““A HOSPITAL BASED CROSS SECTIONAL STUDY TO DETERMINE THE CORRELATION BETWEEN THE NAILFOLD CAPILLAROSCOPY AND RETINAL MICROVASCULAR CHANGES IN TYPE II DIABETES MELLITUS IN A TERTIARY CARE CENTRE”

”


**By**

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**“A HOSPITAL BASED CROSS SECTIONAL STUDY TO DETERMINE THE CORRELATION BETWEEN THE NAILFOLD CAPILLAROSCOPY AND RETINAL MICROVASCULAR CHANGES IN TYPE II DIABETES MELLITUS IN A TERTIARY CARE CENTRE”**

**BLDE (Deemed to be university), VIJAYAPURA, KARNATAKA**


**MD**

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# LIST OF ABBREVIATIONS

1. DM -Diabetes mellitus
2. DR – Diabetic Retinopathy
3. NFC- Nailfold caillaroscopy
4. Glycosylated hemoglobin- HbA1c
5. DCCT- Diabetes control and complication trial
6. UKPDS- UK Prospective Diabetes study
7. PGI2- Prostacyclin
8. NO- Nitric oxide
9. IL- Interleukin
10. PDGF- Platelet derived growth factor
11. CSF- Colony stimulating factor
12. FGF- Fibroblast growth factor
13. TGF- transforming growth factor
14. ICAM- Intercellular adhesion molecule
15. VCAM- Vascular adhesion molecule
16. LDL- low density lipoprotein
17. NADH-Nicotinamide adenine dinucleotide
18. FADH- Flavin adenine dinucleotide
19. ETDRS- Early treatment of diabetic retinopathy study
20. WESDR- Wisconsin Epidemiologic study of diabetic retinopathy
21. NPDR – Non Proliferative Diabetic retinopthy
22. PDR- Proliferative Diabetic retinopthy
23. LED- Light emitting diode
24. NPL- Non- polarised light
25. PL- Polarised light
26. NVC- Nailfold video capillaroscopy
27. IGF- Insulin-like growth factor

## ABSTRACT

**Background:** Diabetic retinopathy(DR) is commonest microvascular complication of diabetes mellitus (DM ) and cause of preventable blindness. Hence, there is a need for early diagnosis of DM and evaluation of the microvasculature changes. Nailfold capillaroscopy (NFC) is noninvasive diagnostic tool to assess microvascular structure of the nailfold which can be used to evaluate diabetic microvascular changes and for correlation between NFC changes, retinopathy, duration of DM and $HbA_1c$ levels.

**Aims and objectives:** To determine the presence or absence of NFC changes in Type 2 DM patients, DR in patients with NFC findings and to correlate capillaroscopic findings with the duration of Type 2 DM, severity of DR, HbA1c and DR.

**Materials and methods:**Type 2 DM patients were included in the study. Patients with raynaud phenomenon,collagen vascular disease,hypertension, nail polish,active skin lesion in proximity to the nail fold were excluded.

Detailed history with duration of diabetes,co-existing medical conditions were recorded.Informed consent was taken. All subjects underwent slit-lamp and dilated fundus examination and classified according to the ETDRS (Early Treatment of Diabetic Retinopathy Study, September1, 2006) guidelines. These findings were recorded in the proforma. Nail fold capillaroscopy was done by a hand held dermatoscope and findings noted.

**Results:** A total of 82 patients were enrolled. 28 were female and 54 were male.52 patients had NFC changes and 25 patients no NFC changes were seen and 5 patients had pigmentated nail fold.12 patients had Diabetic retinopathy and the rest 70 patients were DR negative.Out of 12 patients with DR positive, 8 had NFC changes , 3 patients had no NFC changes and 1 had pigmented nail fold. Out of 70 patients without DR, 44 patients had NFC changes , 22 had no NFC changes and 4 of them had pigmented Nail fold.

- **Conclusion:** Our observations show NFC changes appear to correlate with the duration of DM and HbA1c levels and hence NFC changes can possibly be early markers for the detection of microvascular involvement.
- Further studies are required with appropriate size and study design to validate our observations.

**Key Words:** Nailfold capillaroscopy, Diabetes, Diabetic retinopathy

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# INTRODUCTION

"Diabetes mellitus (DM) is a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of DM include long-term damage, dysfunction and failure of various organs". [1]

The most common cause of mortality and morbidity worldwide are diabetic vasculopathic complications ,with increasing number of affected individuals. Diabetic retinopathy (DR) being a foremost and essential cause of preventable blindness is the most common microvascular complication of diabetes.[2]

Retinopathy, nephropathy, and neuropathy are the extended microvascular complications of diabetes. In the clinical course of micro- and macroangiopathy, several risk factors like duration of diabetes and degree of glycemic control are involved. [3-4]

After understanding the importance of vascular complications in diabetes, there was a need for early diagnosis of diabetes and evaluation of the microvasculature changes. Unfortunately, traditional methods do not detect these complications until they are well-established. Thus, investigations with direct observational tools consisting of ophthalmoscopes, magnifying lenses and capillaroscopy came into play. [5]

Nailfold capillaroscopy (NFC) is an easy, noninvasive, safe and useful diagnostic tool to assess the microvascular structure of the nailfold. Nailfold capillaroscopy is used for the

evaluation of disturbances in the skin capillaries of patients with autoimmune connective tissue diseases, chiefly in systemic sclerosis. [6]

With this knowlegde ,the aim of the current study is to assess the nail fold capillaries to evaluate diabetic microvascular involvement and to determine any correlation between nailfold capillaroscopic findings ,retinopathy, duration of DM and glycosylated hemoglobin ($HbA_{1c}$) levels.

