



Nailfold Dermatoscopic Findings and Its Relationship with Proteinuria

Tırnak Yatağı Dermatoskopi Bulgularının Proteinüri ile İlişkisi

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ABSTRACT

Aim: Proteinuria is estimated to be a marker of microvascular damage. The aim of this study was to identify dermatoscopic findings of the nailfold capillary in patients with proteinuria and the relationship of these findings with the level of proteinuria.

Materials and Methods: Our study is observational cross-sectional study. Eighty five proteinuric patients whose albumin/creatinine ratio was found to be above 30 mg/gr in the spot urine in routine tests and eighty five non-proteinuric patients participated in this study. Proteinuric patients were separated into three groups (microalbuminuria, macroalbuminuria and overt proteinuria). Nailfold capillaroscopy was examined by a specialist dermatologist with a hand dermatoscope.

Results: The presence of at least one capillary dermatoscopic finding was significantly higher in the patient group with proteinuria when compared to the control group (62 vs. 14%, $p<0.05$). Capillary ectasia and presence of giant capillaries, appearance of subpapillary venous plexus, capillary disorganization and decrease in capillary density were found to be significantly higher in patients with proteinuria compared to the control group ($p<0.05$). However, there was no significant difference between the levels of proteinuria with nailfold dermatoscopic findings.

Conclusion: In our study, the presence of at least one capillary dermatoscopic finding was significantly higher in patients with proteinuria. We reported that dermatoscopic examination of nailfold capillaries in diseases with proteinuria might be an indicator of the microvascular damage. Further investigations with more patients are needed in this area.

Keywords: Proteinuria, albuminuria, nailfold capillaroscopy, dermatoscopy

ÖZ

Amaç: Proteinürinin mikrovasküler hasarın bir belirteci olduğu düşünülmektedir. Bu çalışmanın amacı proteinürik hastalarda tırnak kıvrımı kapillerlerinin dermatoskopik bulgularını ve bu bulguların proteinüri düzeyi ile ilişkisini belirlemektir.

Gereç ve Yöntem: Çalışmamız gözlemsel kesitsel bir çalışmadır. Rutin tetkiklerde spot idrarda albümin/kreatinin oranı 30 mg/gr'ın üzerinde saptanan 85 proteinürik hasta ve 85 proteinürisi olmayan hasta bu çalışmaya dahil edildi. Proteinürik hastalar üç gruba ayrıldı (mikroalbuminüri, makroalbuminüri ve aşikar proteinüri). Tırnak yatağı kapiller morfolojisi uzman bir dermatolog tarafından el dermatoskopuyla incelendi.

Bulgular: En az bir kapiller dermoskopik bulgu varlığı proteinüri hasta grubunda kontrol grubuna göre anlamlı olarak daha yüksekti (%62'ye karşı %14, $p<0,05$). Kapiller ektazi ve dev kapiller varlığı, subpapiller venöz pleksus görünümü, kapiller dezorganizasyon ve kapiller dansitede azalma proteinüri hastalarda kontrol grubuna göre anlamlı derecede yüksek bulundu ($p<0,05$). Tırnak yatağı dermatoskopik bulguları ile proteinüri düzeyleri arasında ilişki saptanmadı.

Sonuç: Çalışmamızda proteinürisi olan hastalarda en az bir kapiller dermoskopik bulgu varlığı anlamlı olarak daha yüksekti. Proteinüri düzeyleri ile dermatoskopik bulguları arasında ilişki saptanmadı. Sınırlılığımız hastalarda proteinüri süresinin bilinmemesi ve proteinürinin etiolojisine göre gruplandırma yapılmamış olmasıdır. Proteinüri ile seyreden hastalıklarda tırnak yatağı kapillerlerinin dermatoskopik incelemesinin hastalığın mikrovasküler alanda yaptığı hasarın yaygınlığına dair bir gösterge olabileceğini düşünüyoruz. Bu alanda yapılacak, daha çok sayıda hastanın yer aldığı kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Proteinüri, albüminüri, tırnak yatağı kapilleroskopisi, dermatoskopi

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INTRODUCTION

Nail capillaroscopy is a non-invasive method for imaging of capillary vessel microcirculation by magnifying the proximal nailfold with lens¹. It has an increasing importance among rheumatologists because it can be used in the early diagnosis of patients with systemic sclerosis and gives an idea about the prognosis². Recently, studies are increasing rapidly in terms of diagnostic and prognostic importance of capillaroscopy in diseases that cause microvascular damage such as diabetes and hypertension³.

