Doppler imaging (LDI), optical coherence tomography (OCT), optical microangiography (OMAG) or multiphoton tomography (MPT). The aim was to collect and analyze data concerning types, indications, advantages and disadvantages of modern imaging techniques for *in vivo* psoriasis assessment. This review focuses on two main methods, videodermoscopy and HFUS, which can be included in daily dermatologists'

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practice and which may assist in establishing diagnoses, as well as in monitoring response to topical and/or systemic therapy of psoriasis.

As reported, classical clinical evaluation should be accompanied by imaging evaluation; videodermoscopy provides important data and magnifies the vascular pattern, which may persist in spite of clinical resolution. HFUS allows measurements of skin plaque, thickness being the first parameter to decrease in response to therapy (2).

2. Dermoscopy and videodermoscopy as non-invasive techniques in the diagnosis of psoriasis vulgaris

Dermoscopy offers a horizontal view/section and visualized structures have superficial vascular pattern. Psoriatic lesions assessed by dermoscopy technique offer details on typical feature of vessels, which are uniformly distributed as 'dotted', 'pinpoint' capillaries and coiled (or glomerular) vessels on a light red background accompanied by white diffuse scales. The same dermoscopic feature can be described using red dots (with diameters up to 0.1 mm) or 'red globules' terms (3,4). The vessels are correspondent to capillaries from elongated dermal papillae (5). The identification of other vessel patterns should give clues for other diagnoses apart from plaques psoriasis (6). In other inflammatory diseases, such as lichen planus, porokeratosis, pityriasis rubra pilaris, this capillary pattern can be encountered, although not evenly distributed.

Analyzed skin lesions of vulgar psoriasis called 'target lesions' can be recorded and stored in a computer archive under standardized conditions using videodermoscopy. Psoriasis plaque analysis can be performed with or without immersion fluid (oil or ultrasound gel). The use of videodermoscopy with 15- to 120-fold magnification enables a detailed evaluation of the size and the structure of vessels (Fig. 1). Red dots/globules visualized by over 50-fold magnification are called 'bushy capillaries', 'capillary bushes', 'convoluted basket-like capillaries' or 'basket-weave capillaries'. Other vascular patterns such as hairpin vessels, radial capillaries, globular rings, red lines, comma and lacunar vessels may also be observed. In palmoplantar psoriasis, pinpoint-like capillaries are linearly arranged along the furrows at a 50-fold magnification. Using high magnifications (x100-x400), psoriatic vessels have elongated, dilated and convoluted capillaries pattern (7). Scale removal in hyperkeratotic plaques may reveal typical capillaries pattern and may similarly identify small red blood drops associated with Auspitz's sign (3).

Other two dermoscopic plaque psoriasis criteria are represented by light red background and white superficial scales (3). Scale color is valuable for differentiating plaque psoriasis from other dermatoses with erythema and scales. Yellow scales are suggesting dermatitis as diagnosis (8). Dermoscopic pattern in specific localizations such as scalp, palmoplantar or inverse psoriasis is similar to plaque psoriasis with variations of scaling. Thick hyperkeratotic lesions on palmoplantar areas need scale removal, while in lesions lacking scaling, such as genital or flexural areas, red dots are regularly identified (3).

Dermoscopy may show evolution of psoriatic lesions during therapy and, similarly, it may identify disease recurrence early

or side effects of topical steroids such as linear vessels in skin atrophy before they are clinically visualized (9,10).

Micali *et al* (2) evaluated the therapeutical response in a study conducted on 42 patients with moderate to severe plaque psoriasis treated with biological agents including adalimumab, etanercept and ustekinumab. 'Target' psoriasis plaques at baseline and after 15, 30 and 60 days were monitored by clinical observation, videodermoscopy and HFUS. Specific target lesion ranged from 0 to 8 and included a 4-point scale for quantification of erythema, scaling and infiltration. Results showed that skin thickness improved first, followed by clinical and respectively vascular response. Clinical response, vascular pattern and skin thickness of 'target' psoriasis plaques were reduced by 83.9, 73.5 and 90% in adalimumab-treated patients, by 67.9, 49.7 and 79.3% in etanercept-treated patients; and reduced by 80.9, 66.4 and 80.1% in ustekinumab-treated patients. After 60 days of treatment, skin thickness was the first parameter that improved. Vascular improvement was slower than clinical and ultrasound response. A complete normalization of vascularization (capillaries with diameters $\leq 25 \mu\text{m}$) was absent in all patients despite their complete clinical response and the fact that clinical regression did not correlate with vascular changes. Further investigations are needed to evaluate if persistent 'bushy' capillaries, despite ultrasonography and clinical remission, represent a criterion for disease progression or may be correlated with recurrences rates (2).

