Nailfold capillaroscopy in Sjögren's syndrome: a systematic literature review and standardised interpretation

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ABSTRACT

Objective. *We aimed to identify the role of nailfold capillaroscopy (NC) in Sjögren's syndrome (SS).*

Methods. *The literature was systematically reviewed in three databases. All published original studies which assess patients with SS by NC were revised. A quality assessment was applied to all studies based on population description, presence of a control group, presence of instrumental specifications and/or standardly applied NC methodology, presence of clear descriptions of capillaroscopic characteristics and based on the used statistical analysis. The capillaroscopic findings per study were described in a EULAR consented standardised way. Significant associations of capillaroscopic characteristics in SS patients with clinical and laboratory variables were summarised.*

Results. *The search resulted in 869 hits. Based on title and abstract screening 29 original studies were identified and of these, 14 full texts described an assessment by NC in SS. Seven studies were retained after performing a critical quality assessment. One study compared NC in SS with healthy controls and attested a lower capillary density in SS. Concerning clinical associations, capillary density was associated with Raynaud's phenomenon in two studies and with interstitial lung disease or systemic manifestations in one study each. No association between serologic features (anti-nuclear antibodies, anti-SSA, anti-SSB and anti-RF) and NC characteristics were found.*

Conclusion. *A small number of studies have investigated the role of NC in SS. More studies, including prospective follow-up studies with standard NC evaluation in SS are needed.*

Introduction

Nailfold capillaroscopy (NC) is a non-invasive, reproducible imaging method to assess microcirculation and examine microvascular abnormalities in rheumatic diseases. Its role is well-defined in patients with Raynaud's phenomenon (RP), where NC may discern a primary RP from a secondary due to systemic sclerosis (1, 2). In systemic sclerosis it has a role in the prediction of digital trophic lesions and (putatively) in lung involvement (3-7). Recently, reviews evaluating possible roles of NC in other autoimmune diseases have been published, some of them according to a EULAR (European League Against Rheumatism) consented standardised capillaroscopic description protocol (3, 8, 9).

Sjögren's syndrome (SS) is a common chronic autoimmune disease which affects mainly the exocrine glands. However, also systemic manifestations may occur involving the vascular and nervous systems, the kidneys and *lungs (10-12). SS may occur on its own (primary SS) or may be associated* to another systemic autoimmune disease (secondary SS) (13). In 10–30% of the patients, RP is present, reflecting a possible underlying microvasculopathy (13, 14).

Against this background, the objective of the present study is to systematically review the literature on NC characteristics in SS patients and to summarise the findings using standardised terminology as consented by the EULAR Study Group on Microcirculation in Rheumatic Diseases (EULAR SG MC/RD) (1, 3, 15, 16). Also, associations between capillaroscopic characteristics and SS-related clinical and/or laboratory findings are analysed. Doing so, the role of NC in SS can be clarified.

Methods

Search strategy

All relevant literature in the field of NC and SS published until January 2020 was systematically reviewed using the electronic databases PubMed, Embase and Web of Science. The used search strings with MeSH terms, Emtree terms and keywords, as well as the exclusion and inclusion criteria are depicted in Supplementary file 1, Tables S1 and S2.

Search process

The search process was carried out according to the PRISMA guidelines (17). The titles, abstracts and full texts were independently screened by two reviewers (MCL, KM) in two rounds. The original studies that reported on NC in SS were included. Exclusion criteria were the absence of results that reported on SS as a separated group and studies including less than five SS patients. The first round consisted of the selection of titles and abstracts and those selected by either one of the reviewers were included for further screening. The final articles were retained after reading and judging the full text for in- and exclusion criteria in the second round. Relevant references from retrieved articles were added by handsearching.

