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Study of the correlation between Nailfold capillaroscopic changes and the new potential biomarker of lupus nephritis activity

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Abstract
Background: In the past, researchers have looked for a variety of blood and urinary indicators for lupus nephritis (LN) in the hopes of identifying one that accurately reflects disease activity. Urinary alpha one antitrypsin is a new potential biomarker in detection of lupus nephritis which was discussed in this research. Capillaroscopic alterations have been shown to correlate with disease activity, including LN, suggesting that they may be helpful in assessing disease severity.
Methods: Fifty individuals with SLE (as determined by the Systemic Lupus Erythematosus Disease Activity Index; SLEDAI) who also had at least six nailfolds suitable for microscopic evaluation participated in the research. Complete blood count (CBC), serum creatinine, and other diagnostic tests: blood urea and eGFR, Erythrocyte Sedimentation Rate (ESR), diagnostic marker for lupus (Anti – Nuclear Anti body (ANA), Anti-ds- DNA and Serum complement level (C3&C4), 24-hour urinary protein, complete urine analysis and urinary alpha one antichymotrypsin using ELISA technique in addition to nailfold capillaroscopic changes test (NFC).
Results: Comparison between the normal and minor change group and between normal and major change group according to Urinary ALPH 1ACT, SLE activity, cutaneous manifestation showed high statistical significance $p<0.001$**.** There was Strong positive significant correlation between cases with SLE activity and had capillarscopic changes and high Urinary ALPH 1ACT**.** There was Strong positive significant correlation between urinary ALPH 1ACT, serum creatinine and 24HR urinary proteins.
Conclusions: Urinary ALPH 1ACT is new potential biomarker of lupus nephritis, it was elevated in active SLE cases particularly active lupus nephritis and also with cases with capillaroscopic changes.

Keywords: Nailfold Capillaroscopic Changes, alpha one antichymotrypsin, systemic erythematosus

Introduction
Autoantibody synthesis and complement activation are hallmarks of systemic lupus erythematosus (SLE), a chronic autoimmune inflammatory illness [1, 2].
Endothelial cell injury from autoantibody synthesis and immune complex vasculitis leads to clinical SLE manifestations. Serious multi-organ failure is caused by vascular endothelial injury [3]. Involvement of the kidneys is a frequent consequence that predicts a dismal outlook in the long run [4, 5].
Among the non-invasive imaging methods available, nailfold capillaroscopy (NFC) is the gold standard for analysing the morphology of nailfold nutrient capillaries.
Microvascular anomalies in scleroderma and SLE have been studied using this technique [6, 7]. NFC anomalies have been linked to SLE disease severity, and while alterations in capillary morphology and blood flow are not unique to SLE, they do occur frequently including kidney involvement [8, 9].
A number of serum and urinary markers for lupus nephritis (LN) have been pursued in the past with the hope of finding some which could reflect disease activity in a reliable manner [10]. Urinary alpha one antitrypsin is a new potential biomarker in detection of lupus nephritis which was discussed in this research [9].
Capillaroscopic alterations have been shown to correlate with disease activity, including LN, suggesting they may be helpful in assessing disease severity [10].
Protecting against the onset of systemic organ malfunction, such as renal failure, and bettering therapy for SLE could benefit from more research into the role of microvascular

alterations in the pathogenesis of the disease [11].
The purpose of the research was to evaluate the NFC in SLE cases and to determine whether or not there was a link between NFC alterations and disease activity and kidney involvement.

