Ultrasonography of the nail unit reveals quantitative and qualitative alterations in patients with psoriasis and psoriatic arthritis

Luca Idolazzi¹, Paolo Gisondi², Angelo Fassio¹, Ombretta Viapiana¹, Alessandro Giollo¹, Maurizio Rossini¹, Giampiero Girolomoni², Davide Gatti¹

¹Rheumatology Unit, ²Dermatology Clinic, Department of Medicine, University of Verona, Verona, Italy

Abstract

Aims: The nail unit is a matter of interest both for dermatologist and rheumatologist. The nail is considered one of the possible targets of assessment, especially when ultrasonography is performed.

The aim of the study is to highlight peculiar features and alterations of the nail unit in patients affected by psoriasis and psoriatic arthritis versus healthy controls using ultrasonography. **Materials and methods:** The study sample included 82 patients affected by psoriasis and/or psoriatic arthritis and 50 healthy controls. The patients were consecutively enrolled during their routine visit in the outpatient clinic and they performed clinical and ultrasonographic evaluation of the nail. The evaluation of disease activity was done using Disease Activity in Psoriatic Arthritis (DAPSA), Psoriasis Activity Severity Index (PASI), and Nail Psoriasis Severity Index (NAPSI). **Results:** Multivariate analysis of variance was performed between groups. Post hoc analysis underlined the differences between healthy and affected regarding nail plate thickness (0.063 ± 0.011 cm for patients with psoriasis, 0.065 ± 0.014 cm for patients with psoriatic arthritis and 0.051 ± 0.006 cm for healthy controls, $p < 0.05$). Elementary lesions of nail plate and nail bed were compared using Pearson's chi square test between patients in psoriasis and psoriatic arthritis groups, with no differences except for a trend for onycholysis and crumbling ($p = 0.07$ and 0.06 , respectively) in the psoriatic arthritis group. ROC curves were calculated ($AUC = 0.68$) obtaining also quantitative cut offs for nail plate and nail bed thickness in the affected vs healthy patients. **Conclusions:** Our study shows that ultrasonography may be a potential advantage in clinical practice. Our results strengthen the information already available in the literature and add quantitative parameters for ultrasonography of the nail.

Keywords: nail; psoriatic arthritis; psoriasis; ultrasonography

Introduction

Psoriatic onychopathy (PsO) is one of the hallmarks of psoriasis (Ps) and it is very common, especially in association with plaque psoriasis. It is esteemed that up to 70-80% of patients with plaque Ps have nail involvement [1-3]. Although Ps alone is quite uncommon accounting for only 5-10% of patients with Ps [4] the proportion of patients with isolated nail involvement who will later develop plaque Ps is currently unknown. Conversely,

the strong association between Ps and psoriatic arthritis (PsA) is well known [5]. The prevalence of PsA in patients affected by PsO ranges from 6% to 40% depending on the study design [6]. Ps is closely associated with the development of PsA, correlating to specific subsets of skin manifestations such as scalp and palmoplantar psoriasis [7]. Plaque Ps and Ps of the nails, scalp, and intertriginous areas have been associated with the likelihood of developing PsA which is in turn related to the magnitude of the lesions. Of note, the tightest correlation with PsA has been found for patients with nail disease [8].

The nail unit is a complex structure consisting of several elements: nail matrix, which produces the nail plate; the nail plate itself, namely the common term used to describe the whole unit; nail bed epithelium, responsible for the attachment to the dermis; hyponychium; proximal nail fold; dermis of the nail matrix; and nail bed [9]. Some

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Corresponding author: Idolazzi Luca

Piazzale A. Stefani 1

37126 Verona, Italy

Phone: +390458123996, Fax: +390458127276

E-mail: luca.idolazzi@univr.it

elements, such as the nail bed, nail plate, and matrix, are involved more frequently than others in Ps or PsA. Lesions such as pitting, leukonychia, red spots in the lunula, or crumbling are found in the nail plate. Oil-drop or salmon patches, dyschromia, splinter hemorrhage, and nail bed hyperkeratosis are the typical lesions when the nail bed is involved [10]. These alterations are generally clearly visible to clinical examination and easily recognized by the physician. In this regard, the Nail Psoriasis Severity Index (NAPSI) is a useful and validated tool for the assessment of PsO [11] and it is well accepted also in rheumatology for the assessment of nail involvement in patients affected by PsA [12]. Furthermore, PsA may also be associated with proximal nailfold vascular changes [13] which can be detected with imaging techniques.

