



Post Graduate Thesis Section

## Study of Cutaneous Manifestations and Nail fold Capillaroscopic findings in Diabetes Mellitus and their correlation with Diabetic Retinopathy and Nephropathy- A Cross Sectional Observational Study

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### ABSTRACT

**Objective:** Long-term diabetes can lead to complications including diabetic macro- and microangiopathy. Capillaroscopy is a non-invasive method to evaluate capillary microvasculature which can be used to demonstrate changes in capillary microarchitecture noted in diabetic microangiopathy. The objective of this study was to study cutaneous manifestations of diabetes mellitus (DM), nailfold capillaroscopic changes due to diabetic microangiopathy, as well as to determine association between nailfold capillaroscopy (NFC) and cutaneous manifestations due to DM.

**Materials and Methods:** Two hundred cases suffering from type 2 DM having cutaneous manifestations were enrolled in the study. Patients with autoimmune diseases, smokers and on long-term corticosteroids were excluded from the study. Detailed history was taken and the cutaneous manifestations related to type 2 DM were noted. NFC was done for all ten fingers of all patients. Additional investigations including HbA1c, urine microalbumin and fasting lipid profile were performed.

**Results:** Out of 200 cases, 88 showed positive findings on NFC with the most common finding being altered tortuosity (seen in 85.2% cases). Chi-square test was done to demonstrate association between duration of DM and NFC which showed *P*-value of 0.027, which is statistically significant. Of the cases having nailfold capillaroscopic findings, 69/88 (78.4%) were found to have elevated HbA1C levels, 57/88 (57.9%) were found to have changes of diabetic retinopathy and 56/88 (63.6%) were found to have changes of diabetic nephropathy.

**Conclusion:** NFC can provide key data for determination of vascular damage in diabetic patients and, thus, allows evaluation of progression of the disease making this technique a potential future utility in microvascular disease evaluation.

**Keywords:** Nailfold capillaroscopy, Diabetes Mellitus, Diabetic microangiopathy, capillaroscopy, Cutaneous manifestations of diabetes

### INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous group of disorders characterised by high serum glucose levels and disturbances of carbohydrate and lipid metabolism. Chronic hyperglycaemic state can

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cause various vascular alterations, leading to microangiopathic as well as macroangiopathic complications. Cutaneous manifestations in cases of DM can arise from complex interplay between biochemical, vascular, immune and metabolic changes that occur in DM.<sup>[1]</sup> Vascular involvement in diabetic cases can be demonstrated in form of involvement of vessels at proximal nailfold, retina and kidney with the help of capillaroscope, ophthalmoscopes and urine-analysis, respectively.

Nailfold capillaroscopy (NFC) can provide key data for determination of vascular damage in diabetic patients and, thus, allows evaluation of progression of DM,<sup>[2]</sup> making this technique a potential future utility in microvascular disease evaluation.<sup>[3]</sup> The goal of this study is to demonstrate cutaneous manifestations due to DM and correlate microangiopathic complications due to DM in the form of NFC findings, diabetic retinopathy and diabetic nephropathy.

## MATERIAL AND METHODS

Two hundred cases of type II DM attending outpatient department of dermatology as well as diabetic clinic run by department of medicine were included in this study. Patients with conditions which can alter NFC findings including autoimmune diseases such as scleroderma, lupus, chronic smokers and peripheral vascular disease were excluded from the study. Furthermore, conditions having impact on glucose tolerance such as chronic glucocorticoid use and liver diseases were excluded from the study.

All cases were evaluated for cutaneous manifestations due to DM including infections, metabolic changes and vascular lesions [Table 1]. Detailed history regarding duration, complications of DM and physical examination were noted. Thereafter, NFC was carried out on proximal nailfolds of all ten fingernails using 'Otiez eScope'-DP-M17 dermatoscope (with  $\times 20$  and  $\times 200$  magnification) to determine any microvascular changes in such cases. Liquid paraffin was used as a contact liquid for dermatoscopic evaluation to reduce refractive index difference between skin and air. Being compatible with Windows XP, the images were captured and evaluated over its software. NFC findings needed to be altered in two or more nails to be labelled as abnormal. Most precise morphologic evaluation was obtained from 4<sup>th</sup> to 5<sup>th</sup> fingers due to highest transparency of skin and because of these digits being less prone to trauma.