Patients and Methods

This research was conducted on 50 SLE cases diagnosed according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and proven by renal biopsy if done and have at least six evaluable nailfolds for the microscopic procedure. They were selected from wards of internal medicine department and outpatient rheumatology clinic in Tanta University Hospital during the period from June 2020 to November 2020.
An informed consent was obtained from all participants and the research was done after approval from the Ethical Committee Tanta University Hospitals.
Exclusion criteria include cases under 18 years, [ositive serology for Hepatitis C Virus (HCV), Hepatitis B Virus surface Antigen (HbsAg) or Human Immunodeficiency Virus (HIV)., cases on dialysis or transplantation, cases with diabetic nephropathy, over weight and with 1ry HTN, cases with chronic inflammation or chronic infection, cases with malignancy, other rheumatological disease rather than lupus, Smokers, cases with restrictions to capillary assessment (such as very thick nailfolds or without at least six accessible nailfolds to be examined; for example, gangrene of all digits), and cases who refused to participate or write an informed agreement were not included.
All cases underwent full history taking, clinical examination and laboratory investigations including Complete blood count (CBC), serum creatinine, blood urea and eGFR, Erythrocyte Sedimentation Rate (ESR), diagnostic marker for lupus (Anti –Nuclear Anti body (ANA), Anti-ds- DNA and Serum complement level (C3&C4), 24-hour urinary protein, complete urine analysis and urinary alpha one antichymotrypsin using ELISA technique.
All of the digits were capillaroscopically examined on the same day by a rheumatologist who was blind to the patient's disease activity and test results except the thumbs by (Dino-Lite Digital microscope MED L4N) at Tanta University Hospital. We did not examine gangrenous digits or those with dense nailfolds. The rheumatologist analyzing the images took at least one picture of the nailfold in the center of each finger.
Normal, particular changes (categorized as early, active, and late scleroderma pattern), or non-specific changes were the categories used to characterize the results of the NFC [12].
Modifications in capillary density were rated on a scale from 0 (no change) to 2 (major change)
score 0: normal (6–8 capillaries/mm2, hairpin-shaped loops arranged in parallel rows, absence of haemorrhages), score 1: minor changes (6–8 capillaries/mm2, less than 50% tortuous loops, arranged in parallel rows, with no haemorrhages), score 2: major changes (normal or decreased capillary density, more than 50% tortuous, enlarged loops, disarranged, with haemorrhages) [18].

Statistical analysis

Analysis was performed using SPSS version 21. Quantitative data were presented by Mean ± SD, median, range, Interquartile range and evaluated ANOVA test (in case of parametric data) or Kruskal Wallis (in case of non-parametric data). Numerical and percentage representations of categorical data were used, with the chi-square test or the Monte Carlo Exact test being used for analysis. The linear relationship between the non-parametric factors was analyzed using Spearman correlation. When the P value was less than 0.05, it was deemed important, and when it was less than 0.001, it was deemed extremely so.

Results

Regarding demographic characteristics, no significant differences between 3 groups were seen in age, gender, disease duration as seen in table.1

Table 1: Comparison of demographic data and disease duration between normal, minor and major capillaroscopic findings

	No change (n=16)	Minor change (n=16)	Major change (n=18)	p
Sex				
Male	4	5	5	1.000
	28.6%	35.7%	35.7%	
Female	12	11	13	
	33.3%	30.6%	36.1%	
Age (Years)				0.455
Mean ± SD	29.2 ± 2.93	27.9 ± 3.34	27.8 ± 4.05	
Disease duration (Years)				0.821
Median (IQR)	4 (3.25 - 5)	4 (3 - 5)	4 (3 – 4.25)	

Comparison between the normal and minor change group and between normal and major change group according to ESR, CRP, hematological findings (Hb, Platelets, TLC), serology (High Anti Ds DNA, Low complement) which indicate active SLE, serum albumin, urine analysis [proteins, casts, RBCs], eGFR, renal functions and 24Hr urinary proteins showed high statistical significance p<0.001.

Table 2: Laboratory investigations of different groups

	No change (n=16)	Minor change (n=16)	Major change (n=18)	P
ESR				<0.001*
Mean ± SD	76.6 ± 9.78	97.8 ± 8.75	105.2± 10.7690	
CRP (mg/L)				<0.001*
Median (IQR)	5.5 (4.25 – 6.75)	11.5 (10.25 – 13.75)	12 (11– 13.25)	
Hb(g/dl) Median (IQR)	12 (11 – 12)	9.5 (9 – 10.375)	10 (9.375 – 10)	<0.001*
Platelet x 103/mm3 Median (IQR)	265 (250 – 300)	148 (146 – 153.75)	147.5 (145 – 150.25)	<0.001*

