Can Nailfold Capillaroscopy Be a Screening Tool for Diabetic Retinopathy - A Hospital Based Cross-Sectional Study in Orissa, India

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ABSTRACT

BACKGROUND

The nailfold capillaroscopy (NFC) has been used to analyse capillary micro-architecture in diseases like Raynaud's disease, scleroderma, and other collagen disorders earlier but recently researchers have documented capillaroscopic findings in diabetic patients which correspond to their ophthalmoscopic findings. Every diabetic patient after ten years of the disease is at risk of diabetic retinopathy and should thereby be referred to an ophthalmologist for screening. But for various factors the referral to ophthalmologists is poor and the patients usually present to the ophthalmologist when their vision is threatened. Our study intends to correlate the nailfold capillaroscopic microvascular changes with duration of diabetes, severity of diabetic retinopathy (DR), compare the changes of patients with DR and without DR and determine its role as a screening tool.

METHODS

This was a hospital based cross-sectional study for over 18 months in patients (15 - 75 yrs. of age) with diabetes mellitus. Patients with other vascular disorders were excluded. The study subjects were evaluated for diabetic retinopathy by indirect ophthalmoscopy, fundus pictures and optical coherence tomography. The nailfold capillaroscopy findings were recorded and co-related with fundus findings. Statistical analysis was done by using the STATA software version 15.1.

RESULTS

Two hundred and fifty patients were recruited with 125 patients in each group, patients with and without DR respectively. Poor glycaemic control was seen most commonly in patients with proliferative diabetic retinopathy. The reduced capillary density, tortuosity, microhaemorrhages, neoangiogenesis and avascular areas were seen more frequently in proliferative diabetic retinopathy than non-proliferative diabetic retinopathy and patients without DR. (P value 0.00).

CONCLUSIONS

Changes in nailfold capillaroscopy in diabetics have significant association with severity of DR, duration of diabetes, and glycaemic control. It could be used as screening and early diagnostic tool for non-ophthalmology medical fraternities to refer to ophthalmologist for follow-up and treatment of diabetic retinopathy.

KEYWORDS

Diabetes Mellitus, Diabetic Retinopathy, Nailfold Capillaroscopy, Microangiopathy

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DOI: 10.18410/jebmh/2021/280

How to Cite This Article:
Mohanty G, Padhan P, Chilakamarthy S, et al. Can Nailfold Capillaroscopy be a screening tool for Diabetic Retinopathy - A hospital based cross-sectional study in Orissa, India. J Evid Based Med Healthc 2021;8(20):1479-1483. DOI: 10.18410/jebmh/2021/280

Submission 11-12-2020,
Peer Review 19-12-2020,
Acceptance 01-04-2021,
Published 17-05-2021.

BACKGROUND

Diabetic retinopathy (DR) is a leading cause of vision loss in the world. Prolonged duration of diabetes leads to microangiopathic changes like pericyte loss, apoptosis of endothelial cells and thickening of basement membrane.[1] Every seventh person with diabetes mellitus has been found to have DR. A periodical dilated fundoscopy is the gold standard screening approach, but the referral to ophthalmologist is poor due to various reasons like ignorance, financial constraints, feasibility, and negligence.[2] Under such circumstances, nailfold capillaroscopic findings, which has been found to correspond the ophthalmic findings, may be helpful as a screening tool. Nailfold capillaroscopy has been used to assess morphological and structural changes quantitatively and qualitatively in nailfold capillaries for early diagnosis and monitoring the progression of autoimmune and collagen disorders.[3]

The purpose of our study is to associate the nailfold capillaroscopic changes with duration of diabetes and microvascular changes in DR and also to determine its role as a cost-effective and easy accessible screening tool for non-ophthalmologist consultants.

METHODS

This hospital based cross-sectional study was conducted between September 2018 and February 2020 for patients with diabetes mellitus attending various outpatient departments in our tertiary care hospital. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. A written informed consent was obtained from all the participants.

All diabetes mellitus patients between 15 - 75 years of age were included in our study. The exclusion criteria were essential hypertension, peripheral vascular disorders, Raynaud's disease, systemic sclerosis, lupus, rheumatoid arthritis, mixed connective tissue disorders, Sjogren's syndrome, dermatomyositis, polymyositis.