## OBJECTIVE OF THE STUDY

**The 4 primary parameters will be assessed:**

1. **Presence or absence of NFC changes in all Type 2 DM patients**
2. **Presence or absence of DR in patients with NFC findings.**
3. **Correlation of Capillaroscopic Findings with the duration of Type 2 DM.**
4. **Correlation of Capillaroscopic Findings with the Severity of DR.**
5. **Correlation of Capillaroscopic Findings with HbA1c and DR**

## REVIEW OF LITERATURE:

Diabetes mellitus is characterized by hyperglycemic states and development of specific microvascular disorders such as retinopathy and nephropathy. In developed countries, diabetes is the leading reason for preventable blindness.

Presenting features of type 1 and type 2 DM are:[7]

**TABLE 1:**

| TYPE 1 DM | TYPE 2 DM |
|---|---|
| Onset of disease prior to 30yers of age | Onset of disease after 30 years of age |
| Lean body mass | 80% are obese, elderly individuals may be lean |
| Associated conditions: autoimmune diseases like autoimmune thyroid disease, adrenal insufficiency , pernious anemia, vitiligo, celiac disease | Associated conditions : hypertension, cardiovascular disease, insulin resistance, dyslipidemia, PCOS |

**PREVELENCE**

Based on population census data, there is an an approximate 68 million rural and 39 million urban adults with diabetes in India, totaling to 107 million . Pooled estimates show a relatively high burden of diabetes in rural and urban India, with latest values indicating a prevalence of 15.0% and 19.0% respectively.[8]

## RISK FACTORS

Cholesterol

A high cholesterol level constitutes as a predictor of cardiovascular mortality and elevates the risk of stroke.

Diet

Obesity and overweight is attributed to intake of high calorie and processed food.

Obesity

Obesity and overweight leads to insulin resistence. As the body mass index increases , there is proportionate increase in the risk of developing diabetes. The pandemic of obesity is spreading quick with western culture adoption in developing countries. Metobolic syndrome is also associated with greater risk for diabetes mellitus. [9]

Chronic hyperglycemia and the development of diabetes-specific microvascular changes, such as retinopathy and nephropathy, are the hallmarks of diabetes. Chronic hyperglycemia is a substantial risk factor in the pathogenesis of diabetic microvascular complications in both Type 1 and Type 2 diabetes, according to evidence from the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS).

Although the molecular processes that cause these difficulties are unknown, three major metabolic pathways have been hypothesised to explain the link between high glucose levels and vascular damage in diabetes:

I. increased arterial permeability, procoagulant activity, adhesion molecule expression, and monocyte influx as a result of faster production and tissue deposition of advanced glycosylated end products—actions that may lead to vascular injury

II. enhanced activation of the protein kinase C isoforms a, b1, b2, and d in retinal, renal, neural, and cardiovascular tissues, resulting in blood flow alterations, increased intimamedia thickness, vascular permeability, and abnormal angiogenesis

III. The aldose–reductase pathway was increased, resulting in hazardous sorbitol buildup in neurons. These faulty metabolic processes could affect systemic microcirculation, resulting in diffuse vascular abnormalities. [3]

**ENDOTHELIUM**

The endothelium is the most perplexing surface in our body and forms a complete barrier for blood products. It is also a metobolically and functionally more active surface and communicates with blood and tissues. It balances the mechanism of thrombogenesis with anticoagulation. It plays an essential part of immune system, has a role in regulation of regional circulation, growth, tone . Endothelium plays a key role in the origin , propogation and complication of atherogenesis.

Endothelial cell properties and functions

1. Maintains the barrier permeability

2. Coagulation and Fibrinolysis

   a. Antiplatelet agents secreted by endothelial cells are prostacyclin (PGI2) and nitric oxide (NO)

   b. Ectonucleotidases are produced at its luminal surface

   c. Endothelial cells promote the activity of various anticoagulant pathways, the most significant being the protein C/protein S pathway and thereby maintain blood fluidity.

