

ADVANCED NONINVASIVE DIAGNOSTIC METHODS OF PARASITIC SKIN DISEASES**L.O. Hulei**

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Key words:*parasitic skin disease, noninvasive methods of diagnostics.**A review, based on the database sources, such as Scopus, Pubmed, Medline, was conducted.**The aim of this research was to retrieve up-to-date information about advanced noninvasive diagnostic methods for verification of parasitic skin diseases. The study focused on scabies, pediculosis, demodicosis.*

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Ключові слова:*діагностика, неінвазивні методи, паразитарні хвороби шкіри.***НОВІТНІ НЕІНВАЗИВНІ МЕТОДИ ДІАГНОСТИКИ ПАРАЗИТАРНИХ ЗАХВОРЮВАНЬ ШКІРИ***Л.О. Гулей*

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*Проведено огляд баз даних літератури, таких як Scopus, Pubmed, Medline.**Мета дослідження – вивчення сучасних даних про передові неінвазивні діагностичні методи для верифікації паразитарних хвороб шкіри – корости, педикульозу, демодекозу.***Ключевые слова:***диагностика, неинвазивные методы, паразитарные болезни кожи.***НОВЕЙШИЕ НЕИНВАЗИВНЫЕ МЕТОДЫ ДИАГНОСТИКИ ПАРАЗИТАРНЫХ ЗАБОЛЕВАНИЙ КОЖИ***Л.О. Гулей*

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*Был проведен обзор баз данных литературы, таких как Scopus, Pubmed, Medline.**Цель исследования – изучение современных данных о передовых неинвазивных диагностических методах, используемых для подтверждения паразитарных болезней кожи – чесотки, педикулеза, демодекоза.*

Cutaneous parasitic skin diseases are frequent in human pathology[5]. They are a group of neglected parasitic diseases [28]. The most common are caused by ectoparasites such as scabies, pediculosis (head lice, body lice and pubic lice), demodicosis [17, 23]. The scabies mite (*Sarcoptes scabiei* var. *hominis*) is responsible for 1.5 million disability-adjusted life-years worldwide, as a result of pruritus, insomnia, school and work absences, and psychological distress. Misdiagnosis leads of Head lice infestations lead to 12–24 million missed school days and \$4–\$8 million of lost parental earnings annually in the USA [17]. Thus, prompt and accurate diagnostics is extremely important.

Nowadays, a wide range of equipment and methods exists for in vivo measurements in which assist in monitoring skin diseases, i.e. parasitic diseases [2, 4, 7, 15, 16, 20, 21]. Considering that data on the shortcomings of traditional confirmatory methods of parasitic skin diseases (PSD) are increasingly appearing

in the literature, new developing diagnostic possibilities have been studied [1, 2, 18]. Moreover, many advanced and noninvasive techniques such as videodermatoscopy, dermatoscopy, in vivo reflectance confocal microscopy, and optical coherence tomography have demonstrated improved efficacy in the diagnostics of parasitic skin infections [7, 18, 20, 23]. According to Aktaş Karabay E. et al. (2020) [1], who aimed at detecting Demodex infestation (DI) due to observational case-control study of 127 patients (43 with acne vulgaris, 43 with rosacea and 41 with seborrheic dermatitis) and 77 healthy controls, some limitations of the study were revealed: the lack of an objective scoring system in Demodicosis diagnosis which limits making comments on the association between the severity of the infestation and dermatoses and small sample size is a is another limitation. Furthermore, facial dermatosis, such as rosacea, perioral dermatitis, acne, seborrheic dermatitis are very often accompanied by Demodicosis [6, 23] and

its features, can be visually difficult to detect in those with dark skin phototypes. So, noninvasive objective skin measurement methods for this issue is timely [15, 29]. Mites are small arthropods belonging to the subclass Acari. They live in an enormous number of habitats; often spend their entire lives as parasites. Demodex mites belong to the superorder Acariformes, order Trombidiformes, suborder Prostigmata, superfamily Cheyletoidea, family Demodicidae and genus Demodex. Mites of the Demodicidae family are tiny organisms (usually 0,2–0,4 mm) [14]. A diagnosis of demodicosis or DI is considered when clinical signs/symptoms appear and when more than 5 mites/cm² are present or when they penetrate into the dermis [1, 2, 9, 17].

