



The ultrasonographic study of the nail reveals differences in patients affected by inflammatory and degenerative conditions

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Abstract

Introduction and objectives The nail unit is a subject of interest in several diseases, often involving different medical fields. Even if few data are available for psoriasis and psoriatic arthritis, no data regarding ultrasonography and imaging are present for other degenerative and inflammatory conditions. The aim of this study was to explore through imaging the changes of nail and entheses in inflammatory and degenerative conditions in order to find qualitative and quantitative changes related to distal interphalangeal joints.

Methods The study sample was composed of 51 patients affected by psoriatic arthritis, 31 affected by psoriasis, 37 subjects with rheumatoid arthritis, 34 with osteoarthritis and 50 healthy controls for a total of 203 individuals. Ultrasonography of the nails was performed after clinical evaluation in a cross-sectional study design by blinded ultrasonographers who were blind to patient data. Data about power Doppler signal of the nail bed, tendon entheses, thickness of nail plate and nail bed were recorded.

Results Patients affected by psoriasis and psoriatic arthritis differ from other subgroups, and power Doppler signal at the entheses seems to be an exclusive feature of psoriatic arthritis (Pearson's chi-square of 5297 and $p < 0.001$ with adjusted residuals). Nail plate thickness also differs in psoriasis and psoriatic arthritis, but surprisingly in osteoarthritis, too, with similar results.

Conclusions This study provides qualitative and quantitative data regarding the ultrasonographic features of nails in several rheumatic diseases with a potential role of ultrasonography in characterising them.

Keywords Nail bed · Nail plate · Psoriasis · Psoriatic arthritis · Ultrasonography

Introduction

The nail unit is a subject of interest in several diseases, often involving different medical fields. The strongest link is probably among dermatology and rheumatology, as proposed by McGonagle et al. [1]. The nails are easy to evaluate and they can be studied with imaging techniques such as ultrasound or dermoscopy [2–4]. Several imaging studies make it evident that nail involvement in psoriasis (PSO) could be a trigger of joint

involvement, suggesting a link between joint inflammation and nail disease [5, 6]. Even if the structure is accessible and easy to approach, many aspects are still unclear. There is a strong association between arthritis and nail involvement, even if peculiar lesions as onycholysis are considered [7, 8]. These findings are based on clinical examinations, but few data are available regarding imaging findings. This evidence, described almost exclusively by PSO lesions and psoriatic arthritis (PSA), and the relationship between nail alterations and joint involvement of distal interphalangeal joints (DIP) has been rarely considered in other conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA). Ultrasonography (US) is a feasible technique when you refer to the DIP and also to the nail [9–11]. Gutierrez et al. [12] suggested the nail could be a potential target for the study of psoriatic disease, and the same was recently proposed also by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [11]. US has several potential advantages; it permits a comprehensive view of the nail unit, with clear depiction of its components such as the trilaminar structure of the plate, nail bed,

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matrix, fibres of the extensor tendon of the finger and its entheses and DIP. PSO and PSA are conditions in which US of the nail unit was applied at first. The normal aspect of the nail is a trilaminar band with two hyperechoic layers separated by a hypoechoic one. This structure goes deep below the epidermis in the proximal part of the nail plate, and it ends just above a hypoechoic area that is the nail matrix. The nail bed is the dark area below the nail plate and just above the cortical bone of the distal phalangeal joint. Morphostructural changes are very evident [13, 14], and US of the nail unit may be a promising technique in providing qualitative and quantitative data for evaluating PSO and PSA [15]. US is also a feasible technique for detecting lesions at the entheses. US also describes inflammatory lesions at the entheses, especially in PSA [16]. The subclinical alterations of fibrillar structure, thickening of the tendon and power Doppler within 2 mm by the fibrocartilage, are highly specific for psoriatic disease [17, 18] and an important finding in the diagnostic phase.

DIP joints are not only affected by inflammatory disease, and a more frequent condition is osteoarthritis (OA). The changes due to this condition are very similar to those of PSA [19, 20], especially for osteoproliferative lesions. Neoposition can be variable, from limited to extensive, and the degeneration of the bone can alter also adjacent structures, including ligaments, subcutaneous tissue and probably also the entheses of the extensor tendon of the finger (Fig. 1).

