Brief Report

Nailfold capillaroscopy alterations in androgenetic alopecia: A cross-sectional study

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Abstract

Background: Androgenetic alopecia is considered to be an independent predictor of mortality from diabetes mellitus and heart disease. However, whether androgenetic alopecia causes changes in microcirculation is unknown.

Objective: The objective of the study was to investigate whether alterations in nailfold capillaries occur in androgenetic alopecia patients.

Methods: The nailfold capillaroscopy images of androgenetic alopecia patients and matched controls were collected and analyzed.

Results: The frequencies of avascular areas, dilated, bushy and bizarre capillaries and capillary disorganization, nailfold capillaroscopy scores of 2 or scores both 2 and 3 were significantly higher in the androgenetic alopecia group than in the healthy controls (9.0% vs. 0%, 57.7% vs. 19.2%, 3.8% vs. 0%, 2.8% vs. 1.3%, 3.8% vs. 0%, 38.5% vs. 12.8% and 39.7% vs. 12.8%, respectively).

Limitations: The results of this study may be biased on account of the limited sample size or the presence of an undiagnosed disease in participants which could alter the nailfold capillaries.

Conclusion: Bushy, bizarre and dilated capillaries, capillary disorganization, avascular areas and nailfold capillaroscopy scores of 2 or 2 and 3 were more common in androgenetic alopecia patients than in healthy controls. These findings indicate that abnormalities in microcirculation may be involved in androgenetic alopecia.

Key words: Androgenetic alopecia, avascular areas, bizarre, capillaroscopy, dilated

Plain language summary

Androgenetic alopecia is the most common cause of hair loss. It is associated with metabolic syndrome, hypertension and coronary heart disease, and is considered an independent predictor of mortality from diabetes mellitus and heart disease. However, the common pathway of pathogenesis between androgenetic alopecia and systemic diseases is not clear. In this study, capillaroscope was used to observe the nailfold capillaries of all fingers, except thumbs, in participants with and without androgenetic alopecia. We found that the frequency of capillary anomalies, such as bushy, bizarre, dilated capillaries, capillary disorganization and avascular areas was higher in androgenetic alopecia patients than participants without hair loss. These findings reveal that there may be microcirculation injury in androgenetic alopecia patients which enriches our understanding of the pathogenesis of androgenetic alopecia and connects the pathogenesis of androgenetic alopecia to systemic diseases.

Introduction

Androgenetic alopecia, also known as male pattern baldness, is the combined result of an androgen-dependent process and heredity. It affects 30%, 50% and 80% of men by the ages of 30, 50 and 70 years, respectively.[1,2] While androgenetic alopecia is usually considered a localized disease resulting in hair loss, an increasing number of studies have revealed associations between androgenetic alopecia and systemic diseases, such as

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metabolic syndrome, hypertension and coronary heart disease. Androgenetic alopecia is an independent predictor of mortality from diabetes mellitus and heart disease in both sexes.[3-6] However, whether androgenetic alopecia causes changes in the microcirculation is unknown. In this study, we assessed the microcirculation in androgenetic alopecia patients and matched healthy controls by observing their nailfold capillaries.

Methods

Subjects

A total of 78 men diagnosed with androgenetic alopecia at the outpatient department of dermatology from October 2020 to January 2021 were enrolled. Comorbidities in patients with androgenetic alopecia were assessed based on their medical history and laboratory results in the past year (including routine urinalysis, blood cell count, liver and renal function tests, blood pressure, blood glucose, blood lipid level and electrocardiogram). Age- and sex-matched controls were recruited from healthy individuals visiting the Health Examination Centre of the same hospital over the same period. The control group had normal results for routine urinalysis, blood cell count, liver and renal function tests, blood glucose level, blood lipid levels and electrocardiogram; they had normal blood pressure, a body mass index below 25, no history of autoimmune diseases and no history or clinical manifestations of androgenetic alopecia. This study was approved by the ethics committee of Wuxi People's Hospital (HS2020002). Written informed consent was obtained from all participants prior to their inclusion in this study. The exclusion criteria were as follows: (1) history of diseases that may affect nailfold capillaries, such as autoimmune disorders, Raynaud's phenomenon, diabetes mellitus, hypertension, glaucoma or psoriasis and (2) presence of nailfold hypertrophy or trauma. Although microcirculatory dysfunction is already present in normoglycaemic subjects with metabolic syndrome,[7] not all participants in this study were subjected to the full battery of tests needed to diagnose metabolic syndrome, so we did not use metabolic syndrome as an exclusion criterion. Early-onset androgenetic alopecia was defined as alopecia of a severity of at least Norwood-Hamilton Grade 3 vertex, presenting in patients aged 35 or less.