According to some experts, the gold standard for diagnosing scabies, namely direct microscopic examination of rashes obtained by skin scraping has low sensitivity (only 50%) [2, 18, 23]. In addition, skin scraping may be discomforting, therefore it is not well accepted by patients, who may not cooperate or even refuse the procedure. Moreover, this technique is time-consuming and not suitable to a busy practice. [18]. Levi et al. (2011) [13] convinced that diagnosis of scabies is based on the clinical picture and confirmed by the demonstration of *Sarcoptes*, its eggs or, its feces in skin scrapings or by dermoscopy, but lack of movement of the *S. scabiei* mite can be due to traumatic injury to the parasite during the scraping procedure. Interestingly enough, the polymerase chain reaction (PCR)-based method for detecting *S. scabiei* DNA in skin scrapings too. Nevertheless, the International Alliance for the Control of Scabies (IACS) to overcome the low sensitivities of all conventional diagnostic tests for scabies [3]. Human lice infestations result from *Pediculus humanus capitis* (head lice), *Pediculus humanus humanus* (body lice), and *Phthirus pubis* (pubic lice). Misdiagnosis of pediculosis leads to 12–24 million missed school days and \$4–\$8 million of lost parental earnings annually [17]. Taking everything into consideration, noninvasive real-time imaging technique that has been widely used for the diagnosis of PSD were inspected.

Digital dermoscopy or videodermoscopy (VD) is a noninvasive technique that allows a magnified in vivo observation of the skin with the visualization of morphologic features invisible to the naked eye [33]. It is performed with digital systems connected to a computer and requiring a video camera equipped with optic fibers and lenses that ensure magnification up to X1,000. VD is often employed using a polarized light source or, alternatively, nonpolarized. with the application of an immersion liquid (oil, alcohol, or water) on the skin aimed to minimize light reflection (epiluminescence microscopy). VD allows the inspection of the skin surface down to the superficial dermis, so it is perfectly suitable for the in vivo identification of burrows and scabies mites. VD is effective and sensitive, especially in cases with non-specific clinical features, allowing a detailed inspection of the skin with fast and clear detection of the diagnostic features, such as burrows at magnifications ranging from X40 to X100, and mites, larvae, eggs or feces at higher magnifications (up to X600). Moreover, using these magnifications, the specificity is virtually

100%, as the images obtained are unequivocal: the roundish translucent body of the mite, which is invisible at low magnifications, is clearly evident together with other anatomical structures of the mite, i.e., its legs (anterior and posterior) and rostrum (Figure 1) [18]. In most cases it is also possible to detect mites moving inside their burrows on condition that *S. scabiei* mite was not injured during the scraping procedure before [13]. VD is the process of attaching a dermatoscope to a digital camera system that allows for easy photographic documentation, high-definition capture of lesions for enlarged view on a computer screen, and storage for patient follow-up by specifically designed software systems. For this reason, they are quite expensive [18, 31, 33].



Figure 1. *Sarcoptes scabiei* observed by videodermoscopy at X400 magnification. The mite, localized at the end of the burrow, has a roundish body and pigmented head (arrowhead) and anterior legs (arrow). (Micali, 2016)

Dermoscopy. The dermatoscope is a handheld monocular optical system that enables magnification (10×) of the skin surface with the aid of an illumination system, either polarized or nonpolarized. Most current commercially available devices utilize LED illumination and provide the ability to switch between polarized and nonpolarized viewing [31, 33]. So, we can find the parasite. The diagnostic signs of scabies, described on dermoscopy, include: the classic S-shaped burrow seen as a curvilinear trail of scale; dark, triangular, or V-shaped structure corresponding to the fore portion of the mite (head and pair of legs). This has been variably referred to as the “triangle sign,” “delta glider,” “delta wing jet,” “jet plane” or spermatozoid appearance. The rest of the body of the mite shows up as relatively translucent; the presence of the burrow with the mite at its end has been called the “jet with contrail” appearance or the “jet liner with its trail”; scabies eggs can be seen as ovoid structures lying within the burrows; “mini triangle sign” refers to the maturing scabiatic eggs that show the minute heads of the maturing mite within the egg [10]. But in case of scabies it is possible to observe only the “jetliner with trail” structure visible with low-magnification VD (Figure 2) [7, 18, 22]. The use of X10 dermoscopy in