In the study by Lacarrubba *et al* (11), it was noted that 87% of the examined patients had scalp psoriasis with typical vascular pattern on erythematous background accompanied by scales; this allowed a correct diagnosis of psoriasis. The registered specificity and sensitivity in this study was 88 and 84.9%, respectively, whereas seborrheic dermatitis was excluded. The most common terminology of vessel pattern distribution observed in psoriatic plaques in 77.4% cases (388 out of 501 patients with psoriasis vulgaris) were 'regular', with 'diffuse' and 'homogeneous' erythema. In addition, regularly distributed red dots and 'bushy' glomerular vessels on a reddish background with white scales were described (6,12).

Likewise, the color of the scale was evaluated in a study (10) with a total of 228 psoriatic plaques. Most frequently, the scale was described as 'white', 'whitish' or 'silvery white' and it was observed in a total of 214/228 (94%) psoriatic plaques at specific body sites (scalp, genitalia, folds, palmo-plantar area).

3. High frequency ultrasonography in monitoring therapeutic response in plaques psoriasis

HFUS is a non-invasive method of morpho-functional evaluation for the epidermal and dermal structures, subcutaneous fat and skin appendages. It constitutes a useful imaging method in *in vivo* studies of psoriatic lesions; the indications of this imaging technique are multiple, such as the evaluation of inflammatory diseases including psoriasis, scleroderma or pathologies such as contact dermatitis or acne. It allows high-resolution imaging and direct measurements regarding the thickness and acoustic density of the epidermis, dermis and subcutaneous fat. It generally uses variable frequency transducers (5-20 MHz) that are able to focus on different

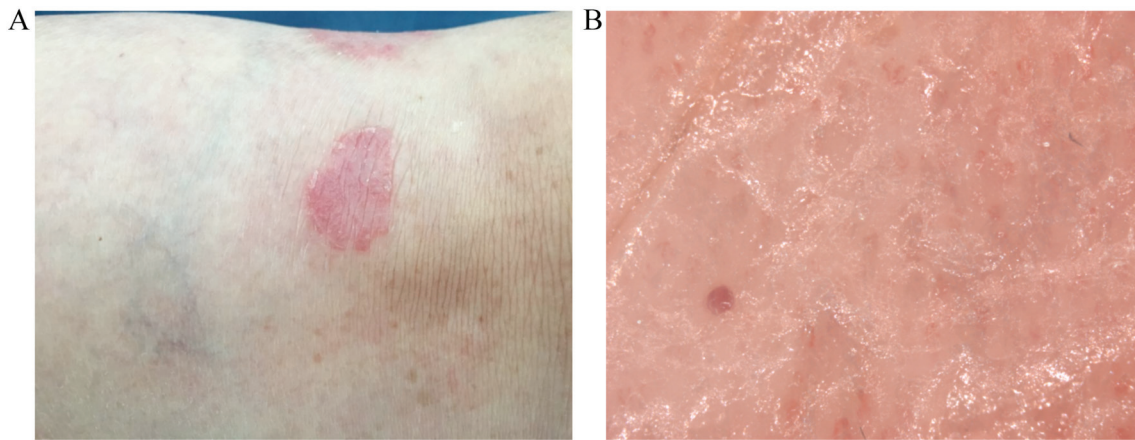


Figure 1. Plaque psoriasis. (A) Clinical image of a round, well-demarcated homogeneous erythematous, slightly scaly plaque situated on extensor surface of lower limbs. (B) Videodermoscopy (magnification, x120) with MicroDermVisiomed® system analysis of a psoriasis plaque in a patient treated with topical therapy (mometasone furoate) and biologicals (etanercept), which shows the presence of dilated, elongated, bushy vessels which are homogeneously distributed on a reddish background.