Acquisition and evaluation of nailfold capillaroscopy images

Nailfold capillaroscopy was performed using a digital microscope (Dino-Lite AM413ZT, polarization) with 200×. Before the test, the participants were seated in a room at temperature 20–25°C for 15–20 minutes.[8] Thereafter, the hands of the participants were placed at their heart level, and a drop of cedar oil was applied to the target nailfold area. All fingers except thumbs were examined, and four images of each finger were captured from four different fields of the middle of the nailfold.[9] Capillaries in the distal row were evaluated by three investigators using a blinded method. The nailfold capillaroscopy criteria are shown in Table 1. A semi-quantitative rating scale was adopted to score the observed capillary abnormalities (0, no changes; 1, <33% capillary alteration or reduction; 2, 33–66% capillary alteration or reduction and 3, >66% capillary alteration or reduction).[10] The mean score was calculated by analyzing four consecutive one mm fields in the middle of the nailfold of each finger, the average scores of the eight fingers were added and the final value was divided by eight.[11] Microhaemorrhages were divided into two types: point dotted and confluent lesions.[12]

Table 1: Nailfold capillaroscopy criteria

Features	Definition
Capillary density	Average number of capillaries per millimetre (usually 7–14/mm)
Tortuous	Arterial and venous limbs are curled but do not cross
Crossed	Arterial and venous limbs cross at least at one point
Ramified	Abnormal connections between arterial and venous limbs, different capillaries or vascular neoplasms
Bushy	Capillaries with many small branching limbs
Bizarre	Abnormal morphology not conforming to the defined categories
Subpapillary plexus	Vascular network at the base of a finger nailfold
Microhaemorrhages	Dark masses attributable to haemosiderin deposit
Dilated	Diameter >20 μm
Giant	Diameter >50 μm
Disorganization	Complete distortion of a regular capillary pattern
Avascular areas	Lack of two or more successive capillaries

mm: Millimetre; μm: Micrometre

Statistical analysis

Independent *t*-test was performed to compare mean ages and nailfold capillary densities between the two groups. The Chi-square test was used to compare the frequency of different capillary morphologies between groups. Fisher's exact test was used when appropriate. All *P*-values were two sided, and $P < 0.05$ was considered to be statistically significant. Data analysis was conducted using SPSS Statistics 20.

Results

Subjects

The case group included 78 male androgenetic alopecia patients with a mean age of 29.91 ± 9.33 years (range, 18–66 years), and the control group included 78 healthy men with a mean age of 32.76 ± 10.93 years (range, 20–59 years). Differences in the ages of these two groups were not significantly different ($P = 0.082$). Seven (9.0%) patients had other diseases, including hyperuricemia ($n = 4$), hypotension ($n = 1$), hypoglycemia ($n = 1$), and hypothyroidism ($n = 1$). The numbers of patients with Grades 2, 3, 4, 5 and 6 androgenetic alopecia according to the Norwood-Hamilton classification scale were 11 (14.1%), 45 (57.7%), 8 (10.3%), 13 (16 .7%) and 1 (1.3%), respectively.

Nailfold capillaroscopy findings

The mean nailfold capillary densities of the androgenetic alopecia group and healthy controls were 7.44 ± 0.89 and 7.35 ± 0.76 capillaries/mm, respectively [$P = 0.50$; Table 2]. The nailfold capillary morphologies of androgenetic alopecia patients are shown in Figure 1. Tortuous, crossed and ramified capillaries, subpapillary plexus and microhaemorrhages were more common in the androgenetic alopecia group than in healthy controls, but differences in these features were not statistically significant. [Table 2]. The frequencies of avascular areas, dilated, bushy and bizarre capillaries and capillary disorganization were statistically higher in the androgenetic alopecia group than in