the diagnosis of scabies has some limitations. Firstly, especially for non-experienced operators, is that low magnification does not allow a clear differentiation between the “jetliner” sign and artefacts induced by scratching, such as excoriations, crusts, bleeding, or small dirt particles. Secondly, low magnification does not allow visualization of eggs and feces, which may often be the only diagnostic clue. In addition, the “jetliner” sign is hardly visible on dark skin, compromising the usefulness of dermoscopy in many countries, and in hairy body areas, where a clear visualization of the skin may be hampered. On top of that, it has been suggested that the use of handheld dermoscopy in or around the genital region may cause embarrassment because of close contact between the dermoscopist’s head and the patient’s skin [18].

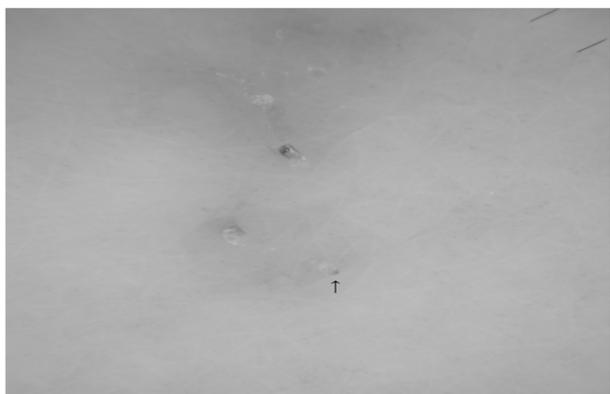


Figure 2. Burrow observed by dermoscopy at X10 magnification. A. The jet-shaped triangular structure corresponds to the pigmented anterior part of *Sarcoptes scabiei* (arrow). (Micali, 2016)

This is relevant in case of a sexually transmitted disease, for example, *Pthirus pubis* that usually appears with itch in the pubic and genital area. Dermoscopy confirms the clinical suspicion by direct detection of the *Pthirus*, whose body is more flattened and larger than *Pediculus capitis*, adherent to pubic hairs and blood-feeding. The blood-filled intestine of *Pthirus* resembles the body of a scorpion (Figure 3). Nits can be detected in *Pthirus pubis* as well [22].

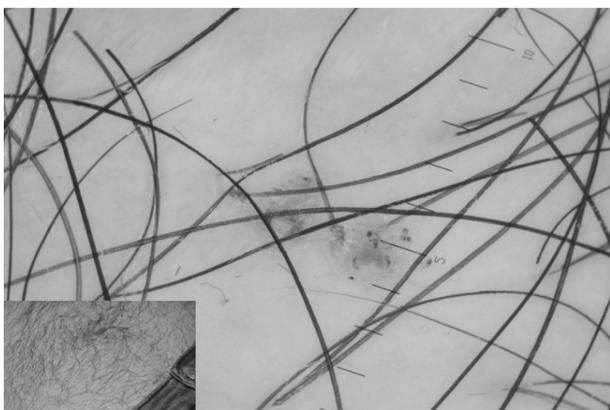


Figure 3. A couple of *Pthirus* found on the pubis of young man. Note the scorpion-like appearance of blood-filled intestine. (Piccolo, 2019)

Segal et al. [27] claimed that dermoscopy allows to visualize enlarged vessels of the skin and Demodex mites on its surface in Demodicosis. However, in this case, it is impossible to detect mites due to localization in the sebaceous glands and in the presence of nodular elements, macroabses [2, 27]. On the other hand, accordingly Friedman P, et al. (2017) [9], under dermoscopy, they observed non-follicular and perifollicular gelatinous threads or filaments protruding out of follicular openings known as “Demodex tails”. They account for the presence of the mite itself. Demodex follicular openings were also identified as dilated follicular openings containing round, amorphous, grayish/light brown plugs surrounded by an erythematous halo. They are both specific features of DD (Figure 4). Therefore dermoscopy may serve as a useful and non-invasive tool for the real-time identification of Demodex infestation, evaluation and follow-up [2, 9].