3. Regulation of vascular tone

   a. Vasoconstrictors: endothelin, Acetylcholine esterase

   b. Vasodilators: NO, prostacyclin

4. contribution in inflammatory reaction and immunity

a. IL-1, IL-6, chemokines

b. Adhesion molecules: VCAM-1, ICAM, E-selectin, P-selectin

4. Neoangiogenesis

5.Prolongation of prothrombotics

a. Von Willebrand's factor

b. Tissue Factor

c. Plasminogen activator inhibitor

6. Cell growth regulation

a. Growth stimulators: PDGF, CSF, FGF

b. Growth inhibitors: heparin, TGF-β

7.LDL Oxidation

8.Extracellular matrix production

a. Collagen

b. Proteoglycans[24]

**ENDOTHELIAL DYSFUNCTION**

Endothelial dysfunction is a key factor in the occurrence of microvascular problems. Smoking, heart failure, hypertension, ageing, and diabetes are all associated with atherosclerosis. There is a link between vascular illness in type 1 diabetes mellitus and type 2 diabetes mellitus and structural deterioration of the vessel wall as well as vascular endothelial dysfunction (T2DM). Low density lipoproteins (LDL) that have been oxidised cause endothelial damage, leading in adhesion and activation of monocytes in the sub endothelial space, activation of macrophages, and subsequent conversion to foam cells.[25]

Hyperglycemia causes an increase in reducing equivalents (NADH and FADH2), which causes an excessive pumping of protons across the inner mitochondrial membrane, resulting in an increased membrane potential. As a result, complex III inhibition is increased, the half life of intermediates coenzyme Q is increased, and oxygen is converted to superoxide ion.

This critical event triggers four pathogenic responses: increased aldose reductase activity, hexosamine synthesis, protein kinase-C activation, and complex gylcation of products.[12,13]

## CAPILLARIES

Capillaries were initially characterised as a small conduit that links the venous and arterial tree by William Harvey.[14] The blood flow in these arteries was originally observed by Antonie van Leeuwenhoek[15]. In 1919, Basher attempted the first capillary blood velocity measurement.[16] In 1964, Zimmer and Demis used a microscope and a television system to study the dynamics of blood flow in human capillaries. Bollinger created a new microscopic system combined with television in 1974, which helped to further simplify capillary hemodynamics.[17] Carrier and Rehberg used cannulation to measure capillary pressure in 1923.[18] In 1930, Landis presented a study on the method of measuring capillary pressure and how it is affected by various physiological and pharmacological treatments. The first dynamic pressure measurements using a servonulling system were conducted in 1979. [19]

Retina, conjunctiva, lips and most significantly nail fold are the only parts of the human body which has got direct reach to the capillaries. Of these, retinal manifestations of systemic diseases is well known and well studied for years. But here we focus upon nail fold capillaries highlighting on variation in diabetes mellitus patients.

Microcirculation is defined as the circulation of blood in arterioles (< 300µm), capillaries and venules. The arteries entering the skin form a deep plexus, the 'fascial' network,

from which individual vessels rise to the border between the subcutaneous adipose tissue and the dermis to form a ‘cutaneous’ vessel network. These vessels then branch out towards different dermal appendages and give rise to arterioles that result in a sub papillary plexus that ultimately results in capillary loops entering the papillary dermis between the rete ridges. From these capillaries the blood is returned to venules that coalesce to intermediate plexuses. Thus, the cutaneous vasculature is rather elaborate and limited to the dermis, while the epidermis has no blood vessels.[20] Micro vessels in the papillary dermis range in size from 10 to 35 µm whereas those in the mid to deep dermis are 40-50 µm with an occasional arteriole as large as 100 µm being observed.[21]

Capillary degeneration and development of acellular capillaries cause a reduction in capillary perfusion and hypoxia. Consequently, capillary neovascularization occurs leading to proliferative DR. Hence, ocular examination and classification according to ETDRS (Early Treatment of Diabetic Retinopathy Study, September 1 ,2006) guidelines is important. [2]

**DIABETIC RETINOPATHY**

Diabetic retinopathy(DR) is a highly precise neurovascular complication of type 1 and type 2 diabetes. Diabetic retinopathy is the primary and most frequent cause of visual loss and visual impairment among adults of 20-74 years. The prevalence of diabetic retinopathy correlates to the duration of diabetes and level of glycemic control. Cause of visual loss from DR is macular edema, retinal detachment, the new blood vessels may bleed leading to complication of preretinal or vitreous hemorrhage, neovascular glaucoma .

Risk factors identified in Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) are :

1.Longer duration of diabetes

2.Greater hyperglycemia

3.Increased blood pressure

4.Dyslipidemia

**TABLE 2**:

| **Classification** | **Examination by ophthalmologist or optometrist** |
|---|---|
| Type 1 diabetes | Within 5 years after onset of diabetes |
| Type 2 diabetes | At time of diabetes diagnosis |
| Women with preexisting diabetes planning pregnancy or who have become pregnant | Before pregnancy or in first trimester |

As diabetic patients remain asymptomatic for longer duration, it leads to a later detection and intervention of diabetic retinopathy. Hence early detection helps to reduce the morbidity of the disease.

At the time of first diagnosis of diabetes, upto one-fifth of patients with type 2 diabetes have retinopathy. Such patients at the time of diagnosis must have an early dilated and comprehensive eye examination by an ophthalmologist or optometrist.