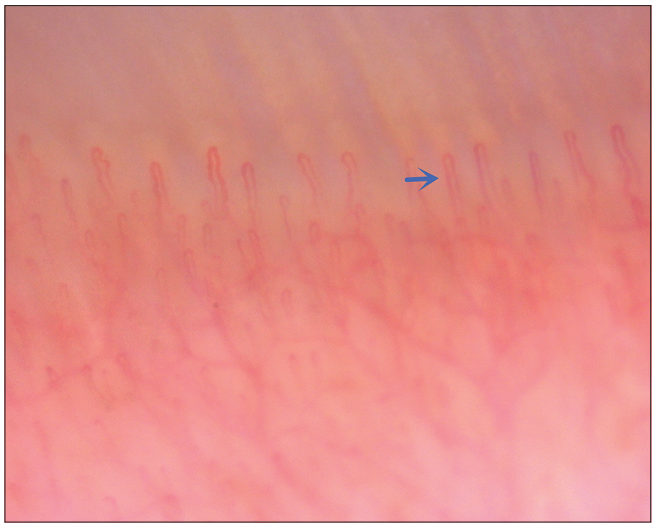

Figure 1a: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Normal capillaries

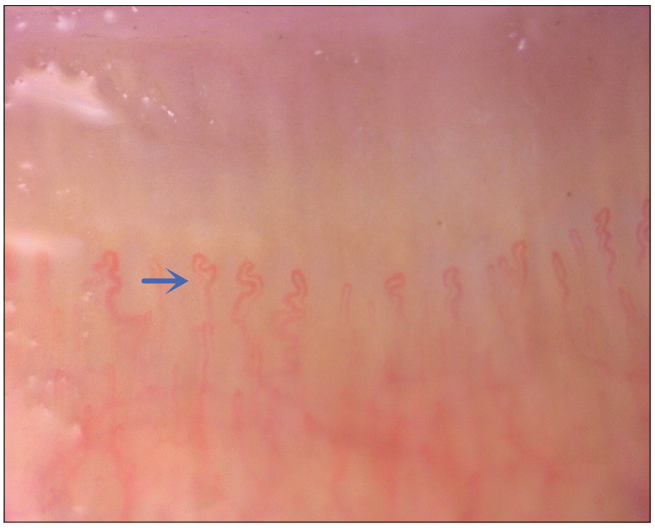

Figure 1b: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Tortuous capillary

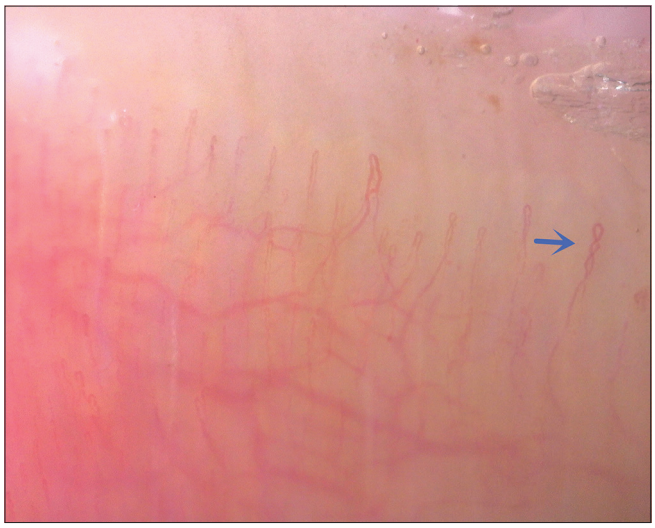

Figure 1c: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Crossed capillary

Figure 1d: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Ramified capillary