Dermatoscopy is a non-invasive technique that allows us to visualize morphological features that are invisible to the naked eye and to establish a connection between skin lesions and their pathological counterparts⁴. Since dermatoscopy is easy and practical method, it has been started to be used instead of nail capillaroscopy, and similar success has been achieved in studies in this field⁵.

The increased excretion of albumin is one of the earliest signs of vascular damage in renal diseases. Many processes, such as diabetes, hypertension, and metabolic syndrome, can trigger the inflammatory response in the body and cause microalbuminuria in the glomerular capillaries due to endothelial dysfunction. Therefore, microalbuminuria is considered to be a marker of diffuse microvasculopathy at various levels, including cerebral, cardiac, and renal microcirculations⁶. Studies have shown that albuminuria is associated with many diseases related to vascular pathology such as retinopathy and heart failure^{7,8}. Numerous studies have provided convincing evidence that greater levels of albuminuria are independently related to mortality, cardiovascular events, and the rate of end stage renal disease^{9,10}.

Measurement of albumin or protein level in 24-hour urine is used to detect albuminuria or proteinuria. In addition, it has been shown that the albumin/creatinine ratio and the protein/creatinine ratio, which is measured more practically in the spot urine, is a successful marker in the detection of albuminuria and proteinuria. Besides, the albumin/creatinine ratio is used to evaluate the degree of microvascular damage in chronic kidney disease⁹.

Based on that albuminuria and proteinuria is an important marker of diffuse microvascular damage, we evaluated the nailfold dermatoscopic findings in patients with proteinuria and the relationship of these findings with the level of proteinuria.

MATERIALS AND METHODS

Our study was planned as a descriptive, observational study in patients with albuminuria. Study participants were the patients of either gender, between the age of 18 and 80 years. Patients

who applied to Muğla Sıtkı Koçman University Training and Research Hospital Nephrology Outpatient Clinic and whose albumin/creatinine ratio was found to be above 30 in the spot urine in routine tests were included in the study. Proteinuric patients were separated into three groups according to the albumin/creatinine and protein/creatinine levels detected in the spot urine. Microalbuminuria was described as the albumin/creatinine ratio between 30 and 300 mg/gr. Macroalbuminuria was described as the albumin/creatinine ratio at 300 mg/gr and above. Overt proteinuria was described as the protein/creatinine ratio at 1000 mg/day and above⁹⁻¹¹. The patient who had macroalbuminuria and overt proteinuria was separated into the overt proteinuria group. Normoalbuminuric and nonproteinuric patients who applied to the dermatology outpatient clinic only for local dermatological diseases (such as tinea unguis, verruca vulgaris) were included in the study as the control group. The study protocol was approved by the Muğla Sıtkı Koçman University Institutional Ethical Committee and was conducted in accordance with the Declaration of Helsinki (decision no: 16, date: 16.12.2021). All participants gave written informed consent.

Exclusion Criteria

Exclusion criteria were having periungual trauma on the nails of the 4th and 5th fingers of both hands or diseases that locally disrupted the nail structure (for example, tinea unguis), having nail polish or aesthetic interventions on the 4th and 5th fingers of both hands, the presence of disease that disrupted the regional peripheral vascular system, such as peripheral arterial disease, systemic sclerosis. Patients with end stage renal disease and malignancies were excluded.

Dermatoscopic Examination

The nailfolds of the 4th and 5th fingers were examined by a specialist dermatologist with a hand dermatoscope (Dermlite 4), in both hands of the patients held at the level of the heart in a sitting position, and recorded on an android phone with a telephone apparatus. The recordings were stored on a personal computer in jpeg format and re-evaluated by the same person without looking at the previous findings. Patients who were interpreted differently in the evaluations made during and after the examination were excluded from the study.

In the nailfold in dermatoscopic examination, previous studies were taken as reference and the specified parameters were evaluated^{1,3,12,13}.