Quality appraisal

Since there are no standards for assessing the methodological quality of NC studies, we have derived a quality assessment process from the COSMIN-OMERACT good methods checklist (Consensus-based Standards for the selection of health Measurement Instruments-Outcome Measures in Rheumatology Clinical Trials) and the recently published papers on the standardisation of the NC technique (3, 18, 19). All included studies were assessed for quality by focusing on technical aspects of the capillaroscopic tool, examined anatomical areas, capillaroscopic outcome parameters and used definitions or descriptions of NC characteristics. It was based on the following seven criteria, formulated as 'Yes' or 'No' questions: Q1 Was the target population well described (fulfilment to defined classification criteria, disease duration, disease activity)?; Q2 Was a (healthy or not) control group present? Q3 Was the used tool well described, including the used magnification, and adequate to evaluate the capillaroscopic characteristics?; Q4 Has the capillaroscopy been performed in a standardised way, being the inclusion of 8 fingers (all except for the thumbs)?; Q5 Was a clear description given of the capillaroscopic characteristics?; Q6 Was the correct statistics used (continuous vs dichotomous/ordinal/nominal scores)?; Q7 Otherwise good methods (no important other flaws in the methodology)?. When the answer was 'Yes' the score was one. If a study did not reach a score of five on seven, it was not qualified for further consideration. All the included articles were at first critically and independently analysed by the two reviewers and jointly scored for quality thereafter.

Data abstraction

Throughout the studies, different NC terminology is used. For reasons of comparability, we interpret all NC findings standardly, following the definitions consented by the EULAR Study Group on Microcirculation in Rheumatic Diseases (15, 16). The quantitative NC parameters included: the capillary density (number of capillaries/mm in the distal row-less than seven capillaries/mm is considered as abnormal), the dimension of the apical capillary segment (dilation 20-50μm, giant >50 μm), the presence of normal morphology (including hairpin shaped, once or twice crossing and tortuous capillaries), the presence of abnormal morphology and the presence of haemorrhages (1, 3, 15, 16, 20). In regards to the qualitative NC assessment, the "stereotype normal", "non-specific abnormalities" and "scleroderma patterns" were extracted per study (3, 21).

At first, the quantitative and qualitative NC assessment in SS was extracted per study. To investigate associations of NC characteristics with SS disease, only those studies, which report a significance level of difference in NC characteristics between SS patients and healthy controls (HC) were considered in drawing general conclusions. A definite conclusion could be made as soon as two qualified independent studies unequivocally reported on the same NC finding ("conclusive"). A NC finding is "inconclusive" related to SS if conflicting results existed among studies or if only one study attested a statistical non-significant association. A NC finding is "suggestive" related to SS if a significant association was found in only one study (no external validation).

Finally, all articles were screened on available information on associations between NC characteristics and (SS-specific) clinical and/or laboratory variables.

Formal meta-analytic techniques were not used to combine the results of the NC studies because of the heterogeneity noted among the various articles, including 1) different study designs, 2) different methods used to perform NC, 3) different descriptions of similar NC findings, 4) dissimilar populations from which the patients were acquired.

Results

Search process

A total of 869 publications were identified using the electronic databases PubMed, Embase and Web of Science (762,84,23 respectively), according to the proposed filters. Ignoring duplicates (n=37), other languages (n=137), animal studies (n=16), and other publication types (n=137), 542 articles remained to be evaluated. After eliminating 513 articles based on title and/or abstract, 29 full texts were analysed with a focus on the in- and exclusion criteria (sample size, classification criteria, result specification) to result in 14 articles that reported on NC findings in SS. A flowchart of the search process is shown in Figure 1.

Study design, sample size and methodology

In Supplementary file 2, Table S3 an overview is given of all included studies (n=14) concerning their study design, sample size and methodology. It reveals the important differences in used NC equipment, as well as the lack of standardisation with regard to the NC assessment.