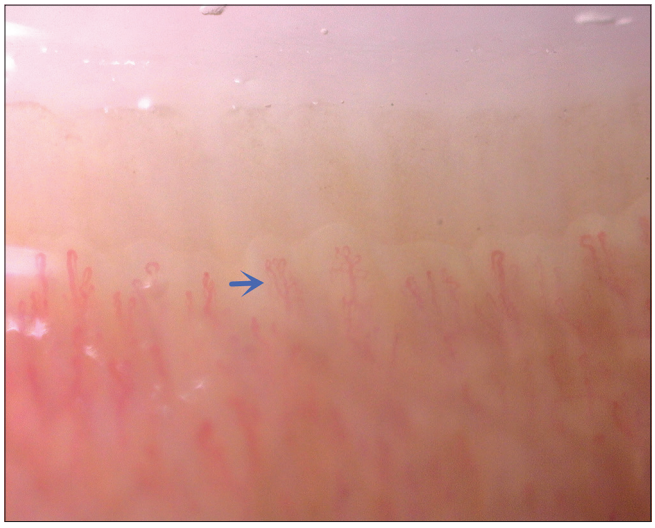

Figure 1e: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Bushy capillary

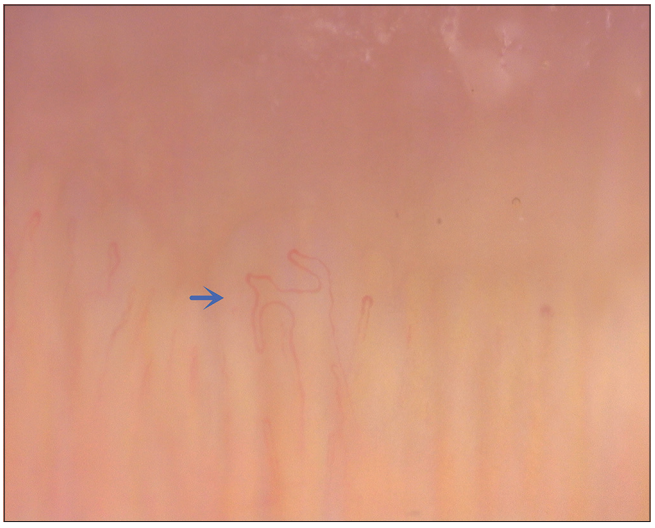

Figure 1f: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Bizarre capillary

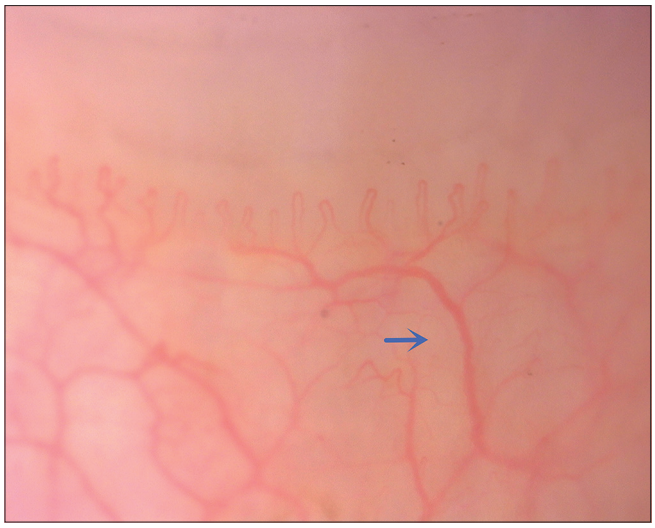

Figure 1g: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Subpapillary plexus

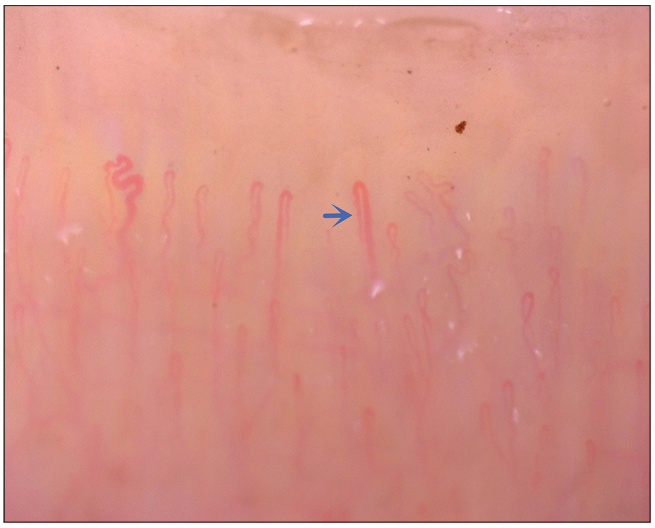

Figure 1h: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Dilated capillary

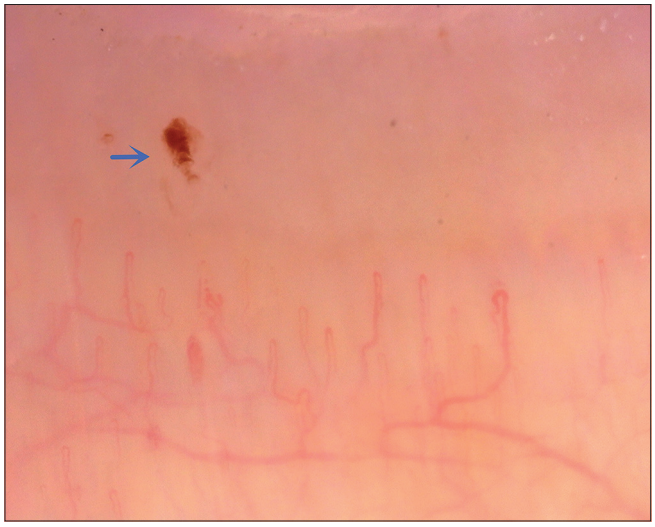

Figure 1i: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Microhaemorrhages (point-dotted)