Diabetic retinopathy is classified according International Clinical Diabetic Retinopathy Disease Severity Scale as : [22]

**TABLE 3:**

| PROPOSED DISEASE SEVERITY LEVEL | FINDINGS OSERVABLE UPON DILATED OPTHALMOSCOPY |
|---|---|
| • No apparent retinopathy | • No abnormalities |
| • Mild NPDR | • Microaneurysma only |
| • Moderate NPDR | • More than just microaneurysms but less severe NPDR |

| | |
|---|---|
| • Severe NPDR | Any of the following and no signs of PDR<br>• more than 20 intraretinal hemorrhages in each of 4 quadrants<br>• Definite venous bleeding in 2/ more quadrants<br>• Prominent IRMA in one or more quadrants |
| • PDR | One of both the following<br>• Neovascularization<br>• Vitreous/preretinal hemorrhage |

## DERMOSCOPY

The term "dermatoscopy" was introduced by Johann Saphier a german dermatologist. Later on Goldman coined the term "dermoscopy". Dermatoscopy, skin surface microscopy, epiluminecsence microscopy are the terms used for dermoscopy. Stolz and Braun-Falco developed the first dermoscope in 1989.[23]

Dermoscope is a noninvasive instrument that magnifies the minute clinical patterns of skin lesions, hair disorders, and various nail changes and also unveils few skin subsurface which are not visible to the naked eye and also to magnifying lens.[24] It is a valuable interface between macroscopic clinical dermatology and microscopic histopathological dermatology.[25]

Principle of dermoscope:

The refractive indices of stratum corneum (1.55) and air (1.0) are different. This leads to reflection of light that is incident on the skin surface and results in the invisibility of structures to the human eyes. Hence, to avoid reflection of light thereby enhancing the

penetration of light, a fluid interface dermoscope and the skin surface is used. Fluid must have refractive index nearer to that of the stratum corneum. This is achieved using interface medium or noncontact polarized light. Both of these result in improved visualization of skin structures. [26]

Parts of dermoscope:

The essentail parts of dermoscope are : [24]

1. **Achromatic lens**: While most instruments give a magnification of 10X, video-dermoscope offer a higher magnification of upto 1000X

2. **In-built illumination system**: Light emitting diodes (LED) provide white light of high intensity and use 70% smaller power than the yellow light emitting classical halogen lamps. Altered illumination can also be acheived by turning off a set of LEDs.

3. **Power supply**: Hand-held instruments are powered by batteries or have rechargeable batteries and handles.

4. **Contact plate**: Contact technique dermoscopy consist of large contact plate (20mm diameter) and small contact plate (8mm diameter) . The contact plates are prepared by multilocated silicone glass. Various methods for sterilization are methylated spirit or 2% glutaraldehyde, boiling or autoclaving at 1340 C for 5minutes. 2 types of plates are those graduated with scales and others are non-graduated.

5. **Inbuilt photography system**: Currently they are considered an essential component of a dermoscope except in the hand-held dermoscope.

**Types of dermatoscope:**

Marghoob et al [27] reviewed various models of dermoscopes and categorized them into the following types:

a) **Dermoscopes with no image capture capability**: Handheld, otoscope-like equipment with no built-in camera or other image collection capability. Adaptors, on the other hand, can be used to connect cameras to certain of these equipment. It uses four different coloured polarised light sources—white, blue (surface pigmentation), yellow (superficial vessels), and red (deep pigment and vessels)—to aid in the visualisation of skin structures, based on the idea that light penetration is proportionate to wavelength.

b) **Dermoscopes with image capture capability**: These instruments have an image capture system built into them or a camera connected to them. This device may also be used to image the entire body (body mapping). There are also lenses that can be put together on a standard or digital camera. Clinical and dermoscopic pictures benefit from a 10X magnification. A video dermatoscope, which has a better quality camera incorporated into the hand piece and displays the image on a computer screen, may be used to take small videos.

c) **Dermoscopes with image capture and analysis capabilities**: These are commonly used to check pigmented lesions prior to surgery in locations where melanoma is common. The patient's previous and new pictures may be compared. Any major change in the lesion provides various colour indications. A machine learning system can assist in determining if a melanocytic nevus is benign or cancerous.

**Dermoscopy procedure:**

Contact or non-contact approaches can be utilised with the dermoscope. The glass plate or contact plate is attached to the surface of the lesion with an interface fluid in contact technique dermoscopy, which uses non-polarized light (NPL). There is no touch with the skin surface with the non-contact approach, which has the extra benefit of preventing nosocomial infections.[28]

Polarised light enables for greater visibility of structures deeper in the skin, whereas NPL allows for better visualisation of structures that are more surface.[29] The dermoscope allows for a horizontal view of the skin; hence, vessels that run parallel to the skin surface are represented as lines, whereas vessels that run perpendicular to the skin surface are perceived as loops. The non-contact method allows for a better vision of vessels since it does not constrict the vascular architecture.[30]

**IMMERSION FLUID**

The immersion oil is the best connection for dermoscopic inspection.[31]

There are four types of linkage or immersion fluid:

I Gels made of water

(ii) Oil

iv) Water and

iii) Disinfectant solutions

The following are the qualities of an ideal immersion liquid:

I It is inexpensive and easy to get;

ii) It clearly displays the structural parameters of skin lesions without changing colour; and

iii) It should create fewer air bubbles.

iv) Non-volatile

v) Can be utilised in unique areas such as the circumocular skin

vi) Should not provide a matte or bright light.