Quality appraisal

The 14 included articles underwent quality review of which seven reached

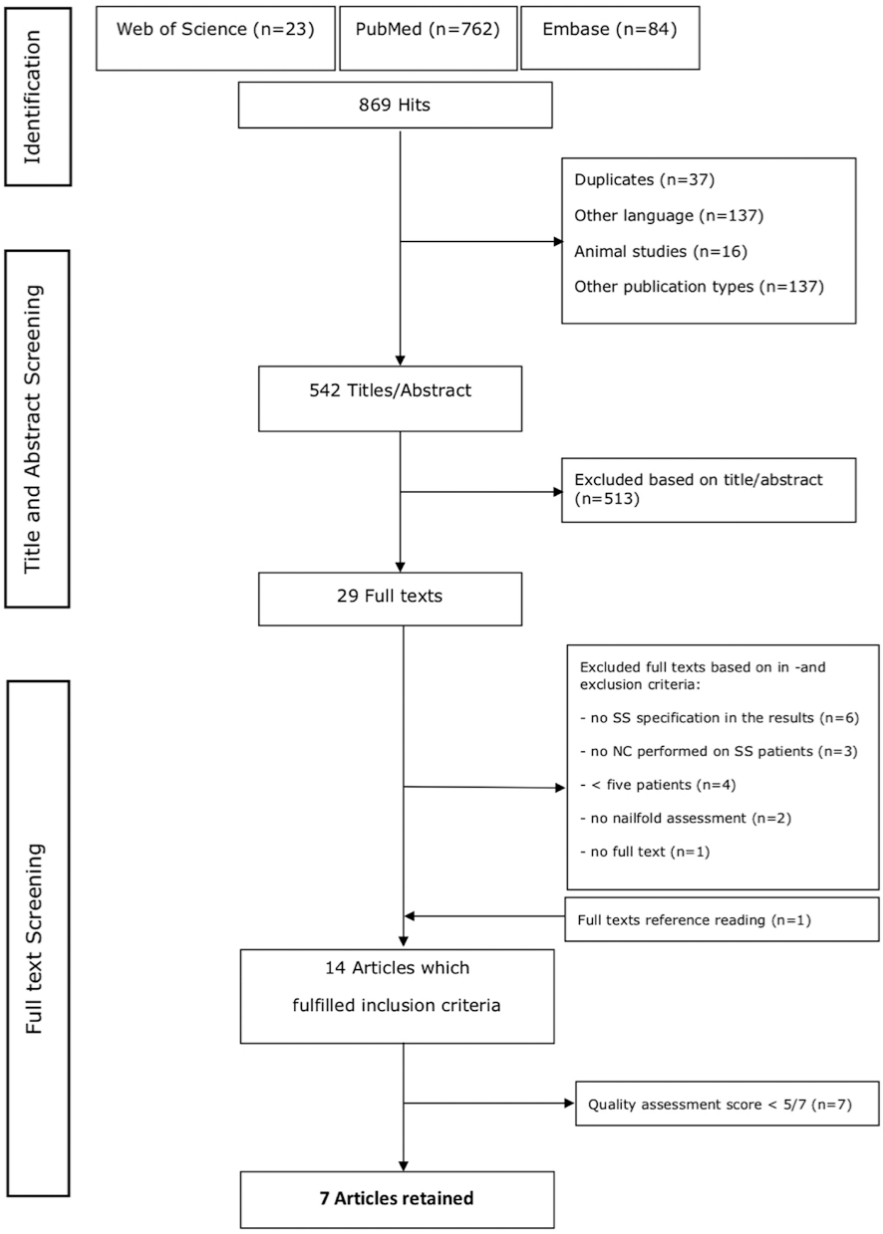

Fig. 1. Flowchart of the search strategy about nailfold capillaroscopy in Sjögren's syndrome.

a "quality check score" ≥5/7 (Supplementary Table S4). Common reasons to exclude articles based on their quality were: the absence of a control group, the lack of clear definitions or descriptions of capillaroscopic characteristics and a presumed lack of sensitivity to detect capillaroscopic abnormalities as too few fingers were examined (less than 8 fingers) (3).

From the seven studies, only two studies included a healthy control group (22, 23). Two other studies included a control group composed of non-healthy subjects (24, 25). We also retained three observational studies, without control group, of good quality (26-28). Table I covers the study design, population characteristics and NC techniques and methodology, all contributing to the quality of each study.

Quantitative assessment of NC in SS

• *Capillary density*
(Supplementary file 3, Table S1)

Two studies evaluated the capillary density at the nailfold in SS patients compared to healthy controls (HC). Capobianco *et al*. described a significant lower density in 61 primary SS patients (30 patients with RP (RP+) and 31 patients without RP (RP-)) compared to 21 HC (p<0.001) and this difference was also significant if only SS patients without RP were considered (p=0.009) (23). Tektonidou *et al*. performed subgroup analysis (RP- patients, RP+ patients and anticentromere antibody positivity (ACA+)/ RP+ patients) instead of comparing the whole SS patient group versus HC. They described a lower capillary density in the subgroup of 16 patients with RP (p<0.00001) and in the subgroup of 10 SS patients with RP and ACA (p<0.00001). The capillary density was not lowered compared to HC in the subgroup of patients without RP (22). Besides these two controlled studies in which the capillary density remains in the normal range, two other papers (not retained in our final summarising table as they did not evaluate HC) observed a normal capillary density in SS patients (primary and secondary SS). In particular, Bernardino *et al*. who described a mean capillary density of 8.8/ mm in 15 patients (all except for one had RP) and Cakmakci *et al*. described a mean capillary density ranging from 9.75-11.2/mm in 18 patients (all without RP) (25, 28).