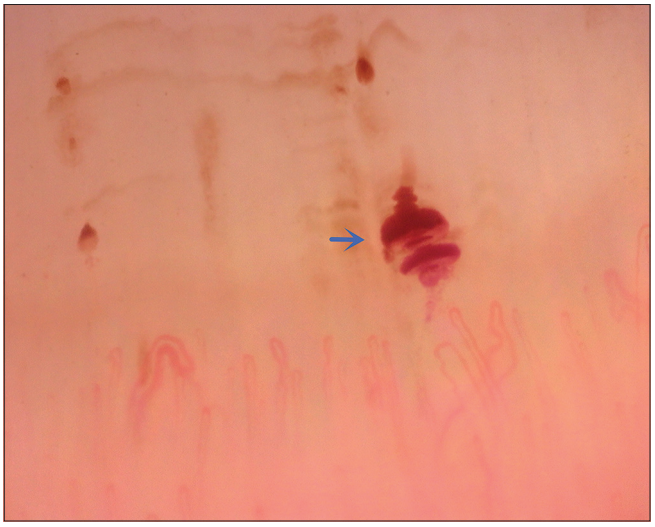

Figure 1j: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Microhaemorrhages (confluent)

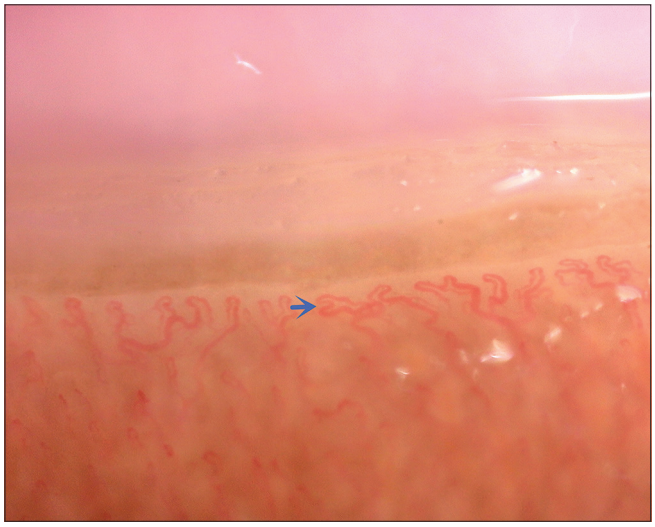

Figure 1k: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Capillary disorganization

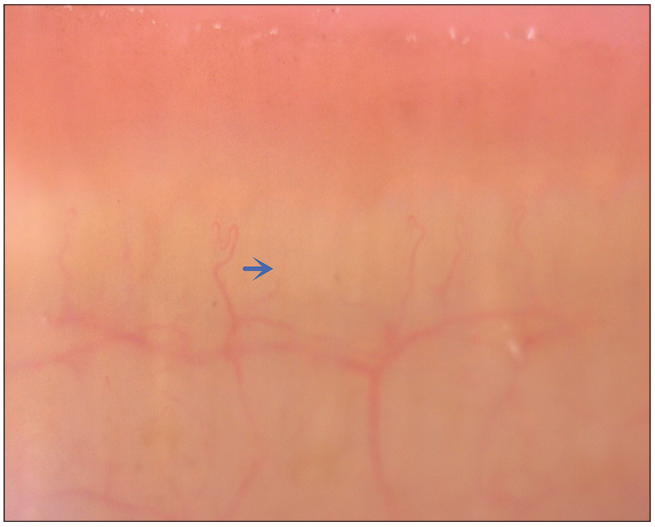

Figure 1l: Nailfold capillary morphology of androgenetic alopecia patients (Dino-Lite AM413ZT, polarization, ×200): Avascular areas

healthy controls [Table 2]. The androgenetic alopecia group also had significantly higher frequencies of nailfold capillaroscopy scores of 2 or 2 and 3 as compared to the control group.