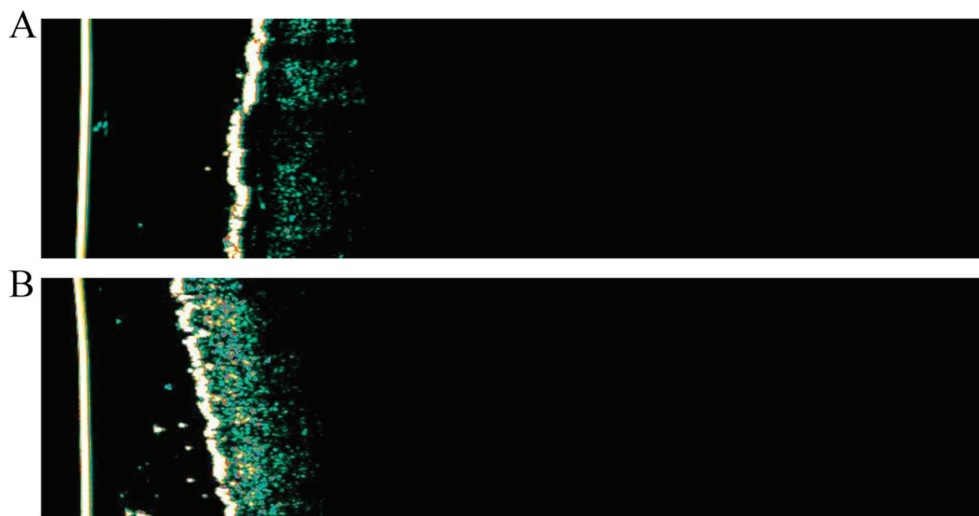


Figure 2. HFUS analysis with Dermascan C USB (20 MHz B-mode) of a psoriasis plaque showing thickening of epidermis with a hyperechogenic band, which represents hyperkeratosis and parakeratosis accompanied by hypoechogenic band, corresponding to the elongation of the dermal papillae (A) in comparison with adjacent healthy tissue (B).

tissue layers. The higher the resolution is, the better the details of the epidermis, dermis, subcutaneous fat and fascia. HFUS offers the classical two-dimensional, B-mode, vertical view/section, which allows *in vivo* cross-sectional images. The lateral resolution is 120 μm with a 22-MHz system and 32 μm with a 100-MHz probe. The penetration depth is 1-12 mm and both the epidermis and the dermis are visualized structures (7). HFUS has several advantages. It represents a real time and non-invasive imaging technique, which is well tolerated by patients. It has no exposure to X-rays and similarly, it has no special restrictions. They are portable and miniaturized medical devices largely accessible for doctors. Ultrasound may provide parameters such as depth of inflammatory lesions, which cannot be physically appreciated. The relevance of assessing the inflammation depth (superficial, intermediate or deep) is important in therapy management, including topical treatment, systemic/topical and systemic treatment, respectively (Fig. 2).

The main utility of HFUS in plaque psoriasis consists of the evaluation of the diseases under treatment. Plaques psoriasis examination using ultrasound shows intermediate inflammation; the main sonographic features are epidermal and dermal thickening and variable vascularization. The examination of psoriasis plaque lesions with HFUS indicates the following: hyperechogenic band representing the epidermis with hyperkeratosis and parakeratosis; echogenic or hypoechogenic band corresponding to the elongation of the dermal papillae as one of the most common features. This hypoechoic band in the upper dermis may be particularly detectable in the most active stages of active disease; hyperechogenic band given by the reticular dermis; subcutaneous hypoechogenic layer; increased dermal blood flow (vasodilatation) within the lesion, due to the local inflammatory process in Doppler examination (13).

