ISSN: 0975-833X

*Available online at http://www.journalcra.com*

*International Journal of Current Research*
*Vol. 15, Issue, 04, pp.24271-24275, April, 2023*
*DOI: https://doi.org/10.24941/ijcr.45046.04.2023*

**INTERNATIONAL JOURNAL OF CURRENT RESEARCH**

# RESEARCH ARTICLE

## SINGLE CENTRED PROSPECTIVE CONTROLLED STUDY ON NAIL FOLD CAPILLAROSCOPY AND CORRELATION WITH NAIL MICROVESSEL DENSITY IN PSORIATIC PATIENTS IN CENTRAL INDIA

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**ARTICLE INFO**

*Article History:*
Received 19th January, 2023
Received in revised form
10th February, 2023
Accepted 11th March, 2023
Published online 18th April, 2023

*Key words:*
Psoriasis, Nail Fold Capillaroscopy, Mean Capillary Density, Obesity, Nail Micro Vessel Density.

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**ABSTRACT**

***Background:*** Psoriasis involves vasculature in the very early stages of the disease leading to impaired capillary permeability, decreased density of capillaries and loss of adhesion between endothelial cell and the matrix of papillary dermis. It is hypothesized that early endothelial dysfunction can be detected at the level of dermal capillary microvasculature. If these changes can be detected and quantified early they would help in the early diagnosis of psoriasis, course of the disease and response to the treatment. ***Methods:*** Single centred prospective controlled study was conducted on 100 patients with psoriasis attending the outpatient department of dermatology between March 2021 and August 2022. Inclusion criteria involved patients above 10 years of age and less than 80 years of age with moderate to severe psoriasis with or without psoriatic arthritis and PASI≥10 or BSA >10% and off systemic treatment for a minimum of 4 weeks. Controls were selected from individuals who had never been diagnosed with psoriasis. Data recorded was statistically analysed by using Chi-square (for ordinal data) or by t-test (for continuous data) and by non-parametric test. A p value<0.05 was considered as statistically significant for this purpose. ***Results:*** The mean age of cases was 39.00 ± 13.93 years and mean age of the control group was 40.31 ± 17.40. Most of the patients affected with psoriasis were in the age group of 30-60 years with a male predominance (M:F -1.5:1). 5% of the cases had bizarre morphology with a relatively lower MCD 6.6/mm than in the controls 8.41/mm. 20.0% and 17% of the cases had dilated Capillaries, tortuous capillaries respectively, while 13% and 11% cases showed haemorrhages and avascular areas respectively. Micro vessel density of psoriatic plaques quantified by IHC showed no significant correlation with any of the capillaroscopic findings. ***Conclusion:*** Evidences gathered support the role of NVC in the assessment of peripheral microcirculatory changes associated with systemic diseases. They provide a window for the visualisation of dermal capillaries, their morphological alterations and structural abnormalities, along with real time assessment of their functional dynamics.



**Citation:** ***Dr. Sonali Gupta, Dr. Poonam Singh, Dr. Garima Goel, Dr. Shreya, K., Dr. Dinesh P Asati and Dr. Kapil Baheti.*** **2023.** "Single centred prospective controlled study on nail fold capillaroscopy and correlation with nail microvessel density in psoriatic patients in central India*". International Journal of Current Research*, 15, (04), 24271-24275.

# INTRODUCTION

Psoriasis is a chronic disease with a varying world-wide prevalence of 0.1 to 11.8% of general population affecting individuals in their third or fourth decade with males being affected two times more commonly than females. It is a chronic, immune-mediated, proliferative disorder with polygenic inheritance combined with environmental triggers such as trauma, infections, drugs, psychological stress. Psoriasis vulgaris is considered as an independent risk factor attributing to increase risk of obesity, diabetes mellitus, dyslipidaemia eventually increasing risks of stroke, myocardial infarction. Early endothelial dysfunction is considered to play role in the pathogenesis of atherosclerosis and several studies demonstrate impaired endothelial function in moderate to severe psoriasis/psoriatic arthritic patients [(1)].