Stratification analysis showed that early-onset androgenetic alopecia patients had lower nailfold capillary densities compared with late-onset patients, but all other nailfold capillaroscopy findings showed no significant differences [Table 3].

Discussion

Nailfold capillaroscopy is a non-invasive inspection tool often used to evaluate microcirculation through examining the morphology and density of capillaries in the finger nailfold area. Nailfold capillaroscopy is mainly used for rheumatic conditions;[13] it may also be used in some non-rheumatic diseases, such as diabetes mellitus, glaucoma, psoriasis and alopecia areata.[14-17] Earlier studies have found that morphologically abnormal nailfold capillaries are not rare in healthy individuals.[18,19] Tortuous and crossed capillaries (also known as meandering capillaries) were common in the present work, and no significant difference between the androgenetic alopecia group and healthy controls was found. Ramified, bushy and bizarre capillaries are neonatal capillaries, they may be promoted by local hypoxia and vascular endothelial growth factor stimulation and are considered a feature of late systemic sclerosis. Ramified capillaries were also visible in healthy persons in the present and previous studies,[12,19] and their incidence in patients and healthy controls was not significantly different. Bushy and bizarre capillaries are rarely visible in healthy persons but commonly observed in androgenetic alopecia patients.

The subpapillary plexus is visible in 40% of healthy adults.[19] This feature may be influenced by local injuries, hyperkeratosis, skin pigmentation and oedema.[20] Microhaemorrhages, including focal and diffuse micropetechiae, are also visible in healthy persons.[12,19] Focal microhaemorrhages may result from micro-traumas sustained in daily life, while diffuse microhaemorrhages may strongly imply an endogenous endothelial injury indicative of a microangiopathy.[21] Point dotted and confluent micropetechiae are similar to focal and diffuse micropetechiae, respectively. In this study, the subpapillary plexus and microhaemorrhages were not significantly different between the two groups.

Table 2: Nailfold capillaroscopy findings in androgenetic alopecia patients and healthy controls

Features	AGA (*n*/total, %)	Control (*n*/total, %)	*P*-value
Capillary density	7.44±0.89	7.35±0.76	0.50
Tortuous	57/78 (73.1)	56/78 (71.8)	0.94
Crossed	64/78 (82.1)	61/78 (78.2)	0.84
Ramified	60/78 (76.9)	41/78 (52.6)	0.14
Bushy	3/78 (3.8)	0/78 (0)	0.04
Bizarre	10/78 (12.8)	1/78 (1.3)	0.009
Subpapillary plexus	51/78 (65.4)	41/78 (52.6)	0.41
Microhaemorrhages	29/78 (37.2)	16/78 (20.5)	0.09
Point dotted	28/78 (35.9)	15/78 (19.2)	0.08
Confluent	1/78 (1.3)	1/78 (1.3)	1.00
Dilated	45/78 (57.7)	15/78 (19.2)	0.001
Giant	0/78 (0)	0/78 (0)	-
Disorganization	3/78 (3.8)	0/78 (0)	0.04
Avascular areas	7/78 (9.0)	0/78 (0)	0.002
NC score			
1	47/78 (60.3)	64/78 (82.1)	0.22
2	30/78 (38.5)	10/78 (12.8)	0.005
3	1/78 (1.3)	0/78 (0)	0.24
2 and 3	31/78 (39.7)	10/78 (12.8)	0.003

AGA: Androgenetic alopecia, NC: Nailfold capillaroscopy

Dilated capillaries are uncommon and giant capillaries are not observed in healthy adults.[19,22-24] Dilation generally represents the first sign of microvessel injury and has been considered to be a potential marker of microangiopathy.[25] In our study, giant capillaries were not visible, but the incidence of dilated capillaries was significantly higher in androgenetic alopecia group than healthy controls. This finding indicates that androgenetic alopecia patients may have a higher proportion of microvessel injury than healthy controls, controls which means that microvessel injury may be associated with androgenetic alopecia.