TLC/mm3) Median (IQR)	8500 (7900 – 8975)	5700 (5562 – 6067)	5750 (5605 – 5910)	<0.001*
ANA				
+ ve	16	16	18	
	32.0%	32.0%	36.0%	
Anti-Ds(IU/mL)				
Normal	15	1	0	
	93.8%	6.3%	0.0%	<0.001*
High	1	15	18	
	2.9%	44.1%	52.9%	
Low complement				
No	15	1	0	
	93.8%	6.3%	0.0%	<0.001*
Yes	1	15	18	
	2.9%	44.1%	52.9%	
Serum albumin				
Median (IQR)	3.9 (3.7 –4)	3.3 (2.925 – 3.4)	3.1 (3 – 3.2)	<0.001*
e- GFR ml/min/1.73m^2				
Median (IQR)	116.02 (88.125 – 126.2)	69.24 (61.23 – 83.25)	68.99 (60.82 – 79.4)	<0.001*
Urea (mg/dl)				<0.001*
Median (IQR)	36.5 (34.25 – 38)	45 (43.25 – 48.75)	47 (44.75 – 48)	
Creatinine(mg/dl)				<0.001*
Median (IQR)	0.75 (0.625 – 0.9)	1.2 (1.1 – 1.275)	1.1 (1.1 – 1.225)	
24 hr protein(mg/24hr)				<0.001*
Median (IQR)	765 (660 – 937.5)	2050 (762.5 – 2687.5)	1500 (1237.5 – 2000)	

Comparison between the normal and minor change group and between normal and major change group according to renal biopsy results showed high statistical significance p <0.001, and between cases having minor and major changes according to renal biobsy results showed statistical significance p = 0.042

Table 3: Comparison of renal biobsy results between normal, minor and major capillaroscopic findings:

Renal biopsy	Normal NFC	Minor changes	Major changes	
No	16	6	3	
	64.0%	24.0%	12.0%	
Class II	0	0	7	
	0.0%	0.0%	100.0%	<0.001*
Class III	0	7	6	
	0.0%	53.8%	46.2%	
Class IV	0	3	2	
	0.0%	60.0%	40.0%	

P (No change&minor) = <0.001*
P (No change&major) = <0.001*
P (Minor change&major) = 0.042*

Comparison between the normal and minor change group and between normal and major change group according to Urinary ALPH 1ACT, SLE activity, cutaneous manifestation showed high statistical significance p <0.001

Table 4: Comparison of ALPH 1ACT, SLE activity, cutaneous manifestation between normal, minor and major capillaroscopic findings

	No change (n=16)	Minor change (n=16)	Major change (n=18)	p
Median (IQR)	**ALPH 1ACT**			<0.001*
	0 (0 – 37.5)	727 (608 – 727)	608 (125 – 691.75)	
SLE Activity				
Not active	15	1	0	
	93.8%	6.3%	0.0%	<0.001*
Active	1	15	18	
	2.9%	44.1%	52.9%	
Cutaneous manifestation				
Absent	15	1	0	
	93.8%	6.3%	0.0%	<0.001*
Present	1	15	18	
	2.9%	44.1%	52.9%	

There was Strong positive significant correlation between urinary ALPH 1ACT, serum creatinine and 24HR urinary proteins, and *p*<0.001

Table 5: Correlation between Urinary ALPH 1ACT,serum creatinine and 24HR urinary proteins

	ALPH 1ACT	
	r_s*	p
Serum Creatinine	0.63	<0.001*
24 HR Urinary protein	0.59	<0.001*

r_s: Spearman Correlation

There was Strong positive significant correlation between cases with SLE activity and had capillarscopic changes with r_s=0.807 and P<0.001 and between cases with SLE activity and high Urinary ALPH 1ACT with r_s=0.827 and P<0.001

Table 6: Correlation between SLE activity, Capillaroscopic changes and Urinary ALPH 1ACT

	SLE activity	
	r_s*	P
Capillaroscopic changes	0.807 (Strong positive significant correlation)	<0.001*
ALPH 1ACT	0.827 (Strong positive significant correlation)	<0.001*

r_s: Spearman Correlation

Discussion

Capillaroscopic finding were observed in 34 cases (68%) of all cases. Minor changes were found in 16 cases 32% (5 males and 11 females), Major changes were found in 18 cases 36% (5 males and 13 females).

This was partially in agreement with the results of research performed by Shenavandeh *et al.* [13], in which morphological changes in NFC were observed in 102 out of 108 (94.4%) SLE cases. Minor changes were found in 33 (30.6%) and major changes in 69 (63.9%) cases. Both studies had no significant differences between 3 groups were seen in age, sex, disease duration.