The demographic profile and clinical history of all patients were recorded. The visual acuity, slit lamp examination and fundus findings were recorded in detail. All patients underwent spectral domain optical coherence tomography (Cirrus HD - OCT Model 500) and its findings were noted down. Fundus pictures (Carl Zeiss - VISUCAM 224) were taken. The patients were examined under nailfold video capillaroscope (Jiangsu Jiahua, JH 1004, China). After 20 minutes of resting at room temperature, immersion oil was applied on the nailfold and findings were recorded. The parameters described in detail were capillary density, tortuosity, neoangiogenesis, microhaemorrhages, abnormal forms and avascular areas as parameters. They were defined as follows: (1) Capillary density: the number of capillaries in a one-millimetre span of the distal row in each finger or toe.[4] Density varies with different populations. We considered 8.7 ± 1.2 as normal standard density in our study.[5] (2) Tortuosity: 2 or more cross capillaries, each over 1 mm in length. (3) Neoangiogenesis: tortuous, bush-like capillaries with marked heterogeneity in size, (a) as the presence of extremely tortuous, bushy, branching, ramified and coiled capillaries, (b) ≥ 4 capillaries within a single dermal papilla, and (c) thin and branching interconnected capillaries originating from a single loop. (4) Microhaemorrhages: 2 or more punctuate bleeds around a single capillary in at least 2 fingers. (5) Abnormal forms: capillaries with abnormal appearance. (6) Avascular areas: loss of at least 2 consecutive capillaries or ≤ 6 capillaries over each 1 mm length.[6] Then the nailfold capillaroscopy findings were correlated with fundus findings and compared between patients with retinopathy and without retinopathy. Participants with nailfold distal capillary appearance in dermal papillae were red in colour, parallel to the surface and hairpin-like were considered normal.

By adopting reporting proportions of tortuosity as 80.6 % and 57.7 % in diabetics with retinopathy and without retinopathy group respectively with 90 % of minimum study power and 5 % level of significance, the required sample size for each group was found to be 92 using the formula for two independent proportion. Considering prevalence of diabetes mellitus, the sample size was considered as 125 for each group of diabetic patients with and without diabetic retinopathy.

Sample Size

$$n = \frac{\left\{Z_{1-\frac{\alpha}{2}}\sqrt{2\underline{P}(1-\underline{P})} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right\}^2}{(P_1-P_2)^2}$$

where,

$$\underline{P} = \frac{P_1+P_2}{2}$$

P_1: Proportion in the first group
P_2: Proportion in the second group
α: Significance level
1-β: Power

Statistical Analysis

It was done by using the STATA software version 15.1 and P - value of ≤ 0.05 was considered as statistically significant. For continuous variables, the data represented as mean ± standard deviation and for the categorical variables, the data are presented as frequency and percentage. Fisher's exact test, Pearson's chi-square test and McNemar tests were used to check the association between two categorical variables. ANOVA test was used to test the significance in difference where there were more than two categories.

RESULTS

Two hundred and fifty patients with diabetic mellitus were included in the study and divided into two groups. One group constituted diabetic patients with retinopathy and the other

without retinopathy. In the group with diabetic retinopathy, 66 patients had non proliferative diabetic retinopathy (NPDR) and 59 patients had proliferative diabetic retinopathy (PDR).

Out of the 250 patients who were under our study, 162 patients (64.8 %) were males, and 88 patients (35.2 %) were females. There were only 2 patients in the age group of 15-20 yrs. with Type 1 diabetes mellitus and rest of the 248 patients were of Type 2 diabetes mellitus. There were 21 patients in the age group of 21 – 40 yrs., 132 patients within the age group of 41-60yrs. and 95 patients within the age group of 61 - 75years. (Table 1)

Eighty percent of the patients without diabetic retinopathy had a good control of diabetes while a poor control of diabetes was noted in 75.8 % (50) of the patients with NPDR and 97.6 % (57) of the patients with PDR (P - value < 0.001 ; Fisher Exact test). (Table 2)