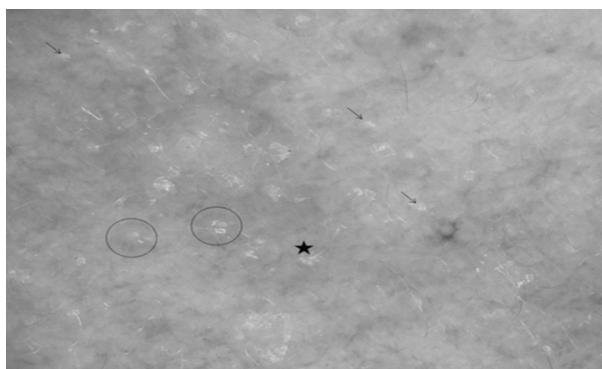
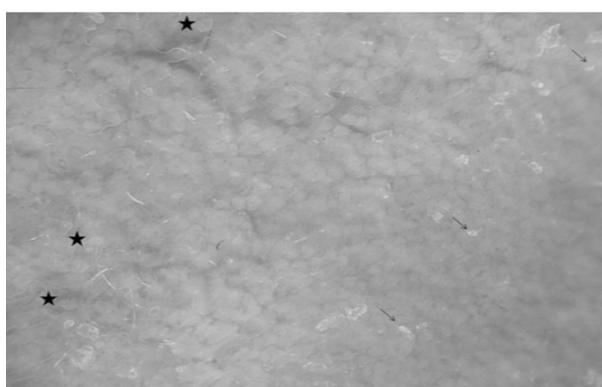


Figure 4. Dermoscopic picture: Demodex “tails” (arrow), Demodex “follicular openings” (star), filaments protruding out of follicular openings (circle), erythema and non-specific scales. (Friedman, 2017)

The first thing that needs to be said is the diagnosis pediculosis may cause some difficulties in patients with scaling conditions of the scalp (psoriasis, seborrheic dermatitis) and when panic is diffuse among communities where pediculosis is spreading [7, 17]. The detection of lice (Figure 5) [7] is difficult through the dermatoscope whereas, nits are well recognizable through trichoscopic examination as ovoid structures anchored to the hair shaft, which appear brown when still vital and translucent with a sharp free end when empty. Through dermoscopy nits can be distinguished from pseudonits, such as hair casts appearing as cylindrical whitish structures surrounding the hair shaft and easy to remove [22].