Comparison between the normal and minor change group and between normal and major change group according to (ESR, CRP, hematological findings, Hb, Platelets, TLC) showed high statistical significance p<0.001, but this wasn't studied in Shenavandeh *et al.* [13], Zhao *et al.* [14], Riccieri *et al.* [9].

Comparison between the normal and minor change group and between normal and major change group according to serology (High Anti Ds DNA, Low complement) which indicate active SLE showed high statistical significance p<0.001.

In contrary to our findings, S Shenavandeh, *et al.* [13], Zhao *et al.* [14], V Riccieri, *et al.* [9], there was no statistical significance between cases with normal NFC, and cases with major or minor capillaroscopic changes according to serology (High Anti Ds DNA, Low complement).

Comparison between the normal and minor change group and between normal and major change group according to serum albumin showed high statistical significance p<0.001 which wasn't documented in other studies.

Comparison between the normal and minor change group and between normal and major change group according to different renal parameters including (urine analysis [proteins, casts, RBCs], renal function tests, 24hr urinary proteins, eGFR and renal biopsy results) showed high statistical significance p<0.001.

In contrast to our findings, to S Shenavandeh, *et al.* [13], Zhao *et al.* [14], V Riccieri, *et al.* [9] showed that there was no statistical significance between cases with normal NFC, and cases with major or minor capillaroscopic changes according to different renal parameters.

Comparison between the normal and minor change group and between normal and major change group according to Urinary ALPH 1ACT showed high statistical significance (p <0.001) and this wasn't studied before.

Comparison between the normal and minor change group and between normal and major change group according to SLE activity, showed high statistical significance (p =<0.001).

This was partially in agreement with the results of research performed by S Shenavandeh, *et al.* [13], in which the disease activity measured by the SLEDAI score was significantly higher in the cases with major changes (p<0.002).

Consistent with the findings of Zhao *et al.* [14], who found a statistically significant (p=0.002) increase in the frequency of nearly all capillary abnormalities in cases with active disease compared to those with inactive disease, our findings showed that cases with active disease had a greater prevalence of these abnormalities.

Comparison between the normal and minor change group and between normal and major change group according, cutaneous manifestation showed high statistical significance (p<0.001).

This was partially in agreement with the results of research performed by S Shenavandeh, *et al.* [13], in which a positive correlation was found between the presence of active skin lesions and the severity of capillary abnormalities (p<0.03).

In contrast, V Riccieri *et al.* [9] showed no statistically significant correlation was found among the different capillaroscopy findings and cutaneous manifestations of SLE.

In our research, there was strong positive significant correlation between cases with SLE activity measured by the SLEDAI score and cases with capillaroscopic changes especially hemorrhage with r_s =0.807 and (p<0.001).

This was partially in agreement with the results of research performed by S Shenavandeh, *et al.* [13], in which the evaluation of the components of capillary changes between active and inactive SLE cases according to SLEDAI score, a significantly higher incidence of capillaroscopic abnormalities most frequently, haemorrhage was seen in the cases with active SLE disease (p<0.04).

In our research, there was Strong positive significant correlation between urinary ALPH 1ACT, serum creatinine and 24HR urinary proteins, and (p<0.001).

This was partially in agreement with the results of research performed by Susianti *et al.* [15], in which there was positive significant correlation between urinary ALPH 1ACT, serum creatinine and protein creatinine ratio.

In our research, there was Strong positive significant correlation between cases with SLE activity and high Urinary ALPH 1ACT with r_s=0.827 and (p<0.001).

This was in agreement with the results of research performed by Aggarwal *et al*. [16], in which median urinary ACT (uACT) levels were significantly higher in the active SLE group compared to all other groups ($p< 0.001$).
In contrary to our findings, Susianti *et al*. [15] observed no statistically significant correlation was found between cases with SLE activity and Urinary ALPH 1ACT.

Conclusions:
Even though there are no recognizable patterns, individuals with SLE frequently exhibit capillary alterations (abnormal capillaroscopy). Major capillary changes were linked with a greater disease activity (SLEDAI score), and some capillary changes may be associated with disease activity, particularly in individuals with active skin involvement. Urinary ALPH 1ACT is new potential biomarker of lupus nephritis, and in our research it was elevated in active SLE cases particularly active lupus nephritis and also with cases with capillaroscopic changes.

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Conflict of Interest: Nil

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