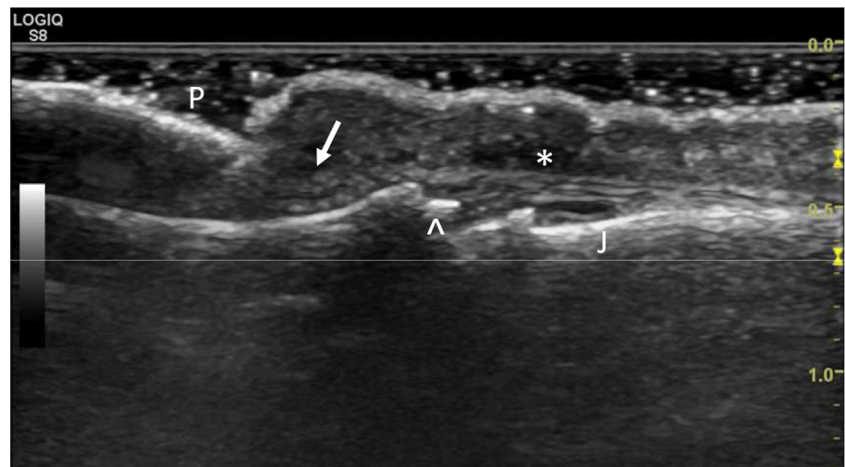
The aim of our study was to explore the changes of nail and entheses in inflammatory and degenerative conditions through imaging, in order to find qualitative and quantitative changes related to DIP.

Materials and methods

Study design and patients evaluation

This was an observational study conducted in the setting of an outpatient clinic for patients affected by rheumatic diseases.

Fig. 1 The nail entheses complex of patients with severe osteoarthritis. The nail plate (P) totally lost its trilaminar aspect, and the area of the matrix (full arrow) is slightly hyperechoic. The extensor tendon entheses (arrowhead) is enlarged, and fibres lose echogenicity when compared to regular fibres of the tendon (asterisk). Effusion can be observed in joint space (J)



Patients were all affected by PSO, PSA, RA or OA. The enrolment period was between May 2015 and November 2017. The enrolment setting was the combined clinic of dermatology and rheumatology for psoriatic disease (for PSO and PSA) and rheumatologic clinic for patients affected by RA and OA. No restriction criteria were applied for age and BMI since the pathologies are very heterogeneous between each of them. The diagnosis for PSO was validated by a dermatologist after collecting medical histories and performing clinical examinations. A concomitant diagnosis of PSA for all patients was also made by a rheumatologist present at this evaluation. OA diagnosis was based on clinical and imaging criteria after the exclusion of an inflammatory disease. Only patients with evidence of disease of the small joints of the hands were enrolled. PSA was classified according to CASPAR criteria [21] and RA according to ACR/EULAR criteria of 2010 [22]. Alterations of the nails other than psoriasis were excluded by the dermatologist as follows: infection by clinical examination and microscopic examination or culture; traumatic onychopathy or other conditions by clinical data and clinical examination. Patients who were taking biologic agents were excluded so as not to compromise the sample with biases due to treatment. The study sample was receiving the appropriate standard of care (conventional DMARDs, painkillers or NSAIDs). Patients taking systemic steroids were excluded. A clinical evaluation was performed to collect data about disease activity and clinical parameters such as weight, height and age, DAPSA, DAS28, PASI and NAP SI. These disease activity indexes were evaluated, but the study was not powered to correlate them to the alterations. In addition, not all the conditions have validated indexes nor was there strong enough evidence for a comparison among the pathological conditions.

Ultrasound procedure

After the clinical examination, the patient was taken to a darkened room and prepared for ultrasound evaluation. The ultrasonographers (IL and ZA) were blind to clinical data and