Immersion oil is more suited as an immersion fluid for identifying the pigment network. Ultrasound gel or immersion oil can be utilised for structural components other than the pigment network. Ultrasound gel is a better option for dermoscopic examination of non-pigmented skin lesions because it is inexpensive and easily removed from the skin, whereas immersion oil is not recommended because it contains chlorinated paraffin and dibutyl phthalate, which are teratogenic, fetotoxic, and carcinogenic.

According to Gewirtzmanet et al ,[32] a 70% alcoholic solution offers the greatest results in terms of picture quality, reducing air bubbles, and improving patient tolerance because it has a milder odour. Alcohol has the ability to reduce the rate of infection transmission, making it a better choice for inflammatory dermatoses.

Because glass has a refractive index (1.52) that is virtually identical to that of skin (1.55), it improves transillumination of the lesion when put over connective fluid covered skin (as in contact plates). Dermoscopy of solid curved regions, particularly the area surrounding the nail plate, is easier using ultrasound gel.[33] It's also good for checking the nail bed, mucosa, genitals, and eyelids. [31]

Because the viscose gel fills up and stays in the gap between the surface to be examined and the contact plate, unlike liquids, the whole curved region of the nail may be viewed when employing gel.

**Nailfold capillaroscopy (NFC)**

A more accurate measuring and storing of capillary data and a better defining, analyzing, and quantifying of capillary abnormalities can be assessed by NFC , and hence it is considered as an extension of the wide field technique. Capillaroscopic study is used for diagnostic purposes in Rheumatology. [6]

According to the Maricq criteria modified by Bergman et al. the nailfold capillary system was assessed for capillary distribution, density, and morphology . The distal capillary rows in the dermal papillae have a parallel course to the nail surface in the normal nailfold and usually seen in their complete length. In healthy individuals these distal capillary rows appear as red and hairpin-shaped. Nevertheless, the characteristic capillaroscopy findings in rheumatic disease are enlarged, giant capillaries, neoangiogenesis, capillary loss, and/or avascular areas.[34]

Procedural management:

Nailfold capillaroscopy is an easy and helpful procedure in evaluating the diseases associated with vasculopathy that may have diagnostic and prognostic value.

**Indications for capillaroscopy** are :

1) Diseases affecting the capillary microarchitecture, like diabetes mellitus
2) Evaluation in Raynaud's Phenomenon
3) Differential diagnosis of collagenopathies

4) Primary diagnosis of Scleroderma [34]

Uyar et al. demonstrated capillaroscopic findings including tortuosity, bushy capillary, neoformation, and capillary ectasia were significantly higher in patients with proliferative DR than patients with non-proliferative DR and without DR. This study demonstrated a strong correlation of microvascular involvement in T2DM and with DR as well as precise detection of nailfold capillary changes by NVC.[2]

Barchetta et al. found out relationship between retinal microangiopathic lesions and capillary vessels changes in patients with type 1 and type 2 DM. On comparison with healthy controls, they reported that DM patients had greater capillary diameters, capillary ectasia, and nail bed edema.[35]

In a different study, the relation between retinal microangiopathy and the presence of bushy capillary and avascular areas in the nail bed was shown.[36]

Chang et al. reported a relationship between DR and tortuous capillaries, bushy capillaries, and capillary enlargement, and noted that in patients with severe DM these capillary changes were frequent. [37]

When compared to healthy controls, patients with type 1 DM showed a larger number of dilated and tortuous capillaries as well as increased capillary density, according to Kuriliszyn-Moskalet et al. They also found moderate to severe aberrant capillaroscopic features in patients with poor metabolic control and systemic involvement . In individuals with diabetes, Meyer et al. discovered a link between morphological capillaroscopic changes such as increased capillary diameter, convoluted capillaries, and decreased capillary density and ischemic vascular reactivity.[2]

Correlation of capillaroscopic changes and DR has been found to be significant, hence proving that NFC can be a diagnostic tool for microvascular alterations in T2DM patients in whom retinopathy is not clinically evident. These results pave the way for prompt detection of T2DM related retinopathy and microvascular complications. Tortuosity, bushy capillary, aneurysm, neoformation, and bizarre capillaries are findings significantly linked to a longer DM duration and DR positive patients. The tortuosity may be the key feature for diagnosis of early DR as suggested by several studies.[2]

Nail fold capillary patterns that are normal and pathological

The capillaries of the nail fold are autonomous and accurately mirror the microcirculation's haemodynamics in the venules and arterioles. The capillary arrangements at the nail fold are in line with the skin's surface, making both the afferent and efferent sections of the capillary loop visible. When compared to efferent segments (diameter of approximately 9–10m), the afferent (arterial) segment is thin and extended (diameter of around 7 m).[38]

The capillaries in the lower limb nail fold are perpendicular to the skin's surface and appear as dots or commas. The tonicity of the capillary bed in the nail fold can also be measured. The capillary density ranges between 30 and 50 per mm2. It's simpler to see the terminal row of capillary loops in fingers and toes since they're parallel to the skin surface.