Capillary density and capillary arrangement are important parameters in nailfold capillaroscopy examination. Normal capillary densities do not significantly vary with age or gender.[18,20,26] Loss of capillaries and capillary disorganization may be associated with hypoxia; thus, these pathological changes are rare in the early stages of systemic sclerosis but become increasingly common with the progression of the fibrotic phase of the disease.[27] A decrease in capillary density is a characteristic indicator of scleroderma;[11,22] indeed, when the capillary density is less than 30 per five mm, the specificity of this finding to diagnose systemic sclerosis is 92%.[28] When vascular density is severely reduced, a microscopic absence of vascular areas may be observed. In the present study, the capillary densities of the androgenetic alopecia patients and healthy controls were similar. Interestingly, the mean capillary density in early-onset androgenetic alopecia patients was less than in the late-onset patients, but the figures were still within the normal range. Qualitative analysis of the abnormal morphologies of early- and late-onset androgenetic alopecia showed no significant differences. No significant differences were observed between patients with and without a family history of androgenetic alopecia, with and without a history of systemic treatment, and with androgenetic alopecia Grades 1–3 versus 4–6 according to the Norwood-Hamilton's classification scale. Avascular areas and capillary disorganization indicate that changes in microcirculation indicative of hypoxia are more common in androgenetic alopecia patients than in healthy controls, despite having a normal mean capillary density. Whether patients with severe hair loss or older patients with early-onset androgenetic alopecia show a marked reduction in vascular density is not clear. Given the limited sample size and the low number of patients with severe androgenetic alopecia included in this work, further investigation of this topic is recommended.

Because the qualitative abnormalities of nailfold capillaries cannot reflect the severity of the capillary change, a semi-quantitative scoring system was developed.[10] Our results revealed that significantly higher numbers of individuals

Table 3: Stratification analysis of nailfold capillaroscopy findings in androgenetic alopecia patients

Features	Onset age			Family history		
	Early onset (*n*/total, %)	Late onset (*n*/total, %)	*P*-value	Yes (*n*/total, %)	No (*n*/total, %)	*P*-value
Capillary density	7.30±0.89	7.90±0.73	0.01	7.42±0.88	7.46±0.91	0.87
Tortuous	50/60 (83.3)	14/18 (77.8)	0.86	41/50 (82.0)	23/28 (82.1)	1.00
Crossed	19/60 (31.7)	2/18 (11.1)	0.14	13/50 (26.0)	8/28 (28.6)	0.85
Ramified	44/60 (73.3)	13/18 (72.2)	0.97	37/50 (74.0)	20/28 (71.4)	0.92
Bushy	49/60 (81.7)	11/18 (61.1)	0.50	37/50 (74.0)	23/28 (82.1)	0.77
Bizarre	1/60 (1.7)	2/18 (11.1)	0.12	2/50 (4.0)	1/28 (3.6)	0.93
Subpapillary plexus	5/60 (8.3)	5/18 (27.8)	0.08	7/50 (14.0)	3/28 (10.7)	0.71
Microhaemorrhages	20/60 (33.3)	9/18 (50.0)	0.40	18/50 (36.0)	11/28 (39.3)	0.85
Point dotted	20/60 (33.3)	8/18 (44.4)	0.56	17/50 (34.0)	11/28 (39.3)	0.75
Confluent	0/60 (0)	1/18 (5.6)	0.09	1/50 (2.0)	0/28 (0)	0.35
Dilated	33/60 (55.0)	13/18 (72.2)	0.52	30/50 (60.0)	16/28 (57.1)	0.90
Giant	0/60 (0)	0/18 (0.0)	-	0/50 (0)	0/28 (0)	-
Disorganization	42/60 (70.0)	9/18 (50.0)	0.46	36/50 (72.0)	15/28 (53.6)	0.44
Avascular areas	3/60 (5.0)	3/18 (16.7)	0.17	3/50 (6.0)	3/28 (10.7)	0.50
NC score						
1	37/60 (61.7)	10/18 (55.6)	0.82	29/50 (58.0)	18/28 (64.3)	0.79
2	23/60 (38.3)	7/18 (38.9)	0.98	21/50 (42.0)	9/28 (32.1)	0.56
3	0/60 (0)	1/18 (5.6)	0.09	0/50 (0)	1/28 (3.6)	0.15
2 and 3	23/60 (38.3)	8/18 (44.4)	0.76	21/50 (42.0)	10/28 (35.7)	0.13
Features	**Systemic treatment history**			**Norwood-Hamilton classification**		
	Yes (*n*/total, %)	No (*n*/total, %)	*P*-value	Grades 1–3 (*n*/total, %)	Grades 4–6 (*n*/total, %)	*P*-value
Capillary density	7.57±0.50	7.41±0.92	0.49	7.45±0.85	7.39±1.00	0.78
Tortuous	6/7 (85.7)	58/71 (81.7)	0.93	47/56 (83.9)	17/22 (77.3)	0.83
Crossed	2/7 (28.6)	21/71 (29.6)	0.97	17/56 (30.4)	4/22 (18.2)	0.40
Ramified	5/7 (71.4)	52/71 (73.2)	0.97	45/56 (80.4)	12/22 (54.5)	0.34
Bushy	4/7 (57.1)	54/71 (76.1)	0.66	45/56 (80.4)	15/22 (68.2)	0.67
Bizarre	1/7 (14.3)	2/71 (2.8)	0.25	2/56 (3.6)	1/22 (4.5)	0.85
Subpapillary plexus	0/7 (0)	11/71 (15.5)	0.17	7/56 (12.5)	3/22 (13.6)	0.91
Microhaemorrhages	3/7 (42.9)	26/71 (36.6)	0.83	17/56 (30.4)	12/22 (54.5)	0.19
Point dotted	3/7 (42.9)	25/71 (35.2)	0.79	17/56 (30.4)	11/22 (50.0)	0.28
Confluent	0/7 (0)	1/71 (1.4)	0.67	0/56 (0)	1/22 (4.5)	0.11
Dilated	5/7 (71.4)	41/71 (57.7)	0.73	30/56 (53.6)	6/22 (27.3)	0.18
Giant	0/7 (0)	0/69 (0)	-	0/56 (0)	0/22 (0)	-
Disorganization	3/7 (42.9)	47/71 (66.2)	0.53	38/56 (67.9)	13/22 (59.1)	0.73
Avascular areas	0/7 (0)	6/71 (8.5)	0.30	4/56 (7.1)	2/22 (9.1)	0.79
NC score						
1	4/7 (57.1)	43/71 (60.6)	0.93	36/56 (64.3)	11/22 (50.0)	0.56
2	3/7 (42.9)	27/71 (38.0)	0.87	20/56 (35.7)	10/22 (45.5)	0.60
3	0/7 (0)	1/71 (1.4)	0.67	0/56 (0)	1/22 (4.6)	0.11
2 and 3	3/7 (42.9)	28/71 (39.4)	0.91	20/56 (35.7)	11/22 (50.0)	0.46