diagnosis of the patient. Only the hand was visible during the examination, and the patient and doctor were not allowed to speak. Even if this procedure was strictly applied, there was still a chance of recognising onychopathy if the nail was clinically affected. Cohen's kappa coefficient between the ultrasonographers was 0.78, previously verified on 70 selected images of the nail unit. The ultrasound examination was conducted with a General Electric Logiq S8 machine or Esaote MyLabClassC with a multifrequency linear probe with setting at 18 MHz. The power Doppler parameters were set selecting a pulse repetition frequency (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. The choice of this site as the only one to be taken into account was based on previous data and studies suggested in literature. In our previous experience [15], we showed that the examination of the second nail of the dominant hand achieved the most remarkable difference among other digits in PSO population compared with controls. The same observations were made by Gutierrez et al. [22]. The nail plate was measured three times in the middle third of the plate, and the same procedure was performed for the nail bed. In order to enhance the accuracy of measurements, the image was magnified using the zoom function during the examination. The mean of the three measurements was then reported both for the nail and bed thickness. Data about power Doppler signal (PDUS) of the nail bed, entheses of the extensor tendon and nail structural alterations were also recorded. The structural alterations were then evaluated using a semiquantitative 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 lose the standard image of a normal plate. The semiquantitative approach proposed by Gutierrez et al. [23] was used for scoring the PDUS 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 a confluent signal in more than 50% of the nail bed area. A score of 1 or 0 was given if PDUS at the entheses or abnormal signal from nail bed and was present or absent accordingly. For this entheses, a PRF of 500 KHz and a signal within 2 mm were considered for the diagnosis of enthesitis. The totality of US evaluations was scanned on both longitudinal and transverse scans and perpendicularly using a large quantity of gel over the skin and nail to provide the correct acoustic interface. No stand-off was used. Particular attention was paid to applied pressure in order to avoid the blanching of PD signal due to the compression by the transducer. The ultrasonographic qualitative parameters compared for PSO, PSA, OA, RA and HC are PDUS of the nail bed, in conformity with the score proposed by Gutierrez et al., and extensor tendon

entheses with a dichotomous score of absent/present. Synovitis and PDUS of the joint were scored accordingly with OMERACT definitions of the APPRAISE study [24].

Statistical analysis

For the determination of the sample size for statistical power, based on an esteemed standard deviation of 0.01 mm and aiming at a power of 95% to detect at least a 0.1 mm difference between patient affected by PSO, PSA, OA or RA and healthy controls (HC), we calculated a sample size of at least 18 patients in each group. No quantitative data are present in literature for a comparison. All statistical analyses were performed using SPSS Version 20 (SPSS, Inc., Chicago, IL, USA). According to the Kolmogorov Smirnov test of the analysis of variance, the continuous variables were tested using analysis of variance (ANOVA) with Tamhane's test for post hoc analysis. The *p* value was considered significant if < 0.05 . Qualitative and ordinal parameters such as DIP involvement or PDUS from joints or entheses were analysed using Pearson's chi-square test, and odd ratios for significant results were calculated where possible.

Data for PSO and PSA and healthy controls (HC) cohorts were already collected but not fully evaluated from a previous study [25].

All 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.

Results

Patients involved in this study were divided in groups according to their medical condition: PSA, PSO, RA, OA and HC. The number of patients and other characteristics of the population are reported in Table 1. Patients were consecutively enrolled during their scheduled visits. The mean age, BMI, nail plate and nail bed thickness and their standard deviation such as percentages for sex subpopulations are reported in Table 1. Thirty-six patients affected by PSA and 12 affected by PSO also had nail involvement. Mean Nail Psoriasis Severity Index (NAPSI) was 12.2 ± 12.7 . The US-targeted nail showed signs of psoriatic onychopathy in 27 out of 48 patients. Seven of them were affected by PSO and 20 by PSA.

With regard to age, differences were found between subjects with RA and OA and other groups ($p < 0.001$); regarding BMI, patients affected by PSO and PSA differ from other groups ($p < 0.001$) (Table 1).

The analysis of nail bed PDUS revealed an unusual trend for patients affected by any disease. Compared with HC, all the groups showed increased vascularisation and only in HC

Table 1 Descriptive statistics of study sample. HC, healthy controls; OA, osteoarthritis; PsA, psoriatic arthritis; PSO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation

	PSO	PsA	RA	OA	HC
Patients (<i>N</i>)	31	51	37	34	50
Sex (male/female)	22/9	26/25	10/27	7/27	22/28
Age (mean ± SD)	48.2 ± 14.8	50.9 ± 14.0	62.5 ± 12.5* (PSO, PSA, HC)	66.8 ± 10.6* (PSO, PSA, HC)	48.5 ± 14.0
BMI (mean ± SD)	28.6 ± 5.0* (RA, OA, HC)	28.5 ± 5.9* (RA, OA, HC)	24.5 ± 5.14	26.4 ± 4.1	24.6 ± 3.9
Nail plate thickness, mm (mean ± SD)	0.64 ± 0.12	0.65 ± 0.14	0.56 ± 0.07	0.63 ± 0.12	0.52 ± 0.06
Nail bed thickness, mm (mean ± SD)	2.5 ± 0.5	2.5 ± 0.4	2.0 ± 0.4	1.8 ± 0.6	2.2 ± 0.2

* $p < 0.05$ (vs groups in brackets)

was this absent or minimal. Residuals highlight the differences between normal population without any signal and any other group (Table 2).