Atherosclerosis is shown to be caused by transfer of inflammatory cells and cytokines from the skin to endothelial tissue and internal organs leading to systemic inflammation. Psoriasis involves vasculature in very early stages of the disease leading to impaired capillary permeability, decreased density of capillaries and loss of adhesion between endothelial cell and matrix of papillary dermis [(2)].It is hypothesized that early endothelial dysfunction can be detected at the level of dermal capillary microvasculature. If these changes can be detected and quantified early they would help in early diagnosis of psoriasis, course of the disease and response to the treatment. Nailfold capillaroscopy is a non-invasive technique for the assessment of peripheral microcirculation by evaluating the morphology of dermal papillary capillaries. In this study we are including a qualitative descriptive analysis of morphology of the nailfold capillaries and quantitative changes (frequency, extent) in capillary patterns and

further correlating these findings withmicrovessel density in skin biopsy samples. Very few studies have used NFC to quantify the capillaroscopic patterns and correlate these changes.

# METHODS

Single centred prospective controlled study was conducted on 100 patients with psoriasis attending the outpatient department of dermatology between March 2021 and August 2022 after IHEC approval. Inclusion criteria involved patients above 10 years of age and less than 80 years of age with moderate to severe psoriasis with or without psoriatic arthritis and PASI≥10 or BSA >10% and off systemic treatment for a minimum of 4 weeks. Patients were excluded if they had diabetes mellitus, hypertension , connective tissue disorders or any other inflammatory disease. Additionally patients who had undergone cosmetic procedure of nails in the last 4 weeks were excluded. Controls were selected from individuals who had never been diagnosed with psoriasis. The sample size was calculated based on the prevalence in central India using the formula described by Kelsey et. al. After obtaining informed consent from study participants, data was collected on a present proforma on age, gender, duration of illness, comorbidities and history of precipitating factors. Detailed general and cutaneous examination was done and Psoriasis Area and Severity Index (PASI), nail involvement, Nail (NAPSI), joint involvement were documented.

Cases and controls were asked to be seated at room temperature of 24°C for 30 minutes and then subjected to detailed nailfold capillaroscopic examination. Nailfold capillaroscopic abnormalities on second to fifth fingers were studied using a USB microscope (Dinolite) (Figure 1) under polarised light and photographed. Quantitative parameters including mean capillary density and qualitative parameters including dilated and tortuous, giant capillaries, neo angiogenesis, presence/absence of a subpapillary plexus and avascular areas were assessed. Images were subsequently coded and stored. Further skin biopsy samples were taken from patients of psoriasis for assessment of microvessel density with CD31 marker using a semi-automated immunostainer VENTANA Benchmark XT (Ventana Medical Systems Inc. Tucson, Arizona)(Figure 2)and MVD was compared with nailfold capillaroscopic changes.

***Data Analysis:*** Data was stored in Microsoft excel and categorised. This categorized data was cross-tabulated against another variable of interest. These cross tables were statistically analyzed by using Chi-square (for ordinal data) or by t-test (for continuous data) and by non-parametric test. A p value<0.05 was considered as statistically significant for this purpose.

# RESULTS

The mean age of cases was 39.00 ± 13.93 years and mean age of the control group was 40.31 ± 17.40 years with no statistical difference between both the groups (p value- 0.557) and a male: female ratio of 2.3 for cases and 1.5 for controls. Majority of the patients (77.0%) had Chronic Plaque psoriasis with mean PASI of 19.29 ± 14.75 (Table 1).11% of psoriasis patients had psoriatic arthritis out of which 4% patients had DIP joint involvement. There was a significant difference between the 2 groups in terms of PASI (W = 745.500, p = 0.005), with the median PASI being highest in the group with joint involvement (Table 2) (Figure 3). 58%of them had nail involvement with NAPSI values ranging from 1-114. The mean NAPSI score of the cases was 17.02. A moderate positive correlation was found between NAPSI and PASI, and this correlation was statistically significant (rho = 0.55, p = <0.001) (Figure 4).No statistically significant association was seen between MVD values ascertained by IHC with PASI score (Figure 5).

**Nailfold capillaroscopic changes in cases and controls:**

- The mean MCD was found to be 6.6/mm relatively lesser than in controls 8.41/mm (p = <0.001) and was found to be least in the