The mean duration of diabetes was 5.5 ± 3.2 yrs. in patients with no diabetic retinopathy, 10.4 ± 3.4 yrs. in patients with non-proliferative diabetic retinopathy and 12.8 ± 4.8 yrs. in patients with proliferative diabetic retinopathy. (P - Value < 0.001; ANOVA test). (Table 3)

Age Group	Number of Individuals
15-20 yrs.	2
21-40 yrs.	21
41-60 yrs.	132
61-75 yrs.	95

Table 1. Age Wise Distribution of Subjects

Categories	Total Number	Diabetic Retinopathy Type			Fisher's Exact test P-Value
		No DR	NPDR	PDR	
Good Control	118 (47.2)	100 (80.0)	16 (24.2)	2 (3.4)	< 0.001
Bad Control	132 (52.8)	25 (20.0)	50 (75.8)	57 (96.6)	

Table 2. Relation between Glycaemic Control and Diabetic Retinopathy

DR Type	N	DM† Duration Mean ± Standard Deviation	Confidence Interval for Mean	ANOVA test P-Value
No DR£	125	5.5 ± 3.2	5.0-6.1	< 0.001
NPDR€	66	10.4 ± 3.4	9.6-11.2	
PDR‡	59	12.8 ± 4.8	11.5-14.0	

Table 3. Relation between Duration of Diabetes and Severity of Diabetic Retinopathy

£ DR: Diabetic Retinopathy
€ NPDR: Non-Proliferative Diabetic Retinopathy
‡ PDR: Proliferative Retinopathy
†DM: Diabetes Mellitus

The nail fold capillaroscopic parameters (nail fold capillary density, tortuosity, neoangiogenesis, micro haemorrhages, avascular areas and abnormal forms) documented in relation to severity of diabetic retinopathy were as described. Reduced nail fold capillary density was seen in 16 % (20) of patients without diabetic retinopathy, in 90.9 % (60) of patients with NPDR and 100 % (59) of patients with PDR. Tortuosity of capillaries were seen in 15.2 % (19) of patients without diabetic retinopathy, 81.8 % (54) of patients with NPDR and 100 % (59) patients with PDR. Microhaemorrhages were seen in 2.4 % (3) patients without DR, 28.8 % (19) patients with NPDR and 83.1 % (49) patients with PDR.

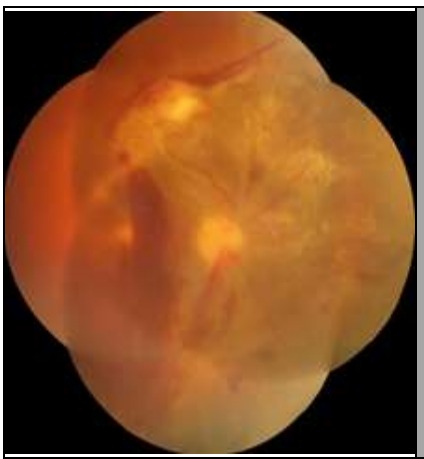

Figure 1A. Fundus Picture with High-Risk Proliferative Diabetic Retinopathy

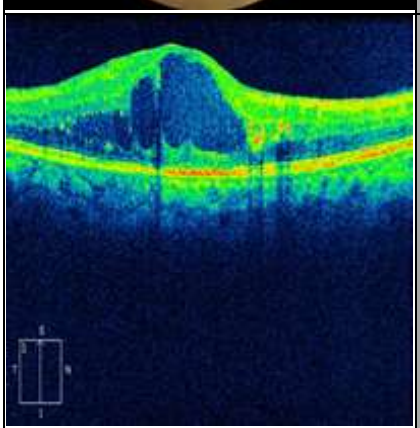

Figure 1B. OCT of the Same Patient Showing Diffuse Cystic Macular Oedema

Figure 1C. Decreased Capillary Density and Tortuosity on Nail Fold Capillaroscopy

Figure 1D. Decreased Density of Capillaries and Microhaemorrhages on Nailfold Capillaroscopy

Neoangiogenesis had been noted in none of the patients without DR, 7.6 % (5) patients with NPDR and 16.9 % (10) patients with PDR. Three patients (2.4 %) without DR nondiabetic retinopathy, 19 patients (28.8 %) with NPDR and 49 patients (83.1 %) with PDR had avascular areas. None of the patients with normal fundus had any abnormal forms. Three patients (4.5 %) with NPDR and 8 patients

(13.6 %) with PDR had abnormal forms. (P value < 0.001; chi square test and McNemar test.). (Table 4) (Table 5) (Figure 1A, 1B, 1C, 1D).