Taking these results together, it is suggestive that SS patients exhibit lower capillary density compared to HC, especially when the patients have RP and/or are ACA positive but the density remains in the normal range (equal to or more than 7 capillaries/mm), though more evidence is needed to confirm (Table II).

• *Capillary dimension*
(Supplementary file 3, Table S2)

The research group of Capobianco *et al*. evaluated the capillary dimension in primary SS patients compared to HC, which showed more giant capillaries in SS but the difference was not statistically significant (23) (Table II). In other studies (which were not retained in the summarising table because of the lack of a healthy control group) capillary dilations and giants were reported in SS patients, sometimes without clear definitions of what was considered as dilated (22, 25, 26, 28). Only Bernardino *et al*. specified in their NC analysis of 15 SS patients, of whom 14 had RP,

Table I. Overview of the retained studies (n=7): design, methodology and population characteristics.

Author, study design#	Sample size (n)	Sex (M/F)	Age (years)	Disease duration (years)	RP/ Serology (n)	Systemic manifestations	Tool	Magnification	n. of fingers/site
Tektonidou *et al*. 1999, case-control	40	3/37	55	9	*14 RP-* *16 RP+* *10 ACA+*	NR	stereomicroscope	NR	4th and 5th fingers (capillary density), other parameters on 10 fingers
Capobianco *et al*. 2005, case-control	61	2/59	49.2	9	*31 RP-* *30 RP+* *1 ACA+* *5 ATA+*	57%	stereomicroscope	6.5-65X	8
Pavlov-Dolijanovic *et al*. 2012, prospective cohort	102	NR	NR	NR	*102 RP+*	NR	stereomicroscope	16-100X	8
Baldini *et al*. 2013, case series	41*	0/41	45	13.6	*0 RP-* *41 RP+/ ACA+*	NA	NR	NR	NR
Çakmakçı Karadoğan *et al*. 2015, cross-sectional	18	2/16	56	4.9	*18 RP-*	100%	NVC	16-100X	8
Corominas *et al*. 2015, cross-sectional	136	6/144**	58	8.2	*92 RP-* *44 RP+*	47,8%	NVC	200X	8
Bernardino *et al*. 2020, cross-sectional	15	0/15	49.5	NR	*1 RP-* *14 RP+*	NR	NVC	200X	8

ACA: anticentromere antibody; ATA: anti topoisomerase 1 antibody; n: absolute number; NA: not applicable; NR: not reported; N(V)C: nailfold (video) capillaroscopy; RP: Raynaud's phenomenon; SS: Sjögren's syndrome.
*All patients had overlap syndrome of SS and (early) systemic sclerosis (ACA+);
**A total of 150 SS patients, 144 women and 6 men underwent NC, 136 of which were diagnosed of SS according to the 2002 criteria of the American-European Consensus Group. The authors only considered these 136 patients in the final result, not specifying M/F ratio.

on the presence of giant capillaries in 33.3% of cases (28). No details were given on the serological profile of these patients, but the authors concluded that this NC abnormality was seen in patients with overlap disease (28).
Although dilated capillaries and giants were observed in SS patients, we conclude that there is not enough evidence to state that primary SS patients have more dilated capillaries compared to healthy subjects (Table II).

• *Capillary morphology (Supplementary file 3, Table S3)*
The only study in which the capillary morphology was analysed in SS patients compared to HC, could not identify significant differences. More specifically, the authors did observe abnormally shaped capillaries, as well as variations of normal morphology, such as tortuous and crossed capillaries, but these changes were not significantly more present in SS compared to HC (Table II) (23). In another study, Tektonidou *et al*. analysed the NC of a subgroup of patients with RP in combination with ACA positive serology (RP+/ACA+) (representing an overlap with "early" systemic sclerosis according to LeRoy) (29). They attested that a type of normal morphology, more specifically tortuous capillaries were as frequently present, but another type of normal morphology, crossed capillaries, were significantly more present in this subgroup, compared to HC. The investigators also observed more abnormal morphology ("bizarre capillaries") in this "overlap" subgroup, as well as in the subgroup of RP+ patients compared to HC (though not reaching statistical significance). These abnormal shapes were absent in the subgroup of patients without RP (RP-) (22).
As such, the limited data do not suggest that the overall group of SS patients, including patients without and with RP, differ concerning their capillary morphologic characteristics (abnormal versus normal) from healthy subjects (Table II).