**Figure 1. USB Dinolite Microscope**

**Figure 2. VENTANA Benchmark XT automated immunostainer**

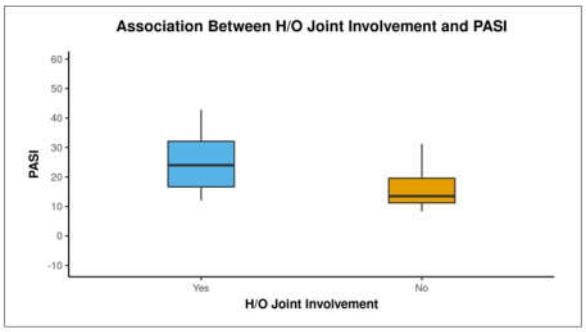


**Figure 3. Association between joint involvement and PASI**

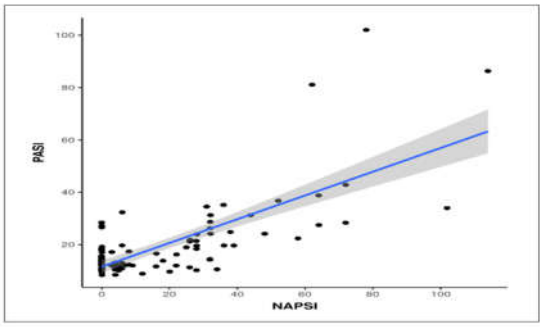


**Figure 4. Association between PASI and NAPSI**

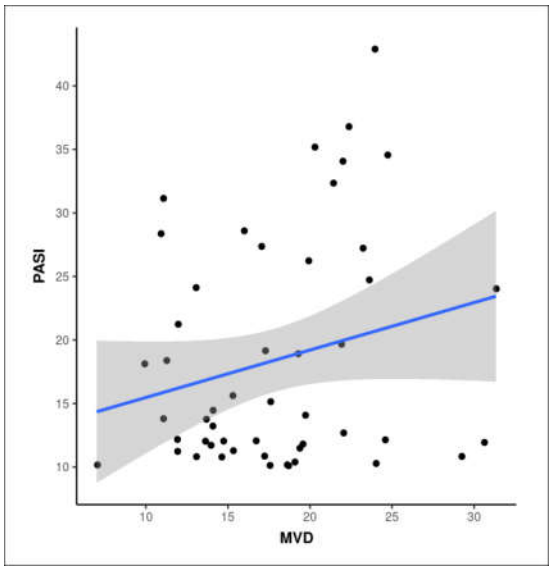


**Figure 5. Association between PASI and MVD**

erythrodermic variant (5.33/mm) followed by the pustular variant(5.75/mm). Further the capillary loop density decreased with increase in PASI and NAPSI values (correlation coefficient-0.5).

- 20.0% of the cases had dilated capillaries while 6.0% of the participants in the control group had dilated capillaries (p = 0.003). Greater number of dilated capillaries were seen in patients with more clinically severe disease in terms of PASI and nail involvement(value – 0.001). However no significant correlation between number of dilated capillaries and involvement of DIP joint was seen.
- 17.0% of the participants in the case group had tortuous capillaries while 6.0% of the participants in the control group had tortuous capillaries ($\chi 2$ = 5.944, p = 0.015). A significant correlation was seen between the number of tortuous capillaries and nail involvement in terms of NAPSI (p value-0.025) but not with PASI or DIP joint involvement.
- 13.0% and 35% of the participants in the case group had haemorrhages and visible subpapillary plexuses respectively when compared to 3.0% and 13% of the participants in the control group. 10% patients had ramified capillaries while none were seen in the control group with a statistically significant difference between the groups ($\chi 2$ = 10.526, p = 0.001). No significant correlation was seen with their presence and PASI, NAPSI, and DIP joint involvement.
- 11 % of the patients had avascular areas while none of the participants in the control group had avascular areas ($\chi 2$ = 11.640, p = <0.001). The presence of avascular areas was seen relatively more in the patients of pustular psoriasis (75%). Further increase in avascular areas was seen in patients with greater PASI and NAPSI scores (p =0.001) (Table 3)(Figure 6,7)

**Relation between MVD of psoriatic plaques with nailfold capillaroscopic changes:** Micro vessel density of psoriatic plaques quantified by IHC showed no significant correlation with any of the capillaroscopic findings (Table 4)(Figure8).

# DISSCUSSION

The mean age (39 years) observed in patients of psoriasis in our study was in concordance with study done by Bilac et al (3) and few other studies done in north India (4,5) with similar peak onset of disease around third and fourth decade. In our study, 11% of patients with psoriasis had psoriatic arthritis out of which 5% of the patients had DIP joint involvement. These were in concordance with a recent review published on 20 epidemiologic studies that showed the prevalence of psoriatic arthritis to be around 7% to 26% (6).