The nail unit has been a topic of interest shared by dermatologists and rheumatologists since McGonagle et al [14,15] raised the attention to the nail enthesis complex as a possible link between skin and joint [5,16]. The nail unit is easy to study thanks to some imaging techniques such as ultrasonography (US) of nails, which has been available since high frequencies probes were introduced in musculoskeletal examination [17–22] and the nail has been considered one of the possible targets for assessing the disease and defining its prognosis [23–25]. A few previous studies of magnetic resonance imaging (MRI) also described the strong relationship between the distal interphalangeal joint (DIP) and the nail [14,26]. The US approach to the nail is also promising, with several chances of application in everyday practice [16,27]. The quantitative approach was explored by Wollina et al [28] with volumetric measurements of the nail and a qualitative description of the image, detailing the alterations which were not evident at clinical examination [19,29]. On the other hand, a semi quantitative approach is probably the most convenient, since a standardized technique can be valid, reliable and feasible for studying alterations in Ps [17,30,31]. In a previous paper we already evaluated the possible implementation of ultrasound examination for revealing changes both in the nail plate and the nail bed [32], showing that quantitative measures can be a promising tool for nail assessment.

Previously, Scarpa et al suggested that imaging could be useful even in patients with not a clear involvement at clinical examination [33], as US can detect subclinical nail alterations, potentially identifying patients affected by PSA before they fulfil the classification sets (e.g. CASPAR criteria).

The primary objective of this study was to evaluate the anatomical changes in the nail revealed by US and to describe the clinical features which can help to better characterize patients affected by Ps and/or PsA. The

secondary objective is to find a quantitative measure of nail ultrasonography which can be useful to discriminate patients with Ps or PSA from healthy controls.

Patients and Methods

Study population

This is an observational study conducted in the setting of a combined dermatology-rheumatology outpatient clinic of the Department of Medicine, University of Verona. In this clinic, patients affected by Ps disease with or without active skin involvement are jointly evaluated by a dermatologist and a rheumatologist in order to provide a more comprehensive assessment of their disease. The study sample included 82 patients affected by Ps and/or PsA and 50 healthy controls (HC). Patients referred to the dermatology-rheumatology outpatient clinic were consecutively enrolled for a period of 6 months after their diagnosis of PSA was confirmed by a dermatologist. Alterations of the nails other than Ps were excluded by a dermatologist as follows: infection by clinical examination and microscopic examination or culture; traumatic onychopathy or other conditions by clinical data and clinical examination. Patients taking biologic agents were excluded *a priori* for study design, reducing the risk of bias due to treatment.

The institutional review board of the Medical School of Verona and the Ethical Committee approved the study. All the procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Declaration of Helsinki of 1975, as revised in 1983.

Clinical assessments

Each patient underwent a physical examination and data on disease activity and anthropometry were collected. Disease activity was assessed with Psoriasis Area Severity Index (PASI), NAPSI, and Disease Activity in Psoriatic Arthritis (DAPSA) respectively for skin, nail and joint domains [34]. C-reactive protein (CRP) was used for DAPSA calculation. The PASI is a measure commonly used in clinical practice and in randomized clinical trials by dermatologists for evaluating not only the extension of the psoriasis but also the thickening, erythema, and scaling of the skin [34,35]. The NAPSI [11] is activity index used by dermatologists for evaluating nails and especially alterations of nail bed and nail plate observed during clinical examination. For assessing joint involvement the DAPSA score was used, taking into account four principal components: patient global and pain visual analog scale (VAS) scores, tender and swollen joint counts, and acute-phase reactant (CRP level) [36].