Nail structural alterations were also evaluated between groups using a semiquantitative score, but the analysis was not applicable because it does not fulfil the assumptions of the chi-square test.

The evaluation of the PDUS of the enthesis revealed that patients affected by PSA have an increased rate of inflammatory involvement of the enthesis that strongly differs from the behaviour of the patients in the other subgroups. The evaluation of standardised residuals (RES) was 4.3 for the subgroup positive for PDUS presence and -2.5 for the negative. In patients affected by RA and HC, the presence of PDUS is very scarce, and they differ significantly from the other groups with RES of -2.4 and -2.9 , respectively.

The ANOVA results show that the patients affected by PSO or PSA have similar values, and they differ from RA or HC, but not from OA if you consider nail plate thickness. With regard to nail bed thickness, PSO and PSA groups differ from RA and OA groups.

RA differs from PSO and PSA for both nail bed and nail plate thickness, but it does not differ from any other conditions (OA and HC).

OA differs from HC for nail plate thickness, and it is significantly increased in OA. Surprisingly, nail bed thickness is lower if compared to HC, PSO and PSA. Reference for post hoc analysis is reported in Table 3.

Discussion

The aim of this study was to evaluate whether US can reveal the differences between inflammatory and degenerative conditions that involve DIP and nail. Nail involvement is very well known in psoriatic disease, and the anatomical link with enthesis is documented [26–29]. The “deep Koebner phenomenon” considers the hypothesis that repeated the over-exertion of peculiar structures such as the enthesis could trigger inflammatory changes which lead to a chronic disease [30]. The nail bed, especially the matrix and nail plate, are deeply involved in inflammatory changes in psoriasis. OA similarly involves DIP joints, with erosive changes and osteoproliferation of the cortical bone [31]. Standard radiology provides very limited differences between OA and PSA [32] and also US provides very few details [33, 34]. In this study, attention was focused on both qualitative and

Table 2 Alterations regarding qualitative and semiquantitative parameters of the nail, joint and enthesis complex. PDUS, power Doppler ultrasonography signal

	PSO	PsA	RA	OA	HC
Patients (<i>N</i>)	31	51	37	34	50
Sex (male/female)	22/9	26/25	10/27	7/27	22/28
Age (mean ± SD)	48.2 ± 14.8	50.9 ± 14.0	62.5 ± 12.5* (PSO, PSA, HC)	66.8 ± 10.6* (PSO, PSA, HC)	48.5 ± 14.0
BMI (mean ± SD)	28.6 ± 5.0* (RA, OA, HC)	28.5 ± 5.9* (RA, OA, HC)	24.5 ± 5.14	26.4 ± 4.1	24.6 ± 3.9
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Nail bed thickness, mm (mean ± SD)	2.5 ± 0.5	2.5 ± 0.4	2.0 ± 0.4	1.8 ± 0.6	2.2 ± 0.2

*Residual value significant with a trend which differs from the standard behaviour towards a pathological feature

^Residual value significant with a trend which differs from the standard behaviour towards a normal feature

Table 3 *p* values from post hoc analysis of ANOVA between groups. Nail plate and bed thickness was reported in the last two rows. HC, healthy controls; OA, osteoarthritis; PSA, psoriatic arthritis; PSO, psoriasis; RA, rheumatoid arthritis