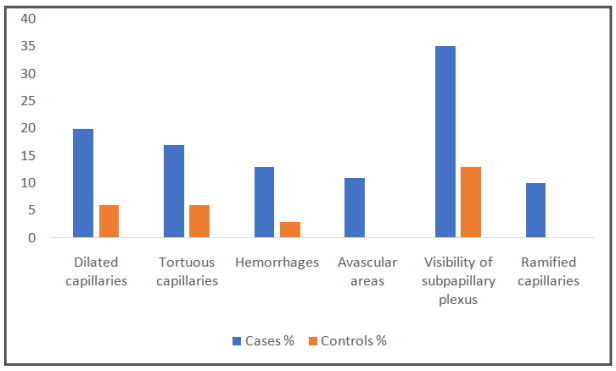


**Figure 6. Nailfold capillaroscopic changes in cases and controls**

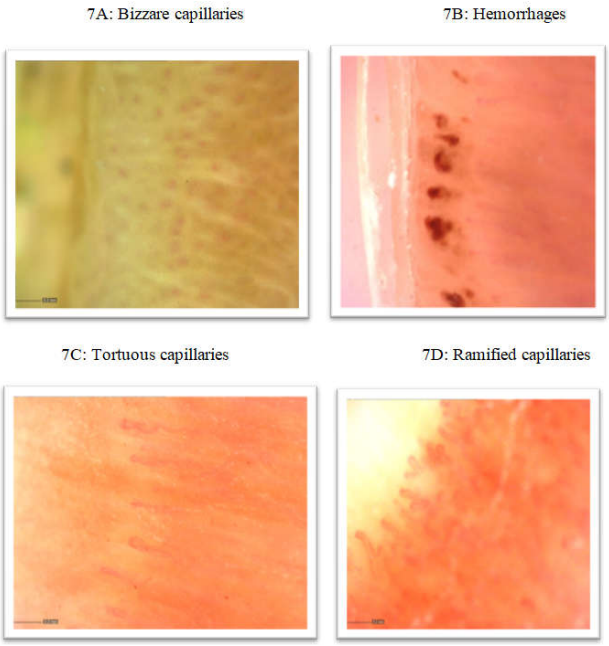


**Figure 7. Morphological changes in psoriatic patients**

**Table 1. Illness details**

| ILLNESS DETAILS | MEAN ± SD |
|---|---|
| BSA (%) | 22.31 ± 19.29 |
| Duration of illness (yrs.) | 5.88 ± 5.55 |
| Precipitating Factors (Yes) | 34 (34.0%) |
| PASI | 19.29 ± 14.75 |
| H/O Joint Involvement (Yes) | 11 (11.0%) |
| DIP Joint Involvement (Yes) | 5 (5.0%) |
| Comorbidities | |
| None | 95 (95.0%) |
| Hypothyroid | 5 (5.0%) |
| Smoking (Yes) | 17 (17.0%) |
| Nail Involvement (Yes) | 58 (58.0%) |
| NAPSI | 17.02 ± 23.90 |
| Clinical Variant | |
| Chronic Plaque | 77 (77.0%) |
| Guttate | 12 (12.0%) |
| Pustular | 4 (4.0%) |
| Erythrodermic | 3 (3.0%) |
| Elephantine | 2 (2.0%) |
| Palmoplantar | 2 (2.0%) |
| H/O Pustules (Yes) | 9 (9.0%) |
| Metabolic syndrome | 24 (24%) |

The mean PASI (28.92)in our study was higher in patients with psoriatic arthritis when compared to patients without arthritis (18.10) with a significant p value. This was similar to results of a meta-analysis (7) which concluded that more extensive skin disease is associated with psoriatic arthritis.

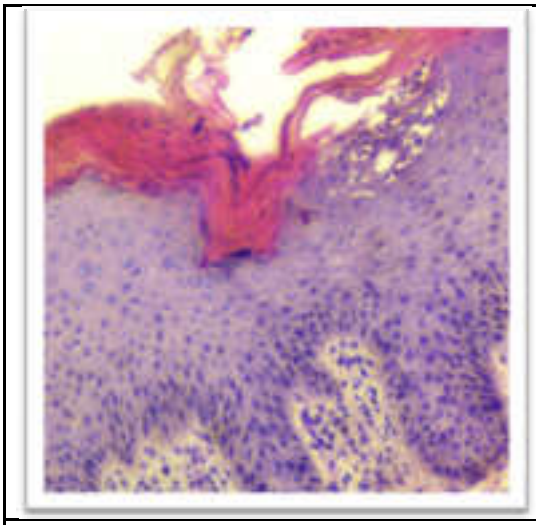

**Figure 8A. Microphotograph showing marked hyperkeratosis, parakeratosis, hypogranulosis, epidermal neutrophilic abscess and acanthosis in a case of Psoriasis (H and E 100x)**