• *Haemorrhages (Supplementary file 3, Table S4)*
Compared to HC, Capobianco *et al*. found a higher presence of haemorrhages in SS patients, though, it was not statistically significant (in 36% of cases, compared to 19% of HC, $p>0.05$) (23). Tektonidou *et al*. found significantly more haemorrhages in the RP+ patients (31.2% of cases with only RP+ and 50% of cases with RP+/ACA+, $p<0.05$) and less in the RP- patients (7.1% of cases, $p>0.05$) compared to 0 cases in the healthy control group, but they did not compare SS patients as one group (22).
As such, even taking these two studies together, the general conclusion on the presence of haemorrhages in SS patients remains inconclusive (Table II).

Qualitative assessment of NC in SS (Supplementary file 3, Table S6)
Capobianco *et al*. and Tektonidou *et al*. both reported on the qualitative assessment of nailfold capillaries in SS patients compared to HC. In this way, Capobianco *et al*. described in seven out of 61 patients (11.5%) a scleroderma pattern. All but one patient with a scleroderma pattern had RP (23). Tektonidou *et al*. showed no significant differences in terms of non-specific

Table II. Summary of the statistically significant differences in the standardised evaluation of capillaroscopic findings between primary Sjögren's syndrome (SS) and healthy controls (HC).

Capillaroscopic characteristics				Significant	Not significant	Conclusion
Quantitative	Capillary density			1 study (23)	0 studies	Suggestive for lower capillary density in SS *vs*. HC
	Capillary dimension		Dilation	0 studies	0 studies	Not conclusive
			Giant	0 studies	1 study (23)	
	Capillary morphology	Normal morphology	Hairpin shaped	0 studies	0 studies	No data
			Tortuosity	0 studies	1 study (23)*	Not conclusive
			Crossing	0 studies	1 study (23)*	Not conclusive
		Abnormal morphology		0 studies	1 study (23)	Not conclusive
	Haemorrhages			0 studies	1 study (23)	Not conclusive
Semi-quantitative				0 studies	0 studies	No data
Qualitative	Normal pattern			0 studies	1 study (23)*	Not conclusive
	Non-specific abnormalities			0 studies	1 study (23)*	Not conclusive
	Scleroderma pattern			0 studies	1 study (23)*	Not conclusive

The capillaroscopic characteristics were interpreted according to the EULAR consented capillaroscopic evaluation (3).
*no *p*-value was given.

findings in the subgroups of RP- patients, RP+ patients and RP+/ACA+ patients compared to healthy controls (p value>0.05). Notably, a scleroderma pattern was reported in eight from the ten SS RP+/ACA+ patients, in two of the sixteen RP+ patients, but in none of the RP- patients (ten out of 40 patients in total [25%]) (22). Likewise, other observational studies indicate that the presence of a scleroderma pattern in SS is not rare (these studies were not retained in the summarising table as they did not include a healthy control group). In the longitudinal study from Pavlov-Dolijanovic *et al*. a scleroderma pattern was reported in 11% of 102 SS patients with RP (27). In another reference SS cohort (32% RP+), in 10.2% of the cases a scleroderma pattern was found (26). Lastly, Bernardino *et al*. described a scleroderma pattern in 33.3% of the SS patients (14RP+/1RP-) (28).
At this moment, the presence of "non-specific abnormalities" in the SS group as a whole, including patients with RP and without, remains to be investigated. It is clear that scleroderma patterns are prevalent in SS, but rather in the subgroup of RP+ patients. Taking this together, it remains inconclusive if the qualitative assessment of NC in SS patients is different from HC (Table II).