Capillaroscopic Findings	Total	No DR£	NPDR€	PDR‡	P Value Chi - Squ	McNemars statistics	P Value
Reduced Nailfold Capillary Density	139 (55.6)	20 (16.0)	60 (90.9)	59 (100)	< 0.001	7.738	0.006
Tortuosity	132 (52.8)	19 (15.2)	54 (81.8)	59 (100)	< 0.001	1.580	0.208
Neoangiogenesis	15 (6.0)	0 (0)	5 (7.6)	10 (16.9)	< 0.001	110.00	< 0.001
Microhaemorrhages	71 (28.4)	3 (2.4)	19 (28.8)	49 (83.1)	< 0.001	48.600	< 0.001
Abnormal forms	11 (4.4)	0 (0)	3 (4.5)	8 (13.6)	< 0.001	114.000	< 0.001
Avascular areas	71 (28.4)	3 (2.4)	19 (28.8)	49 (83.1)	< 0.001	116.000	< 0.001

Table 4. Relation between Capillaroscopic Findings and Severity of Diabetic Retinopathy

£ DR: Diabetic Retinopathy
€ NPDR: Non-Proliferative Diabetic Retinopathy
‡ PDR: Proliferative Retinopathy
†DM: Diabetes Mellitus

DISCUSSION

Nailfold capillaroscopy is a non-invasive, safe technique in examining microvascular changes in nail fold capillaries of scleroderma spectrum disorders and recently the microvascular changes in diabetes mellitus as well. The principle of nail fold capillarioscopy is based on the fact the entire skin has abundance of capillaries, which are perpendicular to the surface, so only the tip is visualized. But at the nailfold, the capillary loops are horizontal and easily visualized along the lengths with a hairpin-like appearance. This enables the capillaroscope to easily capture the morphological details and blood flow.[7]

Four hundred years ago, Johan Christophorous Kolhaus first observed capillaries around the nailfold with a primitive microscope. In 1862, Maurice Raynaud used the phenomenon to differentiate between primary and secondary Raynaud's phenomenon. In 1911, Lombard discovered the visualization of capillaries was easier under immersion oil in the microscope. In 1973, Maricq and Leroy defined the capillaroscopic patterns in systemic sclerosis. Over past decades, American College of Rheumatology has dedicated various studies to standardize the technique further.[8]

A normal capillarioscopy pattern is considered when capillaries are clearly visible and transparent with no pericapillary oedema, sub papillary venous plexus (seen in 30 % population), capillaries are of hairpin appearance, with diameter less than 20 microns, no tortuosity, no dilatation, no microhaemorrhages, no abnormal forms or neovascularisation or avascular areas and normal capillary density of 9 - 13 per one linear millimetre.[7]

The microangiopathic complications of diabetes mellitus are responsible for a huge proportion of morbidities and mortalities in our country, diabetic retinopathy being one of them. Chronic hyperglycaemia results in alteration in metabolic pathways like polyol pathway, advanced glycation product accumulation, protein kinase C pathway and hexosamine pathway, leading to dilatation of blood vessels and blood flow changes in retina and other end organs. Apoptosis of pericytes and endothelial cells along with thickening of basement membrane of the capillaries are the characteristic pathological changes in diabetic retinopathy. They lead to capillary occlusions, retinal ischemia and altered blood retinal barrier. Upregulation of vascular endothelial growth factor due to ischaemic and inflammatory factors are also responsible for increased vascular permeability and neovascularisation.[1] Kuryliszyn-Moska and co-workers studies the relationship of microvascular changes in capillaroscopy, disease feature and endothelial activation factors to demonstrate significantly high interleukin 18 and sE-selectin in diabetic patients with retinopathy.