Retinal evaluation was carried out by an ophthalmologist through dilated fundoscopic examination to determine the changes of diabetic retinopathy. For all cases, laboratory tests included HbA1c to monitor glycaemic control, lipid panel and urinalysis for albuminuria to determine underlying diabetic nephropathy.

The study was approved by the Institutional Ethics Committee for Human Research and funded by IADVL PG Thesis Research Grant 2017.

## RESULTS

Out of total 200 patients, maximum number of cases, that is, 72 (36%) cases enrolled in this study belonged to 60–69 years of age group with mean being  $57.205 \pm 11.3$  years. Out of them, 90 (45%) were male and 110 (55%) were female with male-to-female ratio of 1:1.2. Duration of DM in our patients ranged from 2 years to 26 years with mean duration of  $9.36 \pm 6.08$  years.

In our study, most common cutaneous manifestations in diabetics were recurrent fungal infections (18%), followed by recurrent bacterial infections (17.5%), metabolic manifestations such as acrochordons and acanthosis nigricans (15%) and reactive perforating collagenosis (RPC) (12%). Other manifestations are listed in [Table 1]. [Figure 1] demonstrates cutaneous manifestations seen in our patients.

NFC findings were seen in 88 (44%) cases out of 200. Most common finding on NFC was altered tortuosity in 85.2% cases, followed by dilated capillaries in 43.2% cases as demonstrated in [Table 2]. [Figure 2] demonstrates NFC findings seen in our cases. In this study, it was found that NFC findings were positive most commonly in cases having RPC and diabetic dermopathy and absent in cases having recurrent bacterial and fungal infections.

All cases were, further, evaluated for possible microangiopathic complications due to DM in the form of diabetic retinopathy and nephropathy. Statistical analysis was performed using Chi-square test for trend to demonstrate association between NFC and:

- Duration of DM
- Glycaemic control in the form of HbA1C levels
- Grade of diabetic retinopathy
- Grade of diabetic nephropathy.

For duration of DM, Chi-square value for trend was 4.89 with *P*-value of 0.027 which was highly statistically significant demonstrating that NFC findings were more common in chronic diabetic cases.

All diabetic cases included in the study underwent ophthalmologic examination for evaluation of diabetic retinopathy. Out of total 200 cases, 72 (36%) had changes suggestive of diabetic retinopathy with maximum number of cases: 37 (18.5%) with Grade I changes, that is, mild non-proliferative diabetic retinopathy (NPDR) followed by 27 cases (13.5%) having changes of moderate NPDR. Of the cases having normal NFC, majority, that is, 97/112 (86.6%) cases had normal retinal examination with negative for retinopathy. On statistical analysis by Chi-square test for trend to demonstrate association between grading of diabetic retinopathy and NFC, Chi-square value was found to be 56.37 with *P* < 0.0001, which is highly statistically significant suggesting that abnormal NFC findings were more common in cases having diabetic retinopathy.