Correlates of clinical variables and laboratory values with NC characteristics

• *Raynaud's phenomenon (RP)*

The association of RP in SS patients with capillaroscopic changes was investigated in four studies (22, 23, 26, 28). Two studies looked at the capillary density and concluded that patients with RP had a lower capillary density compared to patients without RP. Capobianco *et al*. found a higher deletion score in RP+ group (p=0.05) and Tektonidou *et al*. found a capillary density (measured in the 4th and 5th fingers) of 8.4+-2.0 in the RP+ group, compared to 9.8+-1.5 in the RP- group (p=0.04) (22, 23). The dimension and the morphology were compared between RP+ and RP- patient groups in one study each. As such, in a case series of 136 SS patients, dilated capillaries were significantly more frequent in the RP+ group (p=0.008) (26). Tektonidou *et al*. found more crossed capillaries (normal morphology) in RP+ patients (p=0.26), though it was not statistically significant. Potential differences in the presence of haemorrhages were evaluated in two studies, both observing more haemorrhages in the RP+ group, but not reaching statistical significance (22, 26). Finally, in three studies a qualitative assessment of the NC had been performed comparing RP+ with RP- SS patients: two studies showed more scleroderma patterns in the RP+ patients, compared to the RP- patients, although again no statistical significance was reached (22, 23). In Bernardino *et al*. the presence of a scleroderma pattern was reported in 5/15 cases, without giving details on the presence of RP in these patients even though, they reported that the scleroderma pattern was not related to the presence of RP (p=0.649) (28).
A summary on NC findings in relation with RP in SS patients is shown in Table III.

• *Serology*

The group of Tektonidou *et al*. observed more capillaroscopic abnormalities in patients with ACA-antibodies compared to ACA-negative patients (lower density, more dilations, more abnormal morphologies and more scleroderma patterns), though no p-values were given and these findings were not validated in other studies (22).
Lower capillary density was not linked to the presence of anti-SSA or anti-SSB (p=0.254 and p=0.076, respectively) (23). Nor was the qualitative assessment different in between the groups

Table III. Summary of the statistically significant differences in the standardised evaluation of capillaroscopic characteristics between Sjögren's syndrome (SS) with or without Raynaud's phenomenon (RP).

Capillaroscopic characteristics				Significant	Not significant	Conclusion
Quantitative	Capillary density			2 studies (22, 23)	0 studies	Significant association of lower capillary density with RP
	Capillary dimension		Dilation	1 study (26)	0 studies	Suggestive for an association of dilated capillaries with RP
			Giant	0 studies	0 studies	
	Capillary morphology	Normal morphology	Hairpin shaped	0 studies	0 studies	No data
			Tortuosity	0 studies	0 studies	No data
			Crossing	0 studies	1 study (22)	Not conclusive
		Abnormal morphology		0 studies	0 studies	No data
	Haemorrhages			0 studies	2 studies (22, 26)	No significant association of haemorrhages with RP
Semi-quantitative				0 studies	0 studies	No data
Qualitative	Normal pattern			0 studies	1 study* (22)	Not conclusive
	Non-specific abnormalities			0 studies	1 study* (22)	Not conclusive
	Scleroderma pattern			0 studies	3 studies** (22, 26, 28)	Not conclusive

The capillaroscopic characteristics were reported according to the EULAR consented capillaroscopic (3).
*no *p*-value was given; **in two studies no *p*-value were given.

with different serotypes ($p>0.05$) (26). The presence of IgM rheumatoid factor and the presence of a nuclear pattern on immunofluorescence was not associated with the capillary density in SS (23).

• *Systemic clinical manifestations*

Capobianco *et al*. grouped all systemic clinical manifestations in primary SS patients (cutaneous or systemic vasculitis, haematologic, neurologic, pulmonary or renal manifestations) and found an association with a lower capillary density ($p=0.022$). This was even the case when the patients with a scleroderma pattern were left out of the analysis ($p=0.029$) (23). In line with these findings, another study found lower capillary density in primary SS patients with interstitial lung involvement, compared to SS patients without (9.75 *vs*. 11.2 loops/mm, $p<0.05$) (25).