Capillary orientation shifts from horizontal to oblique and vertical as one approaches closer to the fingertips. Fagrell's classification, uses vital capillary microscopy to characterise the capillary structure.[39]

The following is the typical capillary pattern:

I. Small vessels are homogeneous and regular in shape

II. Each dermal papilla has one to three capillary vessels

III. Characteristic appearance resembling a hairpin or upside down

IV. Mean capillary density at the periungual level is 9 to 13/mm

V. Mean length of the periungual capillary is approximately 400m.

The main patterns of pathology are:[40,41,42]

• Disorganization in the architecture - aberrant capillary distribution, inhomogeneous loops, and misorientation.

• Enlarged loops might be homogeneous (mega capillaries) or uneven (diameter > 50 m).

• Avascular region if there are no capillaries for an area more than 500m or if two consecutive capillaries are lost.

• Angiogenesis: anastomosed loops (“ball” loops, “glomerular” loops, “bush” loops), branching (“trefoil” loops, “chandelier” loops, “antler” loops, “cactus” loops), tortuosity (single or many crossovers: “corkscrew” loops, “treble clef” loops, “8” loops), tortuosity

• Micro thrombosis and haemorrhage.

• Blood flow is slowed.

**Maricq et al. changed the classification of capillary alterations in the upper extremities.[43]**

**Types of capillaries in the nailfolds**

1. Regular loops

2. Clearly expanded capillaries with arterial, apical, and venous portions expanding (micropools)

3. Massive capillaries

4. Haemorrhage in the capillaries

5. There are no capillaries in the blood field.

**Loss of capillaries in the nailfolds**

A. There are no evident avascular regions

B. There are just a few small avascular areas

C. Capillary loss that is moderate

D. A large avascular zone runs along the margin.

**Changes in the microvascular system in different regions of the skin**

A. There are no noticeable capillaries.
B. Around ulcerations and atrophic white patches, enlarged and ramified capillaries
C. Telangiectasis of the capillaries
D. Enlarged capillaries that are dispersed throughout the body
E. Skin papillary oedema

The different morphological alterations in the capillary loops are described as:

1. Tortuous capillary: Capillary limbs coiled but not crossing over 2. Meandering capillary: Limbs cross over each other 3. Dilated capillary: diameter greater than two times surrounding typical capillaries

4. Giant capillary: capillary width >10 times normal

5. Neoangiogenesis/bushy capillary: the distal loop produces tiny, numerous buds.

6. Focal microhemorrhages: micropetechiae in a single location

Capillary dropout refers to the lack of a single capillary loop.

8. Avascular area: two or more contiguous capillaries from the most distal row are missing.

9. Bizzare capillaries: aberrant morphology that does not adhere to predetermined morphologies

## NFC's traditional use

It helps to identify and diagnose microvascular involvement in a variety of rheumatic illnesses, particularly systemic sclerosis and associated conditions. Giant capillaries, haemorrhages, decrease of capillary density, and regular architecture are all signs of an early pattern. Apart from the usual pattern, ramifications may be seen in active illness.

Loss of capillaries and architecture is a symptom of a late stage of pattern. [44,45] It is important to distinguish between secondary and primary raynaud's illness. [46] dermatoscopy reveals unique patterns for dermatomyositis, overlap syndromes, undifferentiated connective tissue disorders, and mixed connective tissue diseases.

The capillary loss is substantial, and the architecture reflects a late trend in the development of the disease. [44,45] Secondary and primary raynaud's disease must be distinguished. [46] There are unique patterns in dermatomyositis, overlap syndromes, undifferentiated connective tissue disorders, and mixed connective tissue diseases that may be seen during dermatoscopy

Nail fold patterns are influenced by a variety of factors.

The density of dermal capillary loops decreases with age, while dermal volume decreases. Young people's microvasculature is regular, with some horizontal vessels and neatly organised capillary loops. In aged skins, it becomes uneven, twisted, and thicker. As the epidermis atrophy, visibility of parallel vasculature and papillary vascular plexus becomes easier. Dilated and thickened deep veins might also be noticed. With ageing, artery elasticity and endothelial function decrease.The geriatric group had a greater prevalence of increased capillary loop length (12 percent vs. 0%), arteriovenous sludge (36 percent vs. 7%), and notably pronounced sub papillary plexus (63 percent vs. 12). [47]

Age, ethnicity, race, and employment have an influence on the visibility of nail fold capillaries.

In systemic illness, there is evidence of pattern alterations.