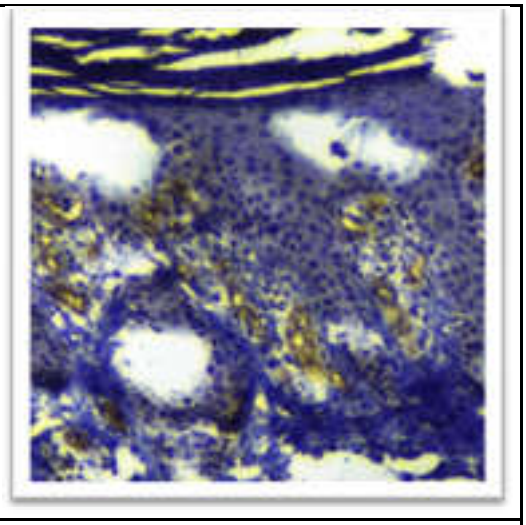

**Figure 8B. Micro vessel density assessment by CD31 in the papillary dermis of a case of Psoriasis (DAB 100x)**

**Table 2. Correlation between Joint involvement and PASI**

| PASI | H/O Joint Involvement | | Wilcoxon-Mann-Whitney U Test | |
|---|---|---|---|---|
| | Yes | No | W | p value |
| Mean (SD) | 28.92 (19.73) | 18.10 (13.70) | 745.500 | 0.005 |
| Median (IQR) | 24 (16.65-32.1) | 13.5 (11.2-19.6) | | |

**Table 3. Morphology of capillaries in cases and controls**

| Morphology of capillaries | Cases | Controls | |
|---|---|---|---|
| Capillaroscopy: Shape | | | 0.098 |
| Inverted U | 95 (95.0%) | 100 (100.0%) | |
| Bizzare | 5 (5.0%) | 5 (5.0%) | |
| Capillaroscopy: Density (/mm)*** | 6.60 ± 0.93 | 8.41 ± 0.77 | <0.001[4] |
| Dilated Capillaries | 20 (20.0%) | 6 (6.0%) | 0.003[3] |
| Tortorous Capillaries | 17 (17.0%) | 6 (6.0%) | 0.015[3] |
| Hemorrhages | 13 (13.0%) | 3 (3.0%) | 0.009[3] |
| Avascular Areas | 11 (11.0%) | 0 (0.0%) | <0.001[3] |
| Visibility of Subpapillary | 35 (35.0%) | 13 (13.0%) | <0.001[3] |
| Ramified Capillaries | 10 (10.0%) | 0 (0.0%) | 0.001[3] |

**Table 4. Association of nailfold capillaroscopic changes and MVD**

| | | |
|---|---|---|
| Capillaroscopy: Density (/mm) | Correlation Coefficient (rho) = -0.14 | 0.315[4] |
| Capillaroscopy: Dilated Capillaries | | 0.641[3] |
| Present | 18.67 ± 5.21 | |
| Absent | 17.69 ± 5.53 | |
| Capillaroscopy: Torturous Capillaries | | 0.695[3] |
| Present | 18.76 ± 6.57 | |
| Absent | 17.70 ± 5.31 | |
| Capillaroscopy: haemorrhages | | 0.497[3] |
| Present | 19.13 ± 6.23 | |
| Absent | 17.70 ± 5.40 | |
| Capillaroscopy: Avascular Areas | | 0.431[3] |
| Present | 19.42 ± 5.93 | |
| Absent | 17.71 ± 5.44 | |
| Capillaroscopy: Visibility of Subpapillary Plexus | | 0.891[3] |
| Present | 17.69 ± 5.67 | |
| Absent | 17.92 ± 5.41 | |
| Capillaroscopy: Ramified Capillaries | | 0.317[3] |
| Present | 22.22 ± 9.90 | |
| Absent | 17.57 ± 5.09 | |

Majority (58.0%) of the participants in our study had nail involvement with the mean NAPSI being 17.02 ± 23.90 with a moderate positive correlation between NAPSI and PASI. (rho = 0.55, p = <0.001). This was in concordance with study by Esteve et al (8) with similar prevalence.

## NAILFOLD CAPILLAROSCOPY

**Nailfold capillaroscopy showing morphology of capillaries of controls and patients:** All the controls and 95% of the patients had inverse U shaped capillaries with 5% patients having bizzare morphology.

This was lesser than the study results obtained by Sivashankari et al(9) and Kamboj et al(1) who reported 15% of the patients with bizarre morphology. The reason for bizarre morphology was assumed probably due to changes in vascular morphology leading to the pathology of psoriasis.