Discussion

The nailfold capillaroscopic assessment in connective tissue diseases other than systemic sclerosis is gaining some interest since the development of simple standardised definitions (1, 3, 15, 16). In conformity with the standardisation of NC, this systematic literature review gives for the first time an overview of the quantitative and qualitative assessment of NC in SS. The capillaroscopic observations from seven qualified studies were used to generate conclusions and to identify its role in SS. Unexpectedly, the available evidence in literature was too low to state that NC in SS differs from or resembles the NC in healthy subjects in all perspectives. Actually, only two studies investigated NC in SS comparing their results with NC data from healthy subjects (22, 23). In this way, Capobianco *et al*. found that SS patients showed a lower capillary density compared to healthy subjects, while all other capillaroscopic characteristics (dimension, morphology, haemorrhages and qualitative assessment) were not significantly different (23). In the study from the group of Tektonidou *et al*., only subgroup analysis had been performed to compare RP+ patients, RP+/ACA+ patients and RP- patients with healthy subjects. They underlined the heterogeneity of NC findings in SS patients with or without "early" overlap features (RP and ACA positivity) and showed more capillaroscopic variations (lower density and more crossed capillaries) and abnormalities (more haemorrhages) in the RP+ subgroup compared to healthy subjects (22). Scleroderma patterns were observed in SS by different investigators in the subgroup of patients with RP (22, 23, 26-28). It is conceivable that this observation is related to the presence of overlap syndrome with (early) systemic sclerosis or mixed connective tissue disease, in which scleroderma patterns are frequently perceived (2, 29, 30). Obviously, more studies are needed to validate these results.

In a second part, this review describes associations between capillaroscopic and clinical or laboratory parameters in SS. In four studies, NC associations with RP in SS were assessed. Two studies revealed significant differences concerning density (lower density in RP+) and one study concerning dimension (more dilated capillaries in RP+) (22, 23, 26). As for the qualitative assessment of NC in SS, we can state that scleroderma patterns were described in higher frequencies in SS patients with RP (though no level of significance was reported) (22, 23, 28). On the other hand, serological features such as ANA positivity, RF positivity, anti-SSA or anti-SSB positivity, were not found to be associated with NC characteristics (23, 26). The capillaroscopic features of primary SS-patients with atypical as-

sociated antibodies, such as ACA, were assessed in one study but no correlation analysis was done (22). Interestingly, two studies suggest an association of lower capillary density with systemic manifestations and ILD respectively (7, 23, 25). More and larger studies are needed to corroborate potential clinical and serological associations with NC characteristics.

Besides these few results on the quantitative and qualitative assessment of NC in SS, this systematic review highlights some major issues. The lack of a standardised application of NC throughout the studies forced us to exclude seven from the 14 studies after quality appraisal. Moreover, the seven retained studies varied in study design (retrospective cohort studies/prospective cohort studies/case series/case-control studies), had different aims and included SS patients based on different classification criteria (31-33). Variations were seen in the represented number of patients with RP in the SS cohorts and some studies included patients with (early) overlap features. Most of the studies included only primary SS patients, but two studies also included patients with secondary SS (secondary to other autoimmune diseases, such as systemic sclerosis, mixed connective tissue disease and primary biliary cirrhosis) (24, 28). This evidently, had implications on the generalisability of the NC results of these studies, which all were subject to sampling bias.

It may be a topic of debate if primary SS patients with a combination of "early" overlap features, such as RP, ANA positivity, the presence of atypical antibodies (*e.g.* ACA, anti-topoisomerase1 antibodies) or puffy fingers should be considered as a distinct disease entity.

Eventually, we could think of the following putative roles of NC in SS:

1. NC as biomarker to identify those patients with overlap features and their possible risk to evolve into another connective tissue disease (e.g. systemic sclerosis, mixed connective tissue disease, idiopathic inflammatory myopathies) (24, 29, 30, 34, 35). It is generally known that patients with RP and ACA in combination with a scleroderma pattern have a higher chance to develop systemic sclerosis (79.5% of cases) (2). Evidently, a detailed anamnesis and clinical examination with identification of symptoms and organ involvement of any autoimmune disease and a subsequent serological analysis remain paramount to reach this target.
2. NC as biomarker to sub-classify the disease into a mild form without systemic involvement and a more severe form of the disease with systemic involvement and increased morbidity and mortality (10, 13, 23, 36). In this case it remains to be investigated in longitudinal studies if NC has a predictive role to identify those at risk for systemic involvement in a later course of their disease.

Conclusion

A small number of studies have investigated the role of NC in SS. In general, there is a lack of data to prove that patients with SS have distinct nailfold capillaroscopic characteristics compared to healthy controls. The role of NC remains, as such, unidentified. Prospective studies in real-life primary SS cohorts with standard application of NC and assessment of SS clinimetrics are warranted.

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Appendix B: The COSMIN-OMERACT Good Methods Checklist adapted for OMERACT Filter 2.1 Instrument Selection needs. *The OMERACT handbook* 20.12.2017 ed. Ottawa, ON, Canada; 2017:20.
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