NC: Nailfold capillaroscopy

with androgenetic alopecia had nailfold capillaroscopy scores of 2 or 2 and 3 as compared to the healthy controls, but no significant difference between these two groups was observed with respect to nailfold capillaroscopy scores of 1. Nailfold capillaroscopy scores (1, 2, 3, 2 and 3) did not differ significantly between androgenetic alopecia patients when stratified by various parameters including presence and absence of family history of androgenetic alopecia, positive or negative history of systemic treatment, early- or late-onset androgenetic alopecia, and Norwood-Hamilton grades of 1–3 versus 4–6 [Table 3]. These findings suggest that androgenetic alopecia patients show more severe nailfold capillaroscopy changes than healthy persons. Pathological changes in microvascular injury may be associated with androgenetic alopecia and seem to persist irrespective of onset and treatment of androgenetic alopecia.

Recently, perifollicular inflammation and oxidative stress were reported to be the possible underlying mechanism of androgenetic alopecia.[29-31] Androgenetic alopecia was associated with increased risk factors for cardiovascular disease; while cardiovascular disease was associated with inflammation, probably due to the close interaction of inflammation with oxidative stress.[32] Hence, we speculate that the nailfold capillaroscopy alterations in androgenetic alopecia patients may be caused by systemic inflammation which is closely related to oxidative stress.

Limitations

The results of this study may be biased on account of the limited sample size or the presence of an undiagnosed disease (e.g., such as metabolic syndrome) in participants which could alter the nailfold capillaries. Future studies involving larger sample sizes which can also investigate any links between nailfold capillaroscopy findings with prognosis and treatment response will be helpful to further verify our findings.

Conclusion

This study found that the bushy, bizarre and dilated capillaries, capillary disorganization, avascular areas and nailfold capillaroscopy scores of 2 or 2 and 3 are significantly more frequent in androgenetic alopecia patients than in healthy controls. These findings indicate that abnormalities in microcirculation may be involved in androgenetic alopecia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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