- Capillary ectasia and presence of giant capillaries,
- Presence of tortuous capillaries and torsion,
- Decrease in capillary density,
- Microhemorrhage,

- Subpapillary venous plexus view,
- Cuticulitis capillary,
- Avascular area,
- Capillary disorganization.

Statistical Analysis

Comparison of the findings between the patient group and the control group was evaluated with the Pearson's chi-square test. Comparison among 3 subgroups separated according to the severity of albuminuria was made with the Fisher's Exact test. Statistical significance was assessed at $p < 0.05$ and all statistical analyses were performed using R software (R software, version 4.0.5, package: arsenal, R Foundation for Statistical Computing, Vienna, Austria; <http://r-project.org>).

RESULTS

Differences in Nailfold Dermatoscopic Findings Between Patients with Proteinuria and the Control Group

As a result of the study, nail dermatoscopy findings among 85 patients with proteinuria and 85 control patients were evaluated. There was no difference between the groups in terms of sex distribution. The mean age of the patients in the proteinuria patient group was $58.3 (\pm 16.5)$ years, and the mean age was $52.6 (\pm 18.7)$ years in the control group. In the logistic regression analysis, it was observed that the results obtained in terms of age and sex did not change between the groups.

The presence of at least one capillary dermatoscopic finding was significantly higher in the patient group with proteinuria

when compared to the control group (62% vs. 14%, $p < 0.05$). Capillary ectasia and presence of giant capillaries, appearance of subpapillary venous plexus, capillary disorganization and decrease in capillary density were found to be significantly higher in patients with proteinuria compared to the control group ($p < 0.05$) (Figure 1). On the other hand, there was no significant difference between the two groups in terms of the presence of tortuous capillaries, avascular area, microhemorrhage and cuticulitis capillaries (Table 1).

Differences Between Nailfold Dermatoscopic Findings According to the Level of Proteinuria

Patients with proteinuria were put in 3 groups, 36 patients with microalbuminuria, 25 patients with macroalbuminuria, and 24 patients with overt proteinuria. The dermatoscopic findings of the patients in these groups were evaluated statistically. There was no significant difference between the patient groups with proteinuria in terms of mean age and sex and there was no significant difference among the microalbuminuria, macroalbuminuria and overt proteinuria groups in terms of nailfold dermatoscopic findings (Table 2).

DISCUSSION

Albuminuria is an important marker of endothelial dysfunction and it is proven that it predicts adverse renal and cardiovascular events in diabetic and hypertensive patients, even in healthy individuals^{14,15}. Microalbuminuria is apparently associated with increased universal vascular sieving of albumin in terms of the transcapillary escape rate of albumin (TER-alb). The pathophysiology of increased TER-alb is unknown, but could be caused by haemodynamics or damage to the functional properties of the vascular wall¹⁶. Putative mechanisms involved in the development of microalbuminuria are increased vascular permeability, impaired systemic endothelium-dependent vasodilation and elevated plasma levels of pro-thrombotic and pro-inflammatory endothelial markers¹⁶.

Nail capillary abnormalities in patients with albuminuria may be another indicator of endothelial tissue damage. Nailfold capillaroscopy enables the study of various aspects of capillaries, including morphology, distribution, density and blood flow. In the literature, capillaroscopic findings have been investigated in many diseases ranging from diabetes, hypertension and glaucoma, which are clearly related to microvascular damage, to rarer diseases such as tetralogy of Fallot, pseudoxanthoma elasticum, acromegaly and chronic viral hepatitis³. In a meta-analysis study about capillaroscopic examinations in non-rheumatic systemic diseases, 10 of 11 studies with diabetic patients found significantly abnormal capillary findings compared to the control group³. In addition to nail capillaroscopy and videocapillaroscopy methods,