Ultrasound procedure

After clinical examination, the patient was led to a separate darkened room for US evaluation. The patient was assessed by two different sonographers blind to clinical data, diagnosis and identity of the patient. Only the hand was visible during the examination and patient and clinician were not allowed to speak. The Cohen's kappa coefficient between the ultrasonographers was 0.78, previously verified on 50 selected images of the nail unit. The US examination was performed using a General Electric Logiq S8 machine with a multifrequency linear probe (Li8-18) with setting at 18 MHz. Power Doppler parameters were set selecting a PRF of 600 KHz and frequency of 10 MHz. The scan was performed in a longitudinal axis by placing the probe in the middle of the second fingernail, dominant side hand. In our previous experience [32] we showed that the examination of the second nail of the dominant hand achieved the most remarkable difference among other digits in Ps population compared with controls. The same result was confirmed later by other authors [19].

The normal aspect of the nail is a trilaminar structure with the first lamina which is hyperechoic, just as the third one, while the second is anechoic. This structure goes deep below the epidermis in the proximal part of the nail plate, ending just above a hypoechoic area that is the nail matrix. The nail bed is evident below the nail plate and just above the cortical bone of the distal phalangeal joint [19,24]. The clinical evaluation of the nail permitted to recognize the elementary lesions of the nail bed and nail plate and these structures were specifically targeted during the ultrasound assessment [37–39]. According to previous data, mean values for the nail bed range from 1.5 to 3 mm [19,37,39].

As no previous data were available in literature, we developed a novel score based on ultrasonographic findings for the assessment of nail plate and nail bed. Several measurements of the nail plate and nail bed were taken at the middle third of the plate (fig 1). In order to enhance the accuracy of measurements, the image was magnified using the zoom function during the examination. The mean of three measurements was then considered for statistical analysis. Nail structural alterations were also assessed as well as the power Doppler (PD) signal of the nail bed and at the enthesis of the extensor tendon. The structural alterations were then evaluated using a semi quantitative score for the magnitude of the alteration. This score provides a value of 0 - if no alteration of the plate is found, 1 - if the double line is slightly altered, 2 - if the alteration is severe enough to provide a large modification of the structure detected by ultrasonography, and 3 - if the alterations completely loose the standard image

Fig 1. Nail unit ultrasonography: a) a complete picture of a nail as it appears at ultrasonography. The nail plate is marked with the letter A, while B is the nail bed. The nail matrix (C) is easily recognizable which is contiguous with the enthesis of the finger extensor tendon. The finger extensor tendon insertion is clearly visible as proximal to the matrix (D); b) magnification of the middle third, reporting an example of how the thickness of nail plate and nail bed was calculated. The thickness was measured three times and then the mean was calculated (i.e. 0.6 mm for nail plate and 2.23 mm for nail bed)

of a normal plate. The semi quantitative approach proposed by Gutierrez et al [40] was used for scoring the PD signal of the nail bed. Briefly, a score of 1 is given for a confluent signal in less than 25% of the nail bed area, 2 for a confluent signal in more than 25% and less than 50% of the nail bed area, and 3 for confluent signal in more than 50% of the nail bed area. A score of 1 or 0 was given if a PD signal at the enthesis or abnormal signal from the nail bed and was present or absent accordingly.

Statistical analysis

Data are reported as mean values±standard deviation (medians and interquartile ranges for variables deviating from normality) or percentages. Accounting for an esteemed standard deviation of 0.02 mm, we calculated that a sample size of at least 22 patients in each group was sufficient to detect at least a 0.2 mm difference between patients affected by psoriatic disease and healthy controls with a power of 95%. No quantitative data are available in literature for a comparison. Between groups, comparisons of continued variables (nail plate thickness, nail bed thickness, PASI, NAPSI, age, and BMI) were performed by univariable and multivariable analysis of variance (ANOVA) with the Tamhane's test for post hoc analysis. Between groups, comparisons of categorical variables (lesions for nail plate and nail bed considered in the PASI score) were performed by the Pearson's chi

Table I. Study sample and results of ANOVA analysis.