**Table 1:** Cutaneous manifestations seen in diabetic cases in the present study.

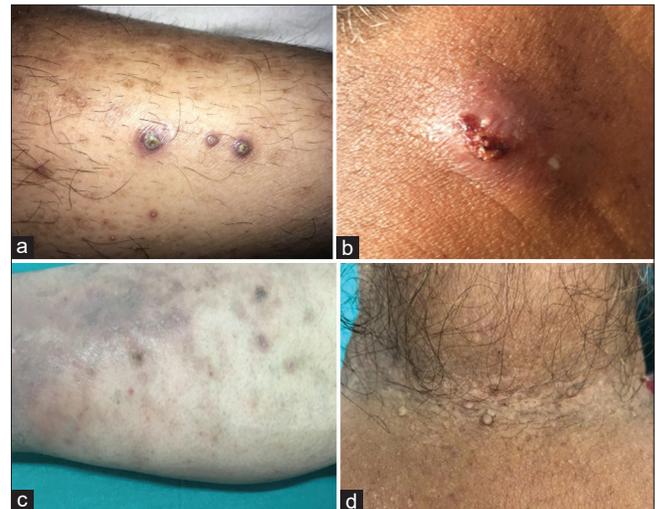
S. No.	Pathogenesis	Cutaneous manifestations	No. of cases (n=200)		
			Males	Females	Total
1.	Vascular damage	• Wet gangrene of the foot	1	2	3 (1.5%)
		• Diabetic dermopathy	12	8	20 (10%)
		• Rubeosis	0	2	2 (1%)
2.	Neurological damage	• Diabetic Foot	5	3	8 (4%)
		• Diabetic foot ulcer	3	1	4 (2%)
3.	Recurrent infections	• Recurrent bacterial infections	18	17	35 (17.5%)
		• Recurrent fungal infections	13	13	36 (18%)
		• Recurrent bacterial+Fungal infections	1	3	4 (2%)
4.	Obesity and hyperlipidaemia-related skin disease	• Acanthosis Nigricans	5	8	13 (6.5%)
		• Acrochordons	1	4	5 (2.5%)
		• Acanthosis Nigricans+Acrochordons	12	18	30 (15%)
		• Xanthomas	2	4	6 (3%)
5.	Treatment related skin manifestations	• Insulin lipodystrophy	1	0	1 (0.5%)
6.	Disease associations and genetic syndromes	• Reactive perforating collagenosis/ perforating folliculitis	13	11	24 (12%)
		• Autoimmune disease (Vitiligo)	1	4	5 (2.5%)
7.	Miscellaneous	• Stiff skin and joints	1	1	2 (1%)
		• Pruritus	0	0	1 (0.5%)
		• Granuloma annulare	0	1	1 (0.5%)

Out of 88 cases having abnormal NFC findings, 56 cases (63.6%) had signs of diabetic nephropathy, with 46 (52.3%) cases detected with microalbuminuria and the remaining ten cases (11%) having macroalbuminuria. On statistical analysis by Chi-square test for trend to demonstrate association between grading of diabetic nephropathy and NFC, Chi-square value was found to be 27.97 with  $P < 0.0001$ , which is highly statistically significant implying that abnormal NFC findings were seen more commonly in cases having worsening diabetic nephropathy.

In terms of glycaemic control, mean HbA1C levels of 200 cases enrolled in this study was found to be  $7.92 \pm 0.0192\%$ . 128 cases, that is, 64% had evidence of poor glycaemic control with HbA1C levels  $>7\%$  with most cases (22.5%) being in the range of 7–8 g% HbA1C levels. On statistical analysis by Chi-square test for trend to demonstrate association between HbA1C levels and NFC, Chi-square value was found to be 20.22 with  $P < 0.0001$ , which is highly statistically significant.

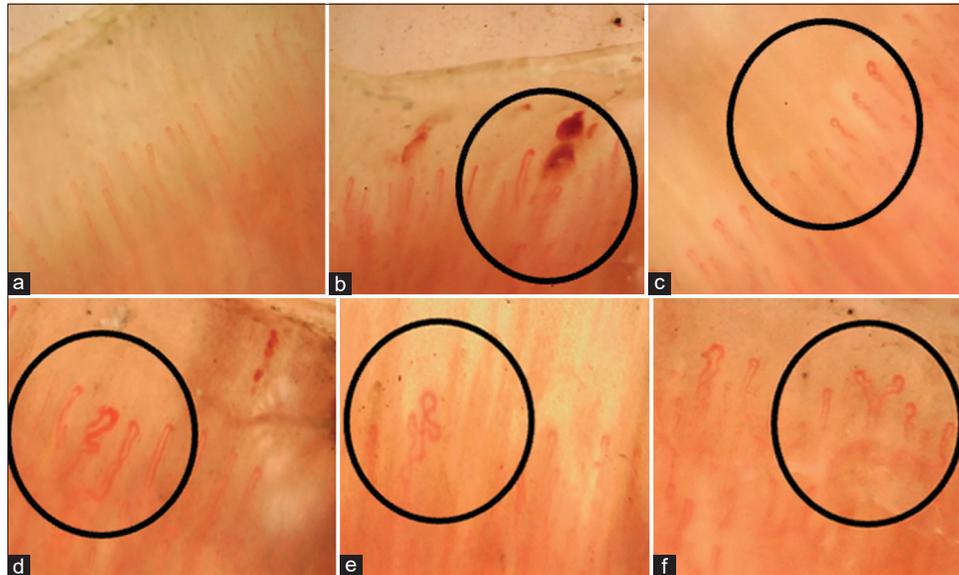
## DISCUSSION

Pathogenesis of cutaneous manifestations in DM could be multi-factorial due to: macrovascular and microvascular damage, neurological involvement and increased susceptibility to infections due to hyperglycaemia to name a few. In a case-control study conducted by Mahajan *et al.*, 64% cases of type 2 DM had cutaneous manifestations, compared to 22% in control group. This difference was statistically highly