Because diabetes is microvascular illnesses, we may anticipate alterations to occur equally throughout our bodies. Several studies have linked different features of diabetes to alterations in microvascular nail folds.

Higher fasting glucose corresponds with capillary rarefaction and also leads in increased capillary blood flow velocity in healthy people, according to research. Insulin resistance and structural alterations in cutaneous vasculature have been found to be unrelated. [48] Resting capillary blood velocity was negatively linked to capillary density in Type 1 diabetes. Other research have shown no link between mean capillary density and age, gender, or body mass.

In the conjunctiva, capillary density was decreased, the venules were enlarged and the resting capillary blood velocity was lower than in matched controls. These observations correlated with duration of diabetes and complications.[49]

Capillary density was reduced, venules were expanded, and resting capillary blood velocity was lower in the conjunctiva than in matched controls. These findings were linked to diabetes duration and complications.[49] Patients with poor glycemic control and overt nephropathy had increased capillary blood pressure in type 1 diabetes.[50] Capillary pressure was normal in normoalbuminuric, normotensive type 2 diabetes.

In both type 1 and type 2 diabetics with long-standing disease, dilated and slightly coiled loops, nodular apical elongation, decreased peak capillary blood flow velocity, and prolonged time to peak velocity of cutaneous microcirculation have been described.[51]

Insulin promotes endothelium-dependent and independent vasodilation in dermal vessels in healthy people and before the establishment of insulin resistance in diabetics. Capillary recruitment and direct changes in vasomotion occur as a result, resulting in enhanced capillary blood flow. [52] In healthy people, the nerve axon reflex, which needs a functioning autonomic nervous system, contributes for 36% of total acetylcholine-induced vasodilation.

Diabetic microangiopathy involves a lack of the normal venoarteriolar reflex, which typically results in a decrease in arterial blood flow, increased precapillary constriction, and the development of excessive capillary pressure.[53] The lack of autoregulation and resulting increase in blood flow increases shear stress on blood vessels, which may stimulate the generation of vasoactive chemicals, vascular leakage, and inflammation.

To try to revascularize the damaged tissue, growth factors encourage the development of new blood vessels from nearby blood vessels. Neovascularization is caused by the interaction

between VEGF and insulin-like growth factor-1, according to studies in experimental animals (IGF-1).

Nail fold capillaries and systemic illnesses can be studied together.When it comes to preventing significant morbidity owing to long term consequences of non communicable illnesses, a simple and reliable screening technique that can cover a wide spectrum of population is needed.

Due to the fact that diabetes is characterised by endothelial dysfunction and microvascular dysregulation, the microvascular consequences could be predicted if we determine the pattern of involvement, if existent, in various organs depending on the length of the disease.

The ophthalmoscopic assessment of the diabetic fundus is standardised in diabetes. A hand-held dermoscopy makes it easy to examine nail fold for capillary anomalies since capillaries are easily accessible. In spite of the highly suggestible linkage between certain capillary morphologies and systemic illnesses such as diabetes, capillary abnormalities and other end organ failures are still far from being connected.

# METHODOLOGY

## 7.1. SOURCE OF DATA:

Diabetic mellitus patients in Department of Dermatology, Venerology and Leprosy, Opthalmology and General Medicine in B.L.D.E (Deemed to be University), Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, will be enrolled for the study.

**Period of study:**

The study will be conducted from October 2019 to September 2021.

**Study design:**

A hospital based cross sectional study.

**Sample size**

With anticipated Proportion of Capillarscopic findings in Diabetes being 83**%** [13] the minimum sample size is 151 patients with 5% level of significance and 6% absolute error.

Formula used

- $n=\frac{z^2\ p*q}{d^2}$

Where Z= Z statistic at α level of significance

$d^2$= Absolute error

P= Proportion rate

q= 100-p

## 7.2 METHOD OF COLLECTION OF DATA:

**Inclusion criteria:**

1. Patients with Type II diabetes mellitus

**Exclusion criteria:**

1. Patients with Raynaud phenomenon
2. Patients with collagen vascular disorders
3. Patients associated with hypertension.
4. Nail polish, acrylic gel which reduces the visibility of the nail fold.
5. Any active skin lesion in proximity to the nail fold.
6. Patients who have had manicure within 2 weeks prior to the study.

**Methods:**

Detailed history with respect to the onset and duration of diabetes, co-existing medical conditions will be recorded (ANNEXURE- VII).

Informed consent for the study will be undertaken from all the patients. All subjects will undertake a complete ophthalmic examination including, slit-lamp biomicroscopy, and dilated fundus examination. and will be classified according to the ETDRS (Early Treatment of Diabetic Retinopathy Study, September1, 2006) guidelines. These findings will be recorded in the proforma .The presence and absence of diabetic retinopathy will be noted. Nail fold capillaroscopy will be done by a hand held dermatoscope (Dermalite DL3™, 3Gen Inc., San Juan Capistrano, CA, USA) and the findings will be noted.