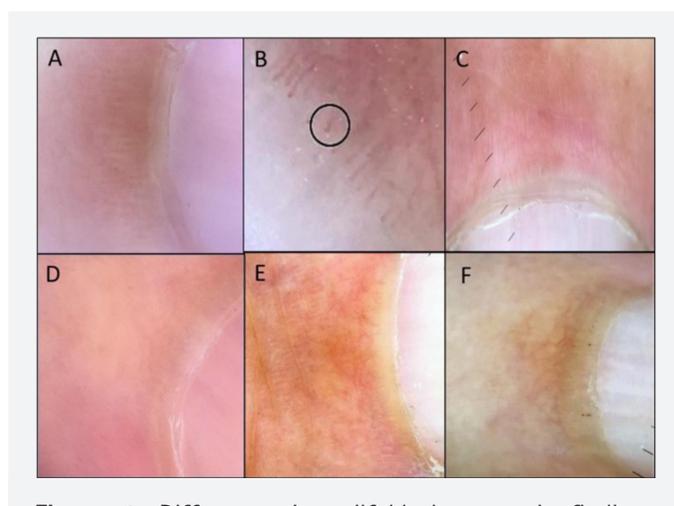


Figure 1. Differences in nailfold dermatoscopic findings between patients with proteinuria and the control group; (a) Normal findings in control group. (b) Capillary disorganization and presence of giant capillaries. (c) Capillary ectasia. (d) Decrease in capillary density. (e, f) Subpapillary venous plexus view (x80 magnification, o: presence of giant capillaries)

Table 1. Comparison of nailfold dermatoscopic findings between patient with proteinuria and control groups

Nailfold dermatoscopic findings	Control (n=85)	With proteinuria (n=85)	Total (n=170)	p value
Ectasia and giant capillaries	4 (4.7%)	15 (17.6%)	19 (11.2%)	0.007
Torsional capillary	7 (8.2%)	15 (17.6%)	22 (12.9%)	0.068
Avascular area	0 (0.0%)	1 (1.2%)	1 (0.6%)	1.000
Microhemorrhage	3 (3.5%)	9 (10.6%)	12 (7.1%)	0.072
Subpapillary venous plexus view	8 (9.4%)	21 (24.7%)	29 (17.1%)	0.008
Cuticulitis capillary	10 (11.8%)	15 (17.6%)	25 (14.7%)	0.279
Capillary disorganization	0 (0.0%)	23 (27.1%)	23 (13.5%)	<0.001
Decrease in capillary density	3 (3.5%)	19 (22.4%)	22 (12.9%)	<0.001

Table 2. Comparison of nailfold dermatoscopic findings between microalbuminuria, macroalbuminuria and overt proteinuria groups

Nailfold dermatoscopic findings	Micro-albuminuria (n=36)	Macro-albuminuria (n=25)	Overt proteinuria (n=24)	p value
Ectasia and giant capillaries	6 (16.7%)	5 (20.0%)	19 (11.2%)	0.935
Torsional capillary	6 (16.7%)	5 (20.0%)	22 (12.9%)	0.935
Avascular area	1 (2.8%)	0 (0.0%)	1 (0.6%)	0.502
Microhemorrhage	5 (13.9%)	3 (12.0%)	12 (7.1%)	0.469
Subpapillary venous plexus view	9 (25.0%)	6 (24.0%)	29 (17.1%)	0.995
Cuticulitis capillary	7 (19.4%)	3 (12.0%)	25 (14.7%)	0.672
Capillary disorganization	8 (22.2%)	10 (40.0%)	23 (13.5%)	0.221
Decrease in capillary density	6 (16.7%)	3 (12.0%)	22 (12.9%)	0.025

more practical and accessible hand dermatoscopes can be used instead of capillaroscopy in recent years. In a study, it is suggested that this method adequately shows the severity of the disease in patients with systemic sclerosis¹⁷. In our study, hand dermatoscope was used to evaluate nail capillary abnormalities in patients with proteinuria.

According to the results of our study, the presence of at least one capillary finding in patients with proteinuria was found to be significantly higher than in the control group. These findings support the knowledge that proteinuria is an indicator of microvascular damage.

Decreased capillary density is a quantitative finding of microvascular injury, unlike other capillaroscopic findings¹⁸. Similar to our study, a decrease in capillary density and the presence of irregular capillary distribution were reported in studies on diabetic patients. In addition, it has been reported that more specific abnormalities such as increase in tortuous vessels and dilated capillaries, microhemorrhages, branched capillaries and avascular areas can be seen in different studies³. In a study in the literature, which argued that albuminuria was associated with capillary sparseness, capillaroscopic examination of the return after arterial occlusion was performed and it was claimed that albuminuria was independently associated with low capillary density¹⁹. In our study, the findings of capillary disorganization and decrease in capillary density were observed to be significantly higher than the control group; however, no correlation was found between the severity of proteinuria and

the decrease in capillary density. This may be related to the wide range of proteinuria causes in our study.