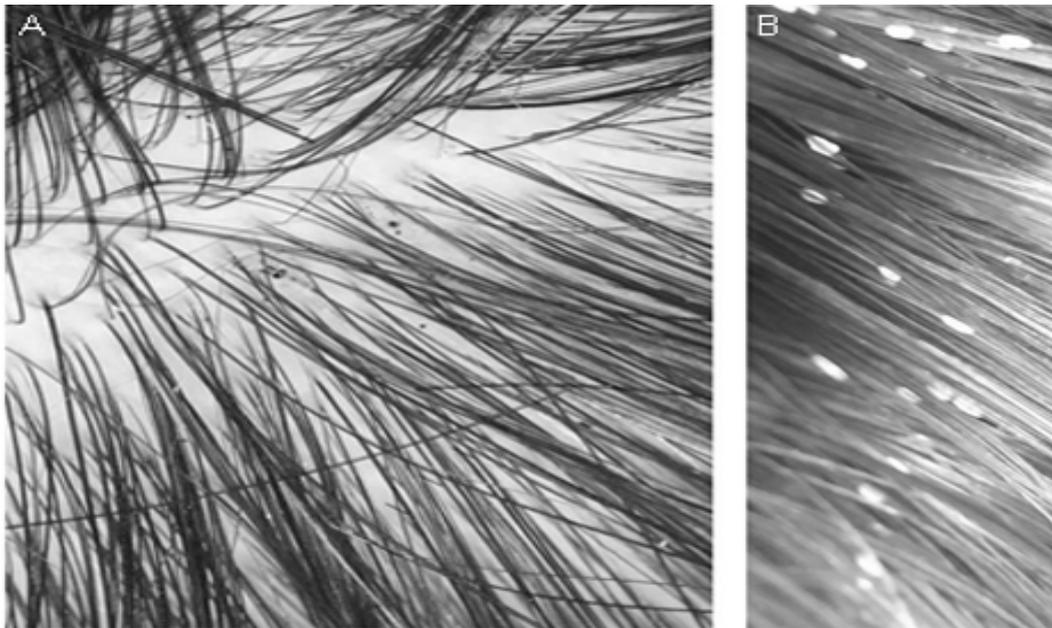


Figure 5. A. Pediculus capitis on the scalp observed by dermatoscopy. B. Nits, attached to the hair. (Cardoso, 2020)

Needless to say, a risk of spreading the PSD through the dermatoscope does exist therefore to avoid this issue following recommendations should pursue [10,22]. To start with, noncontact dermatoscopy should be preferred as the diagnostic approach, and nowadays it is easier because of growing diffusion of polarized handled dermatoscopes, which avoid skin contact. What is more, the use of antiseptics and instrument disinfection after each usage is mandatory. The holding of disposable transparent devices has been abandoned because of interference with the correct visualization of the skin [18, 22,31].

In Micali et al. (2016) opinion, the use of handheld dermatoscopy should be reserved to those cases in which no VD facilities are available, or for a preliminary screening of suspect lesions before skin scraping [18], because artefacts may occur [13]. Dermoscopy has been found to have 91% sensitivity, 86% specificity, 88% positive predictive value, and high diagnostic accuracy [10].

Reflectance confocal microscopy (RCM) (synonym Confocal laser scanning in vivo microscopy (CLSM)) is a novel, noninvasive imaging technique which permits real-time visualization of cellular components in the skin at a resolution compatible to that of conventional histology. As opposed to conventional histopathology, RCM provides a virtual three-dimensional image of the tissue by serial “cuts” at various depths. The system uses an 830-nm wavelength diode laser and provides high optical resolution (horizontal axis 2.0 μm , vertical axis 5.0 μm) to a penetration depth of 200–300 μm depending on anatomical site and skin thickness [12, 13, 23]. RCM is a new diagnostic optical technique capable of horizontally (en face) scanning the skin at different layers by the use of a laser beam reflected according to the refraction index of the different structures encountered. This process results in black/white images showing microscopic details of the inspected area [2,18]. CLSM is a new method for studying the structure of the skin in the form of pictures of white-grey-black shades. Melanocytes

and keratinocytes on the pictures look bright white, air, and serous fluid - black. Confocal laser scanning in vivo microscopy allows you to determine the thickness and visualize different layers of the skin. Thus, the method provides additional information on the composition and structure of the skin. The method of CLSM can be equated to histological examination of the skin with the advantage that the study is performed non-invasively [8, 23]. CLSM may be particularly suited for the diagnosis of cutaneous infestations or infections as most of the pathologic clues are confined to the epidermis. The high resolution of RCM (1.00 μm laterally and 5 μm vertically) allows the visualization of most skin parasites [13]. According to different data, the sensitivity of CLSM is 83-91%, specificity is 95-99% [2]. For in vivo use, there are two commercially available microscopes: VivaScope 1500® and 3000® (Caliber: imaging and diagnostics, Rochester, NY, USA). The standard device, VivaScope 1500®, allows the scanning of a large area (up to 8 \times 8mm), owing to both the mosaic and stack imaging modalities [23]. However, it generally requires an acquisition time of about 10 minutes per lesion and it cannot be used on small or curved surfaces. The handheld compact camera, VivaScope® 3000, is easier to manipulate, allows a faster examination of multiple skin lesions in real time (1-2 minutes per lesion), and has a smaller tip enabling access to hard-to-reach body areas, such as fingers and genitalia [18]. Nonetheless, it is limited by a smaller field of view [23].