Elastography is an ultrasound-based technique used in measuring tissue hardness with two modalities: strain (qualitative) and shear wave (quantitative). Using elastography,

increased tissue stiffness induced by the inflammatory reaction can be compared to the surrounding healthy skin. The response of stiffness, which decreases after topical or oral therapies, can be of great value for the assessment of plaque progression in psoriasis (13).

Indicators of effective therapy are represented by the reduction of epidermal and dermal thickness and particularly the disappearance of the hypoechogenic band from the superficial dermis (13-15). Nail assessment under therapy shows thickness variation of the nail plate and nail bed with objective reduced thickness. In a study with 19 psoriasis patients assessed using HFUS, the average increase in skin thickness in 31 plaques compared with apparently normal skin was an estimated 67% in the whole skin and 200% in the epidermis (14). In a study of 30 patients using 0.05% clobetasol propionate foam 20-MHz HFUS indicated a reduction in lesion thickness with values equal to those of unaffected skin (16). Musumeci *et al* (17) also reported that skin thickness was the first improved parameter during therapy in 20 psoriasis patients treated with cyclosporine prior to clinical improvement.

In nail psoriasis, the involvement may appear without cutaneous plaques. Psoriasis onychopathy can be detected early by loss of bimorph aspect, presence of pitting and irregularities of the nail plate surface. Ultrasonographic morphologic changes include thickening of the nail bed, focal hyperechoic areas and thickening (significant values >2 mm) of both dorsal and ventral plates with a convex nail appearance (13,18).

Power Doppler sonography represents a promising tool in the detection and semi-quantitative evaluation of superficial soft tissue perfusion. In the subclinical forms of the disease, the active status may be detected by Doppler examination identifying the pattern of microcirculation. The therapeutic response can be appreciated by the lesions vascular changes. Early psoriatic arthritis can be distinguished from seronegative rheumatoid arthritis by identifying dotted vessels in periungual tissue at ultrasonographic examination, increasing diagnostic specificity. In a study conducted on 30 patients with psoriasis and 15 healthy participants, 7-14 MHz power Doppler sonography permitted the detection of an increased blood flow signal in active psoriatic plaques (18). Another study showed that 12 patients with plaque psoriasis were evaluated using power Doppler sonography in comparison with clinical appearance, Psoriasis Area and Severity Index (PASI) scores and histologic findings before and after treatment with biologicals such as etanercept and data provided a significant correlation between these examinations. The results showed a significant positive correlation between power Doppler sonography examination, PASI scores and histologic degree of vascularization (19). Psoriasis onychopathy shows hypervascularisation in proximal and distal parts of the nail bed in the active phase of the disease, whereas in chronic phases hypovascularisation is remarked in distal parts. Other parameters of interest are the index of pulsatility, the index of resistivity, the speed and thickness of the nail bed and nail plate (13). The index of pulsatility is the first parameter changing in case of local inflammation and values >1 indicate a subclinical inflammatory process, while values >2 are suggestive of interphalangeal articular changes. An increased index of resistance towards 1, is present in psoriasis onychopathy (13).

The limitations and artifacts of HFUS include the presence of air or irregular surfaces of the skin. In addition, it is a time-consuming procedure and it depends on the operator's experience.

4. Other imaging techniques

RCM is a non-invasive imaging technique that allows *in vivo* imaging of dermatologic conditions, such as pigmented skin lesions, non-melanoma skin cancer (20,21) and several inflammatory diseases, including acute contact dermatitis, discoid lupus erythematosus (22), lichen planus (23) or plaque psoriasis (24-27). It helps to obtain a microscopic morphometric evaluation of plaque psoriasis with a resolution close to conventional histopathology (28,29). Real skin view/section is horizontal and the depth of penetration is 200-300 μm . Visualized structures are represented by epidermis and superficial dermis with a 0.5-1 μm lateral resolution and a 3-5 μm axial resolution (11). RCM identifies hyperkeratosis, parakeratosis, reduced or absent granular layer and papillomatosis. Stratum corneum shows refractile nucleated structures corresponding to parakeratotic keratinocytes (22). Stratum spinosum shows honeycomb pattern of the epithelium, whereas stratum granulosum shows granular layer reduction with presence of cells with bright granules in the center of the nucleus. Dermal papillae correspond to dark holes with small bright dots according to inflammatory infiltrates and papillomatosis (22).