	HC (n-50)	Ps (n-31)	PsA (n-51)	p value
Age	48.44±13.95	48.22±14.7	50.92±13.9	0.51
Male	22	22	26	
BMI	24.61±3.92	28.61±4.95*	28.64±5.84*	≤0.001 vs HC
NPT (mm)	0.051±0.006	0.063±0.011*	0.065±0.014*	≤0.001 vs HC
NBT (mm)	0.22±0.02	0.25±0.05*	0.25±0.04*	≤0.001 vs HC
Clinical nail involvement ¹	0/50	13/18	32/19	<0.04 Ps vs PsA
US involvement ²	0 (0%)	1 (3%)	5 (9%)	n.a.
US involvement ³	15 (30%)	13 (41.9%)	13 (25.5%)	0.49 vs HC
PASI	n.a.	5.22±5	2.65±3.4	0.056
NAPSI	n.a.	4.35±10.6	8.51±11.4	0.28
DAPSA	n.a.	n.a.	15.5±9.3	

Data are presented as a mean±standard deviation or percentage. n- number of patients; BMI: body mass index; NPT: nail plate thickness; NBT: nail bed thickness; n.a.: not applicable; HC: healthy controls; Ps: patient group with psoriasis, PsA: patient group with psoriatic arthritis; ¹: ratio between patients with involved or not involved nails at clinical examination; ²: absolute number and percentage of patients who show US qualitative alterations and had no nail involvement at clinical examination; ³: absolute number and percentage of patients who show US nail involvement if the proposed cut off is applied; US involvement: not reported as “present at clinical examination”; PASI: Psoriasis Area Severity Index; NAPSI: Nail Psoriasis Severity Index; DAPSA: Disease Activity in Psoriatic Arthritis; * = p≤0.001 vs HC

square test and odds ratios were calculated for significant results. Significant correlations between nail plate thickness and other variables (PASI, NAPSI, BMI and DAPSA) were analyzed by stepwise linear regression. Receiver operating characteristic (ROC) curves were plotted to assess the accuracy of nail plate thickness and nail bed thickness in discriminating HC from patients. All statistical analyses were performed using SPSS Version 20 (SPSS, Inc., Chicago, IL, USA) and statistical significance was identified by two-tailed p<0.05.

Results

Evaluation of nail plate and nail bed thickness

Fifty-one patients with PsA constituted the PsA group ('PsA') and 31 patients with Ps the Ps group ('Ps'). Fifty healthy controls ('HC' group) were enrolled as well. Data on demographics, anthropometry and disease activity are reported in Table I. The ANOVA showed significant differences between groups for BMI, nail plate and nail bed thickness. BMI was significantly lower in HC than patients (p<0.01). Nail plate thickness and nail bed thickness were also significant lower in the HC group (p<0.05). The post hoc analyses revealed no differences between groups, but patients affected by PsA had a higher PASI (p=0.056 vs other groups).

Evaluation of alterations of nail bed and nail plate

The patients found with abnormalities of the items categorized in NAPSI score was compared between Ps and PsA groups using the Pearson's Chi square test or Fisher's exact test when appropriate. Leukonychia, red spots in lunula, and splinter hemorrhages were excluded from this analysis due to the small number of cases.

Table II. P values of Pearson's Chi Square test for power Doppler ultrasonography nail bed and nail entheses.

	Nail bed	Nail entheses
Ps vs PsA	0.883	0.789
Ps vs HC	< 0.005	0.06
PsA vs HC	<0.001	< 0.001

The data show values regarding the comparison between groups; Ps: patient group with psoriasis, PsA: patient group with psoriatic arthritis; HC: healthy controls.