		PSO	PSA	RA	OA	HC
Nail plate thickness	PSO	–	NS	0.021*	NS	<0.001*
	PSA	NS	–	0.002*	NS	<0.001*
	RA	0.021*	0.002*	–	NS	NS
	OA	NS	NS	NS	–	<0.001*
	HC	<0.001*	<0.001*	NS	<0.001*	–
Nail bed Thickness	PSO	–	NS	0.003*	<0.001*	NS
	PSA	NS	–	<0.001*	<0.001*	0.002*
	RA	0.003*	<0.001*	–	NS	NS
	OA	<0.001*	<0.001*	NS	–	0.012*
	HC	NS	0.002*	NS	0.012*	–
		PSO	PsA	RA	OA	HC
Nail plate thickness, mm (mean ± SD)		0.64 ± 0.12	0.65 ± 0.14	0.56 ± 0.07	0.63 ± 0.12	0.52 ± 0.06
Nail bed thickness, mm (mean ± SD)		2.5 ± 0.5	2.5 ± 0.4	2.0 ± 0.4	1.8 ± 0.6	2.2 ± 0.2

*Significant with *p* value < 0.05

quantitative parameters to clarify the differences in US and finding possible determinants for differential diagnosis.

Power Doppler signal of nail bed (nail PDUS) in PSO and PSA was not so different from RA and OA. The data suggest that PSO and PSA do not affect so much the vascularisation of the nail bed while healthy controls rarely show increased PDUS. However, data regarding OA was quite unexpected; it seems there is a diffused hypervascularisation of nail bed, especially if a low grade of involvement is considered. There is no apparent explanation for this, but mechanical influence and secondary deformities may be considered, which could potentially lead to an altered biomechanical function and over-stress of the appendage. A local effect induced by inflammatory chemokines could also be an interesting hypothesis. However, given the data provided by this study, nail bed should be considered a weaker imaging biomarker than nail plate in a discriminating diagnosis.

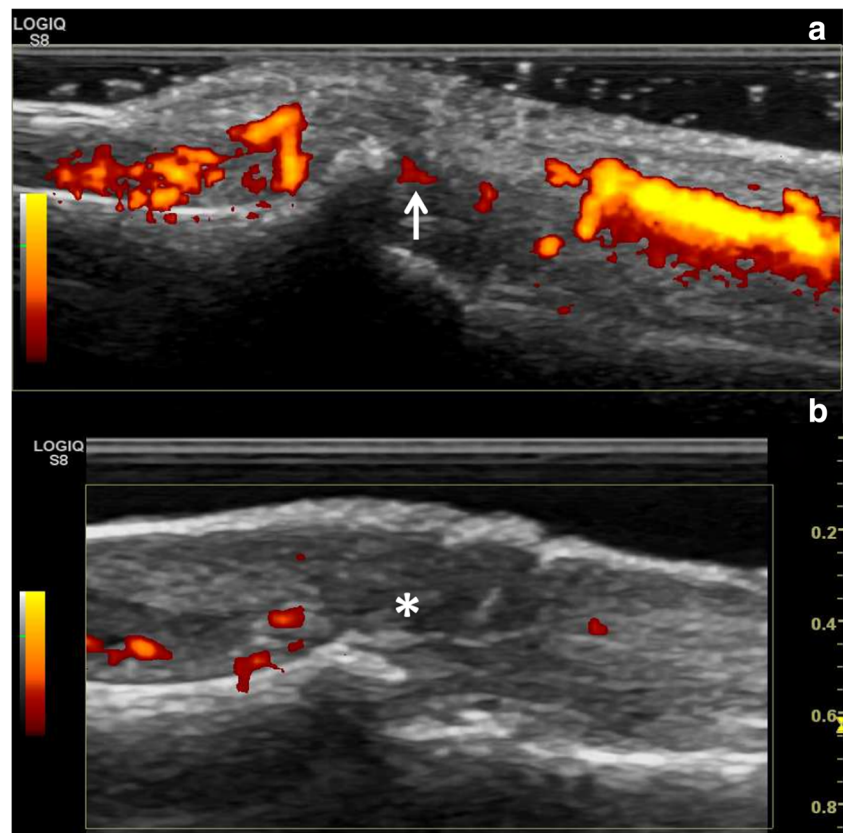
Data regarding PDUS at the enthesis were of interest. The data indicate evidence for enthesis involvement in nail and PSA in an almost exclusive way. As shown in Table 2, patients affected by PSA had a strong and significant diversion from the other groups, with a net prevalence of power Doppler found at the enthesis site (Fig. 2 and Table 2 for reference).