**Figure 1:** Various cutaneous manifestations in diabetic cases in the study (a) Reactive perforating collagenosis (b) Carbuncle (c) Diabetic dermopathy (d) Acanthosis nigricans and acrochordons.

significant ( $P < 0.001$ ).<sup>[4]</sup> Most common manifestations were bacterial (pyodermas) and fungal infections similar to the present study, followed by neurological manifestations such as paraesthesia and pruritus, diabetic dermopathy and metabolic manifestations such as acrochordons and acanthosis nigricans. In a study of 500 diabetic cases carried out by Ragnatha *et al.*, signs of insulin resistance, acrochordon (26.2%) and acanthosis nigricans (5%) were common, followed by fungal (13.8%) and bacterial (6.8%) infections.<sup>[5-10]</sup>



**Figure 2:** Nailfold capillaroscopic findings (a) Normal nailfold capillaroscopy showing hair pin shaped capillaries with uniform density and distribution (b) Microhemorrhage (c) Altered tortuosity (d) Dilated capillaries (e) Bizarre capillary (f) Bushy capillary.

**Table 2:** Nailfold capillaroscopic findings in diabetic cases.

S. No.	Nailfold capillaroscopic findings	No. of cases (n=88)	Percentage
1.	Altered tortuosity	75	85.2
2.	Dilated capillaries	38	43.2
3.	Giant capillaries	16	18.2
4.	Angiogenesis	15	17
	• Meandering (criss-cross)		
	• Bizarre capillaries		
	• Bushy capillaries		
5.	Capillary dropouts	1	1.1
6.	Microhemorrhage	1	1.1

The essence of capillaroscopy is to examine, non-invasively and safely, the morphology of nailfold dermal papillary capillaries.<sup>[11]</sup> Capillaries lie horizontally, permitting examination of their entire morphology. In nailfold, distal capillary row in the dermal papillae runs parallel to the surface of the nail. Subsequently, the capillaries of the distal row are visible in their whole length and appear as red, hairpin-shaped loops that lie parallel to the axis of the finger. Proximal nailfold being an acral area is affected early, as well as maximally, by disorders affecting microvasculature. Normal proximal NFC shows a characteristic appearance of a hairpin or upside down U pattern with regular distribution and homogeneous morphology of small vessels, and with one to three capillary vessels in each dermal papilla. The number of capillary vessels at the periungual level is 9–13/mm (mean).<sup>[12]</sup>

Very few studies are available for NFC in diabetic cases. In an observational study of 115 diabetic cases by Hsu *et al.*, cases

with type 2 DM showed significantly higher frequencies of reduced capillary length (29.6%), irregular capillary distribution (35.7%), abnormal capillary morphology (59.1%) and NVC score alteration compared to the control subjects.<sup>[9]</sup> Type 2 diabetic cases with chronic clinical complications had a higher frequency of enlarged capillaries and nodular apical elongation.<sup>[13]</sup> Meyer *et al.* observed tortuous, dilated capillaries and normal capillary density in cases with DM type I and II when compared against a control group.<sup>[14]</sup> Rajaei *et al.* studied the capillaroscopic changes in cases with DM and demonstrated that ramified and tortuous capillaries were more frequent in these cases, compared to a control group.<sup>[15]</sup>

In the study by Maldonado and Rios, the most frequent alterations were tortuous capillaries in 63%, capillary cross-linking 59%, avascular areas 48% and ectasias 31%. Other alterations found were giant capillaries in 14%, ramified capillaries in 11% cases. [Table 3] demonstrates comparison of nailfold capillaroscopic findings in diabetic cases in the present study and similar study conducted by Maldonado *et al.*<sup>[2,16]</sup>