We found no statistically significant difference between groups for nail plate crumbling, oil drop discoloration, onycholysis, and hyperkeratosis, although a trend was noticed for onycholysis and crumbling (p=0.07 and p=0.06, respectively). Nail pitting was found more frequently in the PsA group than the Ps group (OR 9.41, C.I. 0.15-0.99, p=0.03).

Nail abnormalities on physical examination were found in 40% of patients affected by Ps and 62.7% affected by PsA. Conversely, the proportion of patients who had loss of trilaminar structure (any grade) despite a normal physical examination was 3% in Ps (1/31) and 9% in PsA (5/51) groups.

We found a significant difference in PDUS of the nail bed when comparing HC and Ps and HC and PsA. Likewise, the PDUS at the entheses was higher than HC (Ps vs HC 13.7% vs 2.5%; PsAs 29% vs HC 3%). Statistical differences are shown in Table II.

Correlations and ROC curves

We used stepwise linear regression to establish correlations between either nail plate thickness or nail bed thickness as the dependent variables and PASI, NAPSI, and BMI as predictors. Nail plate thickness was signifi-

Fig 2. ROC Curve Analysis a) for nail plate thickness (AUC 0.809) and b) for nail bed thickness (AUC 0.68). The ROC curves shown are between people affected by PsA vs healthy controls since the curves calculated for Ps patients are truly similar.

cantly related to nail bed thickness and NAPSII (R^2 0.363 and 0.464, respectively, $p \leq 0.001$). Nail bed thickness was significantly associated with nail plate thickness and NAPSII (R^2 0.363 and 0.464, respectively, $p \leq 0.005$). No correlation was found between nail plate thickness or nail bed thickness and DAPSA in the PsA group.

Finally, we obtained ROC curves for the different possible cutoff of nail plate thickness and nail bed thickness discriminating HC from the PsA group and the Ps group (pooled). The area under the curve (AUC) was similar when comparing either the two groups with HC. AUC for nail plate thickness was 0.809, showing good accuracy. Conversely, the ROC curve for nail bed thickness showed poor accuracy (fig 2) and no cutoff was calculated for it. A nail plate thickness above 0.63 mm was able to discriminate HC from patients with a sensibility of 70% and a specificity of 78%. When applied to patients who had no involvement of the nails, the cut off revealed that 15/50 HC, 13/31 PSOs and 13/51 PsAs are correctly classified, without differences between groups (Table I).

Discussions

We assessed with US 82 patients and 50 healthy controls to evaluate the presence of nail involvement and subclinical alterations in Ps and PsA. Previous data from literature are scarce, though overall nail ultrasonography has been shown to be more useful than clinical evaluation alone in detecting nail lesions [17,41]. Nails are one of the possible targets in the psoriatic spectrum [24] and their involvement is strongly related with the development of PsA, especially for the enthesal subset [15,41]. Our mANOVA analysis strongly highlighted the differences in nail plate and bed thickness between patients and healthy controls, but not between Ps and PsA patients. PASI had an almost significant trend ($p=0.056$,

with a higher mean in PsA group) and this is in line with available data reporting that psoriatic patients with severe skin involvement are more likely to develop joint disease. Conversely, an unexpected result of our study is that the magnitude of joint inflammation assessed with DAPSA was not related to nail bed or nail plate thickness. Of note, most of our patients had a small number of joints involved thus disease activity was mild to moderate in most patients, according to the proposed cut offs of DAPSA score [36].