**Nailfold capillaroscopy showing mean capillary loop density in cases and controls:** In our study results similar to study results by Bhushan et al. the mean MCD was 6.6/mm that was relatively lesser than in the controls 8.41/mm (W = 808.000, p = <0.001). The MCD was found to be least in the erythrodermic variant (5.33/mm) followed by the pustular variant (5.75/mm). Further the capillary loop density decreased with increase in PASI and NAPSI values (correlation coefficient-0.5). Our findings of diminution in both nailfold capillary bed density and dimensions of the arterial and venous capillary limbs suggest that vascular injury, previously noted in ultrastructural studies, may play a part in the pathogenesis of psoriatic arthritis.

**Nailfold capillaroscopy showing dilated capillaries in cases and controls:** A positive correlation between dilated capillaries in cases with PASI values was observed inconcordance with study results by Sivashankari et al(10) who reported 14 out of 42 patients with psoriasis had dilated capillaries in the range of 11- 15microns. However no correlation was seen with DIP joint involvement probably due to very limited number of patients with psoriatic arthritis in our study population. Further the available USB microscope could not measure the exact diameters of the afferent and the efferent limb diameters of the capillaries hence leading to probable errors.

**Nailfold capillaroscopy showing presence of tortuous capillaries in cases and controls:** Our study results obtained are similar to results by Riberio et al who reported tortuous capillaries in 17.3% of patients but lesser than the results by Santosh et al where tortuous capillaries were reported in 25% of the patients. Both the authors Santosh et al and Elmesiry et al observed no correlation between the tortuosity of capillaries and skin disease severity similar to our results. Tortuous capillaries are most important finding of nail fold capillaroscopy and may be most important contributing factor in pathology of psoriasis as they indicateneo angiogenesis.

**Nailfold capillaroscopy showing presence of haemorrhages in cases and controls:** We found no significant correlation with presence of haemorrhages and PASI, NAPSI, and DIP joint involvement. This was in concordance with study results obtained by Kamboj et al (1) where haemorrhage was seen in 10% patients of all types of psoriasis. Presence of haemorrhages is considered an indicator of early vascular damage. Vascular injury occurs to a greater extent leading to leakage of red blood cells out of capillaries presenting as haemorrhagic areas on NFC in psoriasis.

**Nailfold capillaroscopy showing avascular areas in cases and controls:** The presence of avascular areas was seen relatively more in the patients of pustular psoriasis (75%). Further increase in avascular areas was seen in patients with greater PASI and NAPSI scores (p =0.001). The presence of avascular areas can be explained by the sluggishness of blood flow leading to raised levels of angiogenic factors such as transforming growth factor beta, platelet-derived growth factor and vascular endothelial growth factor affecting the morphology and physiology of the capillaries.

**Nailfold capillaroscopy findings with visibility of subpapillary plexuses in cases and controls:** Our results were in concordance with results by Kamboj et al that reported the presence of subpapillary plexus in 40% patients highest being in erythrodermic psoriasis. Sluggishness of blood flow and neo angiogenesis were probably the reasons for visibility of subpapillary plexuses.

**Association between micro vessel density and NFC changes:** Micro vessel density of psoriatic plaques quantified by IHC showed no significant correlation with any of the capillaroscopic findings. No studies in literature have compared NFC findings with MVD in psoriasis plaques. Overexpression of VEGF correlates well with increased MVD in lesional skin of psoriasis patients. Raised serum VEGF levels also result in microcirculatory changes in the nailfold capillaries. As NFC is a non-invasive technique NFC changes can act as prognostic markers for angiogenic therapy, especially in early stages to minimize the progression of disease to more severe stages.

**Limitations**

We could not assess the diameters of afferent and efferent limbs of capillaries as available instrument used was USB microscope.

- NFC changes with disease progression and changes before and after treatment could not be evaluated due to no follow up.
- Due to limited resources, Immunohistochemistry of skin biopsy specimens could be carried out on only 50 patients with psoriasis.
- The study included few patients with DIP joint involvement and hence correlation of NFC changes specifically with DIP joint involvement was limited

# CONCLUSION

It can be concluded that NFC can help predict the clinical course as well as help prognosticate follow up of patients with psoriasis to psoriatic arthritis. Therefore earlier institution of therapy can limit the progression of the disease. To our knowledge this was first observational study to correlate the nailfold capillaroscopic changes with MVD in psoriatic plaques.

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