Mean HbA1C levels of 200 cases enrolled in this study was found to be  $7.92 \pm 0.0192\%$  as compared to the study carried out by Barchetta *et al.*, in which mean HbA1C level was  $7.5 \pm 1.8\%$ , Ghosh *et al.*<sup>[17]</sup> and Hsu *et al.*,<sup>[9]</sup> with mean HbA1C levels of  $8.99 \pm 1.06\%$  and  $7.2 \pm 1.2$ , respectively. Focusing on metabolic control, chronic hyperglycaemia affects the capillary endothelia, generating microvascular architecture changes, that can be evidenced by use of capillaroscopy.<sup>[18]</sup> Furthermore, the disease evolution has shown that duration

**Table 3:** Comparison of nailfold capillaroscopic findings in the present study versus study by Maldonado *et al.*

Nailfold capillaroscopy findings	Present study	Study by Maldonado <i>et al.</i>
Altered tortuosity	85.2%	63%
Dilated capillaries	43.2%	31%
Giant capillaries	18.2%	14%
Angiogenesis	17%	59%
Capillary dropouts/avascular areas	1.1%	48%
Microhemorrhages	1.1%	-

can contribute to capillaroscopy changes, Kuryliszyn *et al.* found an escalating appearance of ramified capillaries in diabetic cases with a prolonged evolution time (of more than 10 years).<sup>[19,20]</sup> Bollinger and Fagrell showed similar data, in which they described more capillaroscopic alterations in diabetic cases with a disease evolution of over 10 years.<sup>[21]</sup>

In the study of 115 diabetic cases by Hsu *et al.*, the frequencies of reduced capillary length, irregular capillary distribution, abnormal capillary morphology, enlarged loop and abnormal flux were increased in the subjects with HbA1c  $\geq 7\%$ ,<sup>[9]</sup> which is similar to our study, in which abnormal NFC findings were more common in cases with poor glycaemic control. In another study, approximately 63% of study population had high glycaemia levels  $>110$  mg/dL, from which 100% presented tortuous capillaries, 93% cross-linked capillaries, 22% giant capillaries, 17% arborified capillaries and 12% visibility of subpapillar venous plexus.<sup>[22]</sup>

In study conducted by Abdollahi *et al.*, frequency of retinopathy in cases with diabetic dermopathy (44%; 30 cases) was significantly greater than in cases without dermopathy (15%; 17 cases;  $P < 0.0001$ ).<sup>[23]</sup> Retinopathy showed a statistically significant association with dermopathy (odds ratio [OR]: 3.60; 95% confidence interval [CI]: 1.53–8.44;  $P = 0.003$ ) and diabetes duration (OR: 3.36; 95% CI: 1.67–6.77;  $P = 0.001$ ). It supports that diabetic dermopathy might be used as a telltale sign of diabetic retinopathy, necessitating more intensive ophthalmologic care, especially in long-lasting diabetes.

In terms of diabetic nephropathy, study of 115 diabetic cases by Hsu *et al.* showed positive correlation between nailfold video capillary score and the number of microvascular complications (Spearman correlation coefficient, 0.211;  $P = 0.039$ ) which included diabetic retinopathy and diabetic nephropathy.<sup>[9]</sup>

## CONCLUSION

Cutaneous manifestations in cases of DM can arise from a complex interplay between the biochemical, vascular, immune and metabolic changes that occur in the diabetic

state. It includes a variety of infective and non-infective conditions and can be the presenting complaint prompting the diagnosis of DM. NFC can serve as an early marker for microvascular involvement in various rheumatological and non-rheumatological conditions affecting vasculature, more involved due to its acral location. Microvessel capillaroscopy study seems to be very interesting in diabetes, because microangiopathy is the most common and fearsome complication of diabetes and also because it seems that the alterations of cutaneous microvessels constitute the earliest manifestations of the disease. Significant association was found between abnormal NFC findings in diabetic cases and poor glycaemic control, grades of diabetic retinopathy and diabetic nephropathy. It can be thus used as an early marker/predictive tool for microangiopathic involvement in cases suffering from DM in the form of diabetic retinopathy and nephropathy and, thus, can be useful to prevent impending complications.

## Limitations of our study

There was no control group in this study. More number of controlled trials are, therefore, required to confirm the findings of the present study in terms of association of NFC with cutaneous manifestations, duration of DM, diabetic retinopathy, diabetic nephropathy and HbA1C levels.

## Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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## Conflicts of interest

There are no conflicts of interest.

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