The absence of differences between HC and affected groups suggests that nail alterations might be constitutive of psoriatic disease and then it could be a target for discriminating healthy subjects from patients with Ps or PsA. In addition, not all lesions detected by clinical examination are able to discriminate between the groups. Intriguingly, in spite of large confidence intervals which suggests caution with the interpretation of our results, only patients with nail pitting had more than 9 fold increased risk of having Ps. One of the most interesting remarks was the high prevalence of increased nail plate thickness despite the absence of abnormalities at clinical evaluation. Approximately 3% of Ps and 9% of PsA patients had increased nail plate thickness and ultrasonographic alterations not detectable at clinical examination

Linear regression models showed a good correlation among nail bed thickness, nail plate thickness and NAPSII. Our findings strengthen the idea that nail-enthesis complex is crucial in developing microalterations of the nail plate and the thickening of the nail bed and suggest that nail involvement is not only limited to the nail plate but also to the nail bed. This supports the hypothesis that all nail structures are affected in an inflammatory setting even though it should be stressed that we found subclinical abnormalities in most of the cases. Whether the primary site of inflammation is the nail and secondarily the enthesis or vice versa is still a matter of debate, as observed from other studies [42]. The proximity of the matrix to the joints and tendon structures makes it quite difficult to discriminate the timing of those events.

Another point of interest is the study of quantitative parameters of the nail. In literature these data are still lacking and we have already urged the need for a parameter standardization in clinical practice [32]. Indeed, a quantitative measure discriminating the healthy from the pathological nail could be useful in clinical practice. In this study we provide some evidence that US may be useful in borderline cases, whenever clinical examination is not sufficient alone to find the presence of the disease, such in the case of minimal nail involvement. In this view, nail plate thickness was the parameter which

obtained the best AUC. However, we found no significant differences in nail measures between Ps and PsA patients, the ROC curves being similar when plotting either Ps or PsA patients against HC, confirming that the nail complex modifications could discriminate psoriatic patients from healthy subjects, irrespective of the arthritic involvement. Our proposed cut off of 0.63 mm for nail plate thickness achieved the best sensibility and specificity for discriminating patients from healthy controls. Furthermore, our results must be interpreted considering the standard error of the ultrasound machine. Since the maximum power of imaging resolution is estimated by the manufacturer at 1/10 mm, the most logical value as a cut off for nail plate thickness is 0.6 mm. This value retains a very good sensibility even if with a slight decrease in specificity. When we applied this cut off to our study population, we could detect US abnormalities in up to 80% of cases. Since there is no statistical significance between patients vs HC for the thickness itself, this cut off is not sufficient. This observation implies that subclinical alterations are found more frequently with US than with standard examination. This might be particularly useful during the classification of the patient, for example considering US for the evaluation of nail alterations if CASPAR criteria are applied, although we acknowledge these are preliminary and not conclusive findings and they should be implemented with caution in clinical practice.

US has been proved to be a valid and feasible instrument for the assessment of PsA and Ps, and it is able to give just as detailed information as more advanced imaging techniques [17,43], though its routine application in everyday practice has not been proposed yet. The predictive value of the findings should be a matter of interest for further studies, in order to provide a possible role of the cut off in this setting. An in-depth analysis is also required to address peculiar features of PsA subsets (e.g. the inflammatory pattern involving the distal interphalangeal joints).

Although our results provided quite a comprehensive view of the nail features in PsA and Ps as well as their relationship with joints and clinical examination, this study has also some limitations. Firstly, to adequately visualize the nail structure a high frequency probe is needed, as previous studies [20] suggested that only a frequency above 18 MHz can provide an accurate imaging definition of the nail and enthesis complex. Secondly, the specificity of our proposed cut off is low as a number of patients do not show nail abnormalities at clinical examination despite having quantitative or qualitative US changes. For the intrinsic limitations of US, its routine employment might mislead the clinician to diagnostic

conclusions, thus we suggest to use this cut off primarily when the clinical presentation is suggestive but not sufficient alone to make the diagnosis. Finally, it is unknown whether other joint conditions than PsA can have similar nail ultrasound abnormalities.

Our study supports the use of nail US and remarks its potential advantages in PsA and Ps. Moreover, our results show that some quantitative parameters may be useful in the ultrasound assessment of the psoriatic nail. In conclusion, the role of nail US in psoriatic disease needs further research but there is increasing evidence suggesting that it could give useful information for clinical practice in selected patients.

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