RCM has been suggested as a diagnostic tool for scabies [7, 13, 18, 23]. It allows for the identification of the burrow, a tortuous large segment at the level of the stratum granulosum/spinosum, recognized by the characteristic honeycomb pattern of the surrounding epidermis, and of the mite, an ovoid body with head in the anterior part and short legs (length 30 μm , width 25 μm) (Figure. 6, 7). Detection of the eggs (15 x 8 μm), containing mite embryos, and of the high-refractive fecal material can also be performed. The technique is time-

consuming, as the examination of each lesion requires about 10 minutes; however, the use of the new handheld device has significantly shortened the duration of the test.

it allowed facilitating quantification of mites to be useful in Norwegian scabies [18]. RCM might be useful in the clinical situation to determine scabicide efficacy [13].

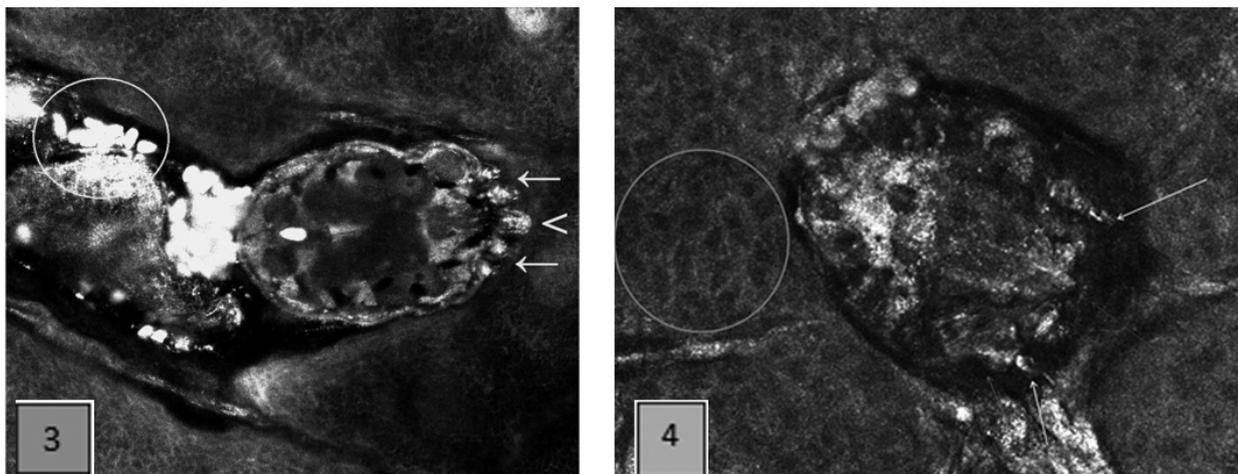


Figure 6. *Sarcptes scabiei* observed at the end of a burrow by handheld confocal microscopy.

The technique enables a detailed visualization of the head (arrowhead) and of the anterior legs (arrows). The feces appear as high-refractive roundish structures (circle). (Micali, 2016)

Figure 7. RCM image at 5.97 μm below the outer skin level. The ovoid body of the *S. scabiei* mite is visible inside the hyporefractive burrow. Two anterior legs (white arrows) including the coxa (blue arrow) as well as the head (red arrow) are discernible. (Lewi, 2011)

Today the usage CLSM in dermatology is considered to be one of the most promising methods, despite the fact that it has a number of disadvantages (obtaining relatively surface images up to 200 μm , which limits the possibility of studying deeper layers of the skin, images, the high cost of equipment and its operation and, as a consequence, inaccessibility for a larger number of dermatologists) [2, 12]. One of the advantages of the method is the ability to detect and quantify *Demodex* folliculorum on the facial skin of patients with rosacea and acne by counting mites and follicles per unit area [2].