As expected, there is also a significant absence of PDUS in patients with RA and HC. Enthesitis seems to be a marker of PSA even when compared to patients affected by PSO and especially at the DIP site. This observation is quite new, and only Acosta-Felquer et al. [35] have suggested this concept. PDUS found at extensor tendon enthesis in PSA group can be explained by a nail enthesis hypothesis and might be a useful imaging marker to distinguish DIP involvement caused by PSA from RA or OA. Another interesting point for future studies would be the study of nail enthesis also on toes or

fingers different from the second dominant finger, in order to find the same lesions. Nail psoriasis is a risk factor for psoriatic arthritis [36], and clinical involvement is an easy and feasible predictor in everyday practice. Previous experiences from our group [15] stated that subclinical involvement can be discovered using US. The ANOVA showed that nail plate thickness is different in psoriatic disease, RA, OA and HC. The differences discovered seem to underline that thickening of nail plate is linked with alterations proximal to nail matrix and related to bony alteration of the DIP joint when an osteoproliferative process occurs. Osteoarthritis and inflammatory involvement show no differences between groups while the strong difference observed in RA and HC suggests there is a definite diversion from these conditions. The most evident explanation probably belongs to the nature of the disease. The repeated strain due to inflammation or mechanical trauma caused by osteophytes may lead to a local alteration and subsequent thickening. This is interesting if the Koebner phenomenon is considered for nail matrix also: the more the stress, the higher the chance of developing a site involved by the disease. This theory is very appealing for psoriatic disease, but it does not provide any rationale for osteoarthritis. This hypothesis, however, is sustained in some way by the US findings of patients from RA group, which show features like the HC.

Nail bed thickness could be quite puzzling. As expected, no differences were evident between PSO and PSA groups. We also expected to observe similar data in OA group, but PSA and PSO patients differ from OA patients. RA patients have a different behaviour from those affected by psoriatic disease (any grade) but not from OA group or HC. Another unexplained observation is that OA patients differ from all the

Fig. 2 PDUS signal at nail enthesis complex of the DIP. In **a**, the nail and DIP of a patient affected by psoriatic arthritis is depicted. Despite the important signal of nail matrix and vessel, a clear PDUS signal is spotted only at the tendon insertion. Differently, in **b**, the nail and DIP joint of a patient affected by osteoarthritis. Even if degenerative elements like osteophytes and calcifications (asterisk) are common also in this pathology, the PDUS signal at the enthesis site is very rare, as it is for psoriasis and rheumatoid arthritis



groups but not from the ones affected by RA. Apparently, this evidence is much more difficult to justify since the data on PDUS would suggest a profile similar to the one observed for psoriatic disease.

The study has several limitations. The study sample is not homogeneous. This limitation is difficult to overcome because the conditions have different peaks of incidence. The BMI also differs between groups accordingly with a different incidence of obesity in PSO and PSA. Another limitation of this study is the absence of patients treated with biologic agents. The authors discussed this matter while setting the exclusion criteria and decided to consider the use of biologics as an exclusion element because of their strong effect on periarticular features in inflammatory conditions. There is a lack of consensus in the use of US standardised measurements in nail evaluation; thus, data comparison with other experiences from the literature is not easy. Another point is about the Doppler evaluation performed by machines of different brand. Since no study compared algorithms of different machines and data provided in studies by several brands are coherent each other, it is assumed by default that differences do not impact on data quality, but it is a theoretical assumption. The patients' jobs were not recorded for all patients, and the choice of studying only one finger with US could also be a limitation. The decision to evaluate only one finger was made because data published in the literature refer to one finger as

well and also to provide a quick and easy reference for clinical practice. This is an evident limitation that could be tested in further comparative studies. Even if the conclusions are quite good, we suggest using data provided by US carefully because of the lack of data on the subject. The conclusions of this paper should be considered as a partial support to the differential diagnosis in specific conditions.

Conclusions

In conclusion, the data support the concept of the nail enthesis unit and the fact that it is in some way involved in different pathological conditions. No exclusive feature belongs only to one or another disease, but the data suggest that peculiar lesions can be found only in certain diseases. These lesions seem to be well correlated with clinical signs, as reported in literature. US of the nail should be considered one of the possible and promising targets in these conditions to enhance the diagnostic process. Nail ultrasonography may provide important information in discriminating pathological conditions affecting DIP. Data from the PDUS at enthesis and measurements of nail thickness may be a promising target and help clinicians in the differential diagnosis process.

Compliance with ethical standards

All 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.

Disclosures None.

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