Diabetic retinopathy presents with microaneurysms, haemorrhages, retinal oedema, hard and soft exudates, neovascularisation, and fibro-proliferation in retina. The diagnosis of diabetic retinopathy depends on the detection of these microangiopathic lesions on fundoscopy by the ophthalmologist.[1] According to Early treatment diabetic retinopathy study (ETDRS), the chances of diabetic retinopathy in a diabetic patient increases to more than 90% if the duration is more than 10 yrs. in Type 1 Diabetes Mellitus. So early diagnosis of diabetic retinopathy is crucial. Our study compared the capillaroscopic changes in diabetic patients with diabetes retinopathy and without diabetic retinopathy taking into consideration changes in capillary density, tortuosity of capillaries, presence of microhaemorrhages, abnormal forms, avascular areas and neoangiogenesis.

A typical diabetic pattern on nailfold capillaroscopy has not been described but few documentations have been made by studies associating the capillaroscopic changes to the presence or absence of diabetic retinopathy. Maldonado et al. demonstrated nailfold capillary changes in diabetic patients with characteristic pattern tortuous, cross-linked, capillaries with reduced density, dilatations and avascular area which collaborated with the ophthalmological findings. In 18 % of patients with capillarioscopy changes, diabetic changes were also found in retina. They did not associate the findings with the severity of diabetic retinopathy.[3] Rajaei and co-investigators reported increased tortuosity and neoangiogenesis as the common changes in diabetic patients. They also investigated the capillary vessel diameter along with structural changes on nailfold capillaroscope to find increased diameters of arterial arms in patients with retinopathy.[9] Kaminska-Winciorek studied nailfold capillaroscopy changes in in juveniles with type1 diabetes mellitus patients separately. The presence of mega capillaries, abnormal loops and altered capillary densities were seen more in diabetes mellitus of longer duration and with high HbA_1C.[10] Barchetta used a score (0 -3) to quantify the the video nailfold capillaroscopy with various parameters like capillary length, distribution, morphology, density and dimension, haemorrhages, oedema, exudates, subvenous plexus and flux along with ophthalmoscopic and retinal fluoroangiographic documentation.[11] The studies later carried out by various investigators have also recorded

reduced capillary density, tortuosity, ectasia, neoangiogenesis, haemorrhages, abnormal form and avascular zones as the common findings in diabetic patients, which significantly co-related with presence and degree of diabetic retinopathy, duration of diabetes and control of diabetes.[11,12,13,14,15] They also observed the microangiopathic changes were independent of age and sex.[9,11]

Our cross-sectional study demonstrated reduced capillary density and tortuosity in 100 % of patients with proliferative diabetic retinopathy and 90.9 % and 81.8 % respectively in case of NPDR along with microhaemorrhages, neoangiogenesis, vascular areas. Abnormal forms of capillaries were seen in a smaller number of patients in our study viz., only 4.5 % in patients with NPDR and 13.6 % in patients with PDR. Reduced capillary density (16 %) and tortuosity (15.2 %) was also seen in patients with no retinopathy. Our findings demonstrated that not only the severity of the changes in capillaries increased with increasing severity of diabetic retinopathy but microangiopathy also appeared before appearance of diabetic retinopathy. They correlated with the glycaemic control and other microangiopathic complications too. The nailfold capillaroscopy appeared to have a role in prognosis along with being a cheap and non-invasive screening tool.

CONCLUSIONS

Changes on nailfold capillaroscopy in diabetics had significant association with severity of diabetic retinopathy, duration of diabetes, glycaemic control, and appeared before appearance of diabetic retinopathy. Nail fold capillaroscopy can be a useful tool in identifying patients of high risk of DR and other microangiopathic complications of diabetic mellitus in view of it being a quick, cost effective, safe, non-invasive, and simple adoptable technique.

Our major limitation was that we did not have healthy control groups. The subject size of type 1 diabetes was small, so comparison and distinction between type1 and type 2 diabetics was not possible.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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