Sattler et al. [25], examining the skin of patients with rosacea, described the presence of *Demodex* in the form of rounded or long conical structures. CLSM makes it possible to visualize mites located in deeper layers of the skin that are not accessible for scarification. This method has a high potential of diagnostic capabilities, namely, it makes it possible to scan various layers of the skin, which allows determining the depth of the mites ($\approx 46.63 \mu\text{m}$) and corresponds to the level of the granular layer of the epidermis; counting the number of *Demodex* in the follicle ($N = 3.37$) and setting the size of the mites (which is equal to 0.024 microns) (Fig. 8) [11]. Turgut et al. [30] revealed a mean number of mites per infested follicle of 3.17 ± 0.96 in papulopustular rosacea, 1.90 ± 1.14 in erythematotelangiectatic rosacea, and 0.74 ± 1.02 in controls ($P < 0.001$). Experts emphasize that one of the most prominent pros of CLSM is the absence of traumatization of the epithelium and the painfulness of the procedure [2].

Demodex was defined as rounded or long cone-

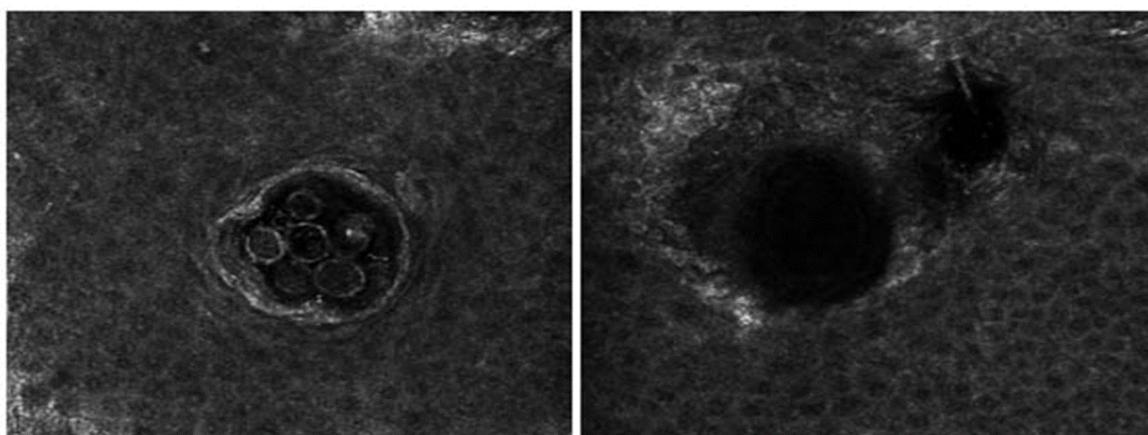


Figure 8. Images obtained using confocal laser scanning microscope VivaScope 1500® Lucid Inc., Rochester, NY). Hair follicles and sebaceous glands with the presence (left) and absence (right) of *Demodex* mites

shaped formations in hair follicle orifices and sebaceous glands. (Kubano, 2016)

Ruini et al. (2017) [24] reported that the density of Demodex mites in patients with rosacea under therapy can be monitored by using RCM: a reduction in the brightness of residual mites and a loss of definition of their bright contours after topical application of ivermectin 10mg/g cream was observed.

In recent years high-definition (HD) optical coherence tomography (OCT) (synonym: line-field confocal optical coherence tomography (LC-OCT)) is a non-invasive optical technique recently developed for skin examination in vivo. It provides real-time, high-resolution vertical images with an isotropic resolution of $\sim 1 \mu\text{m}$ and a penetration depth of $\sim 500 \mu\text{m}$ [19, 26]. These devices have been developed that can potentially be used for the visualization of intrafollicular demodex mites, for quantification of skin changes, and for evaluation of treatment effects due to the higher resolution [32]. OCT is a noninvasive imaging method. Using infrared broadband light sources, images of superficial skin layers can be obtained in vivo and real time. The OCT system consists of an interferometer that simultaneously analyzes the entire depth of the tissue with vertical scans. Two-dimensional images, similar in appearance to those seen in ultrasound but with a significantly higher resolution, are generated. Some systems can also yield composite three-dimensional images. OCT might prove useful for the diagnosis of parasitic infestations of the skin with scabies mites and the naturally occurring demodex mites have been demonstrated with OCT, allowing visualization of the main skin components, including the stratum corneum, viable epidermis, papillary dermis, and appendages [18]. Burrows that were created subcorneal by Scabies mites were visualized in vivo with OCT [8]. Five cases were observed [4], where scabies mites were identified in the vertical images as an ovoid structure (mango-/almond-shaped) measuring approximately $0.20 \times 0.30 \text{ mm}$ or less in the epidermis just beneath the stratum corneum (Figure 9). In the horizontal images,