The presence of giant capillaries, microhemorrhages and avascular areas in capillaroscopy has been called the "sclerodermoid pattern" and has become a reference pattern in rheumatology². In our study, a significant difference was observed in the presence of ectasia and giant capillaries in the capillaries between the proteinuria and control groups. No significant difference was observed in terms of microhemorrhages, presence of tortuous veins and presence of avascular area. Considering that diseases causing albuminuria/proteinuria can occur with many different pathogeneses besides scleroderma, the absence of capillary findings in sclerodermoid pattern is an expected result of the study.

The appearance of the subpapillary venous plexus is a capillary appearance that becomes evident with slowed blood flow and age¹³. There was a significant difference between the patients with proteinuria and the control group; however, considering the high mean age of the patients in our study, the specificity of this finding in relation to patients with proteinuria should be investigated by evaluating the younger age group as well.

Cuticulitis vein is a capillaroscopic finding characterized by only high-intensity small red dots in which the appearance of the vessel body is lost, representing hyperemia and interstitial edema²⁰. In a study by Maldonado et al.²¹, it was observed to be significantly higher in diabetic patients compared to the control group, and this situation was found to be associated

with the presence of retinopathy. In our study, no significant difference was found between the two groups in terms of the presence of cuticulitis vessels. Large-scale studies are needed to determine the predictive value of this finding in patients with proteinuria.

In the literature, the effect of poor glycemic control and disease duration on microvascular changes in patients with diabetes was evaluated, and it was emphasized that clinical and metabolic measurements should be taken into account in order not to cause biased results²². In the study of Kuryliszyn-Moskal et al.²³ with patients with type-1 diabetes, it was shown that capillaroscopic findings were associated with poor metabolic control and that branched capillary findings progress in people with a disease duration of 10 years or more. In another study, the mean diabetes duration of patients with capillaryoscopic findings was 12.8; it was determined that this period was 8.5 years in patients with no abnormal capillary findings²¹. In our study, no significant correlation was found between the severity of proteinuria and abnormal capillary findings. However, the duration of albuminuria or proteinuria was not known in the patients, so we may not have been able to detect the development of microvascular changes over time.

Although nail capillaroscopic findings have been proven in many different diseases, the results differ widely from each other. In a study examining the capillaroscopic differences between never-smokers and non-smokers, significant differences were found between two groups²⁴. In addition, in a study on elderly dyslipidemic women treated or not with lipid-lowering therapies, Lopes et al.²⁵ reported that they did not observe any difference in capillary density compared to the control group.

We could not find any study in the literature on nailfold capillary morphology and abnormalities in which dermatoscope was used in patients with proteinuria. One of the most important limitations of our study is the lack of previous videocapillaroscopic examination in patients with proteinuria. We believe that studies with nail capillaroscopy and videocapillaroscopy, which provide more detailed observation of microvascular changes in patients with proteinuria, will expand our knowledge of microvascular changes. In addition, we think that studies evaluating the effects of the diseases causing proteinuria and the duration of proteinuria on these findings may more accurately reveal the role of capillaroscopy in the follow-up of patients with proteinuria.

Study Limitations

Previous videocapillaroscopic examination in patients with proteinuria was not performed. The duration of proteinuria was not known in the patients, and no grouping was made according to the etiology of proteinuria.

CONCLUSION

As a result, we propounded that dermatoscopic examination of nailfold capillaries in diseases with proteinuria might be an indicator of the extent of damage caused by the disease in the microvascular space. Large prospective studies of nailfold capillary examination in patients with proteinuria are needed to evaluate this hypothesis.

Ethics

Ethics Committee Approval: The study protocol was approved by the Muğla Sıtkı Koçman University Institutional Ethical Committee and was conducted in accordance with the Declaration of Helsinki (decision no: 16, date: 16.12.2021).

Informed Consent: All participants gave written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.T.A., Concept: C.T.A., D.G.G., Design: C.T.A., D.G.G., Data Collection or Processing: C.T.A., D.G.G., Analysis or Interpretation: C.T.A., D.G.G., Literature Search: C.T.A., D.G.G., Writing: C.T.A., D.G.G.

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