Ardigo *et al* (22) obtained in more than 90% of 36 psoriasis vulgaris cases features of psoriasis vulgaris that were correlated with histopathological examination. Similarly, normal skin from 12 healthy control patients was compared with histopathological evaluation of psoriasis skin samples. In psoriasis cases, acanthosis with 75 to 300 μm thickness compared to normal skin (60-90 μm) was observed. Dermal papillae diameter was more than 100 μm and it was compared (bigger than 80 μm) with those from similar topographic areas of normal skin in the control group (22).

OMAG is an imaging technique that reproduces dynamic tissue bed microcirculation and blood perfusion using 2 mm imaging depth (29). 3D microcirculation assessing may be used in the diagnosis, treatment and management of human skin diseases, such as psoriasis vulgaris, skin cancer or hemangiomas. Ultra-high sensitive OMAG may reveal dense network of microvessels in psoriatic lesions and blood vessel elongation in comparison with normal skin (29).

Using fast scan B with a 1310 nm system, the capillary flow may be achieved with a imaging rate of 300 frames/sec and 3D imaging needs 5 sec to complete. Very slow blood flows at ~ 4 $\mu\text{m}/\text{sec}$ may be also revealed using this sensitive technique (30).

Laser Doppler perfusion imaging system is intended for visualization of skin blood perfusion and captures images based on Doppler effects, obtaining 2D cutaneous blood flow maps (31,32). Studies in psoriatic skin show that, in cutaneous psoriatic lesions, the blood flow is 9-13 times greater than the normal skin blood flow. Similarly, perilesional skin has a greater blood flow between 2.5 and 4.5 times in comparison with healthy skin (33).

Murray *et al* (34) studied the cutaneous blood flow in 23 plaques on the forearms of 20 patients with chronic plaque

psoriasis using dual wavelength laser Doppler perfusion. Perfusion was determined within the plaque, in uninvolved skin adjacent to the plaque and in nonadjacent skin. Results showed that perfusion in psoriatic plaques was increased as imaged by 633 nm (red wavelength) or 532 nm (green wavelength) in comparison with adjacent and nonadjacent uninvolved skin for both deeper (large) and superficial (small) vessels (34).

The effect of calcipotriol in 13 patients with plaque-type psoriasis who started twice a week PUVA was studied using LDI (35). In each patient, 2 plaques on symmetrical body sites were assessed. Calcipotriol therapy was used twice daily for one site, and placebo to the other; response was evaluated weekly for 6 weeks. Blood flux was measured using a scanning laser-Doppler velocimeter. In nine calcipotriol-treated plaques of 11 patients who completed the study it either cleared before the placebo-treated plaque ($n=7$), or was consistently judged to be better ($n=2$). Mean blood flux was identified significantly lower in the calcipotriol-treated plaques than in those treated with placebo from the third week of study. There was a median reduction in the UVA dose of 26.5% for calcipotriol compared with placebo in the 7 patients whose psoriatic lesions were cleared at the end of the study (35). Therefore, this technique may be used in assessing pathophysiology and treatment response in psoriasis (34,35).

MPT provides *in vivo* non-invasive virtual skin histologic examination with ultra-high subcellular resolution. Horizontal and vertical optical 3D images ($0.36 \times 0.36 \times 0.001 \text{ mm}^3$) of the region of interest with resolution down to $200 \mu\text{m}$ tissue depth are obtained using this imaging technique. It is based on fluorescent emission of excited molecules of endogenous fluorophores such as melanin, elastin, collagen, keratin and flavoprotein, which are detected with photomultipliers. This technique indicated pigmented lesions, psoriasis and skin aging in the evaluation (36).