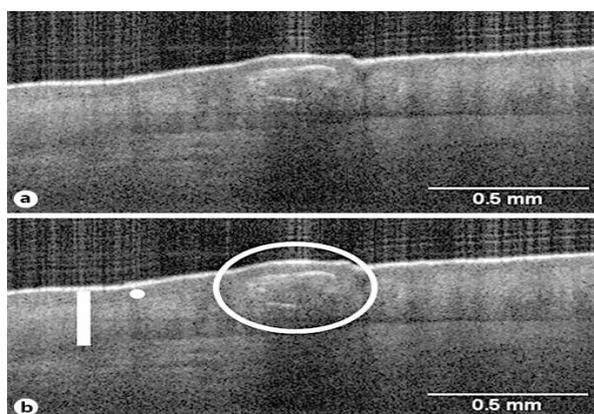


Figure 9. a, b Vertical OCT image of the skin of an interdigital finger web. The mango-shaped mite (encircled) is surrounded by the hyperreflective burrow wall. The mite is just below the stratum granulosum (white dot). The epidermis is indicated by a white bar. (Banzhaf, 2013)

the mite measured $0.30 \times 0.15 \text{ mm}$. The optical density of the mite was the same as the surrounding tissue, but the mite was delineated by, respectively, a hyporeflective fringe (lumen of the burrow) and a hyperreflective fringe (the scaly burrow wall). In some images, a burrow behind the mite was visualized as well, depending on the scan direction. The lumen of the burrow appeared hyporeflective and either ovoid in cross section or longitudinal depending of the cut. However, it could also appear hyperreflective if scaly.

The OCT system used provides the possibility of combining multiple images acquired in stacks into 3D datasets, potentially increasing accuracy and more detailed, non-real-time analysis. S. mites also present in the upper part of the stratum granulosum and not only within stratum corneum. Demodex mites are situated corresponding to hair follicles and their degree of presence can be demonstrated with HD OCT [21] in 20 patients with demodex-related skin diseases [16]. OCT enabling treatment monitoring in demodex-related diseases. Maier T. et al. [16] due to HD-OCT images depicted mites in the en-face mode as bright round dots in groups of 3-5 mites per hair follicle. In the patients with demodex-related disease, a mean number of 3.4 mites per follicle were detected with a mean number of 2.9 infested follicles per area of view compared to a mean of 0.6 mites in 0.4 infested follicles in the controls. Regarding resolution and penetration depth the OCT technique is taking a middle position in comparison to other noninvasive imaging device in dermatology such as RCM [34].

Conclusions

In general, dermoscopy's utility of advanced noninvasive diagnostic methods for PSD confirmation is obvious as the supplementary method. They are non-invasive, painless, and highly diagnostic. We also agree that PSD prompt identification and management can provide rapid clinical improvement and return a patient to the normal lifestyle [17]. On the whole, dermoscopy is non-invasive imaging methods with the advantage of visualizing in vivo structures with low resolution whereas RCM or CLSM high one. As far as we concerned, RCM or CLSM and OCT seem to be effective methods but expensive ones. Presumably, expenses are likely to come down with more widespread indications and increasing availability of neoteric noninvasive techniques with dermatologists. Although all of them might be useful in the particular clinical case to determine PSD treatment efficacy, such as scabies, pediculosis, demodicosis. Thus, to improve and optimize the provision of dermatovenereological care dermatologists have to keep pace with the changing times. We have supported Sweileh W.(2017) that this study is useful for people interested in advancing research in this field [28].

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