Koehler *et al* (37) evaluated comparatively MPT and confocal laser scanning microscopy (CLSM) in different dermatological entities. Both methods were used for 47 patients (31 male, 16 female, aged between 24 and 88 years) with dermatological disorders including psoriasis, actinic keratosis, seborrheic dermatitis, angiomas, melanocytic nevi, malignant melanoma, pemphigus vulgaris and scarring. The results revealed that both methods are suitable for *in vivo* imaging of superficial skin layers and may therefore be useful in dermatological practice for the diagnosis of skin diseases. Synergies of the combination of MPT and CLSM may be obtained in order to benefit from the fast overview given by CLSM and the detailed imaging of skin structures provided by MPT.

OCT represents a non-invasive technique for morphological investigation of tissue based on the principle of Michelson interferometry. The light sources used are low coherent superluminescent diodes operating at a wavelength of $\sim 1300 \text{ nm}$ and OCT offers two-dimensional images with a scan length of a few millimeters, a resolution of $\sim 15 \mu\text{m}$ and a maximum detection depth of 1.5 mm in near real-time (32). High-definition OCT offers high lateral resolution of $1\text{--}3 \mu\text{m}$ (38-40). The measurement is non-invasive and has no side effects (36). Inflammatory skin diseases show thickening of the epidermis and reduction of the light attenuation in the dermis. The evaluation of therapy, such as swelling of

the horny layer due to application of a moisturizer and the monitoring of changes over time are possible. Due to its high resolution, this technique is an interesting addition to other morphological techniques (36,41). It may offer visualization of stratum corneum, papillary dermis and appendages in various dermatologic conditions. In psoriasis, it may reveal imaging of hyperkeratosis, acanthosis and the entrance signal is higher than in normal skin; likewise, it may evaluate the thickness of the epidermis (39). Dilated signal free cavities that correspond to dilated blood vessels of elongated dermal papillae may be identified (40).

In a study of 23 patients with psoriasis vulgaris treated with topical corticosteroids, cyclosporine and phototherapy, the mean epidermal thickness of psoriatic lesions was evaluated (41). The authors reported that epidermal thickness was $30\text{--}40 \mu\text{m}$ greater than that of normal skin, and these values decreased from initial registered values of $157.1 \mu\text{m}$ to a mean value of $128.84 \mu\text{m}$ after therapy. These measurements correlated with other parameters of disease, such as psoriasis area and severity index (PASI) (42).

5. Conclusions

The need for more reliable non-invasive assessment techniques in dermatology is increasing. Available imaging techniques vary in their sections, depth of penetration, lateral and axial resolution and in visualized structures. Besides clinical evaluation, high definition imaging techniques, such as dermoscopy and HFUS, may help in better monitoring psoriasis vulgaris.

Dermoscopy is useful in diagnosing and assessing psoriatic lesions in special locations, such as the scalp, nails, palms, soles and genital regions. The most common vascular feature of skin psoriatic lesions identified with dermoscopy using a 10-fold magnification is the presence of red dots/globules in a regular distribution. A detailed visualization of the cutaneous vessels is facilitated by videodermoscopy with a >50 -fold magnification and, most commonly, it reveals the presence of bushy (glomerular) vessels. The vascular changes are accompanied by a light red or pink background.

HFUS is an effective method that can be utilized alongside the physical examination for the diagnosis of inflammatory diseases, such as psoriasis vulgaris, providing accurate information on skin and nail anatomy; it is especially indicated for the assessment of therapeutic response in long-term follow-up (12,42,43).

RCM and OCT may compare to virtual histopathology and may provide high resolution microscopic imaging of cutaneous psoriatic lesions. Other imaging techniques including LDI, OMAG or MPT represent advanced high-definition promising imaging techniques and require further study.

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Authors' contributions

All authors contributed to the acquisition of the data and critical revision of manuscript for important intellectual content. IAG and LGS performed videodermoscopy and HFUS techniques and wrote the manuscript. LS, IAP, DV and MC wrote review sections about dermoscopy and ultrasound. EAP, AIP and TT searched data about the other imagistic techniques. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of The Clinical Emergency County Hospital 'Sf. Spiridon' (Iasi, Romania) and by the Research Ethics Committee of The 'Grigore T. Popa' University of Medicine and Pharmacy (Iasi, Romania). Written informed consent was obtained from all the patients prior to publication.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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