**Methodology:**

***Procedure****:*

*Nail fold Capillaroscopic examination:*

An interface gel will be applied on the nailfold of all participants after 20 minutes resting at a room temperature of 20–24◦C for better visualization. Capillaroscopy will be done on all fingers at ×10 magnification with a hand held dermatoscope (Dermalite DL3™, 3Gen Inc., San Juan Capistrano, CA, USA). Images from the proximal nail fold of each finger will be recorded in polarised mode of dermatoscope using an attached digital camera. For each patient , a total 10 images will be obtained. Followed by the assessment of the nailfold capillary system for capillary distribution, density, and morphology according to the Maricq criteria modified by Bergman *et al*.

The abnormal findings that will be observed for are:

1. Tortuosity
2. Neoangiogenesis
3. Microhemorrhage
4. Extravasation
5. Avascular area and neoformation
6. Bizarre capillary
7. Capillary ectasia
8. Megacapillary

***ASSESSMENT OF FREQUENCY, COMPARISON AND CORRELATION*** **:**

**The 4 primary parameters will be assessed:**

6. **Presence or absence of NFC changes in all Type 2 DM patients**
7. **Presence or absence of DR in patients with NFC findings.**

8. **Correlation of Capillaroscopic Findings with the duration of Type 2 DM.**
9. **Correlation of Capillaroscopic Findings with the Severity of DR.**
10. **Correlation of Capillaroscopic Findings with HbA1c and DR**

## 7.3: INVESTIGATIONS:

Following investigations will be done: $HbA_{1c}$

## STATISTICAL ANALYSIS:

- Numerical variables will be presented as Mean(Median) ±SD, and categorical variables will be presented as frequency(%) and diagrams
- The Chi square test will be used to associate the variables of categorical variables.

**7.4: HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR BLDE UNIVERSITY:**

- **YES**

## RESULTS

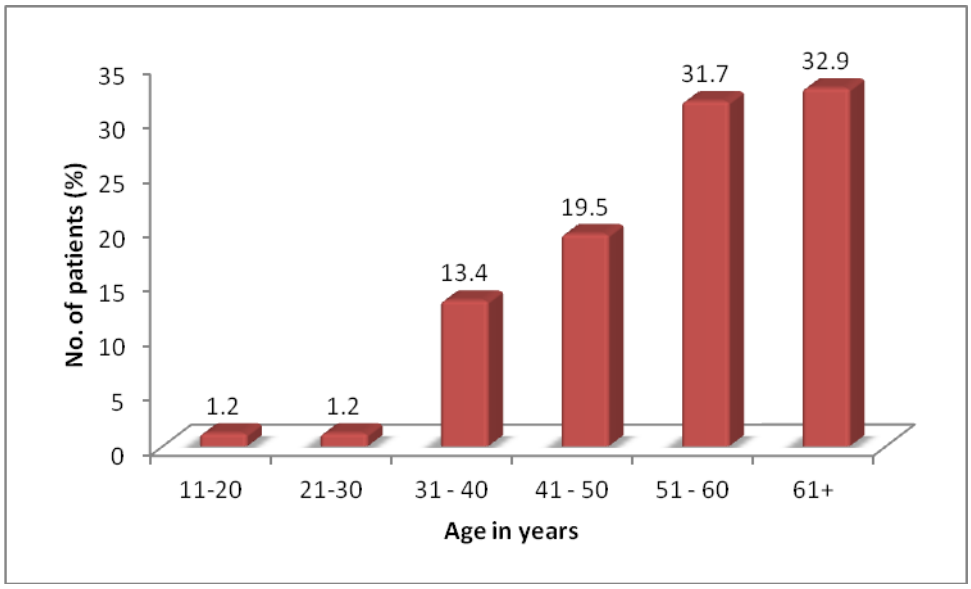
A hospital based prospective cross-sectional study was conducted from October 2019 to July 2021. A total of 82 patients with Type II Diabetes mellitus were included in the present study.

**Age distribution**: The age of the patients enrolled in the study ranged from 18 years to 76 years. Table 4 and Figure 1 presents the age distribution of the patients included in the study. Elderly population in the age group of above 61 years, constituted the majority of study population with maximum of 27 (32.9%) patients followed by 26 (31.7%) in the age group 61-70 years followed by adults 41-50 years with 16 (19.5%)patients, 11(13.4%) in the age group 31-40 years and 2 (2.4%)in age group less than 30years.

**TABLE 4:**

| Age(Years) | No. of patients | Percentage |
|---|---|---|
| 11 – 20 | 1 | 1.2 |
| 21 – 30 | 1 | 1.2 |
| 31 – 40 | 11 | 13.4 |
| 41 – 50 | 16 | 19.5 |
| 51 – 60 | 26 | 31.7 |
| 61+ | 27 | 32.9 |
| Total | 82 | 100.0 |

**FIGURE 1:**


35
30
25
20
15
10
5
0
No. of patients (%)
1.2
1.2
13.4
19.5
31.7
32.9
11-20
21-30
31 - 40
41 - 50
51 - 60
61+
Age in years

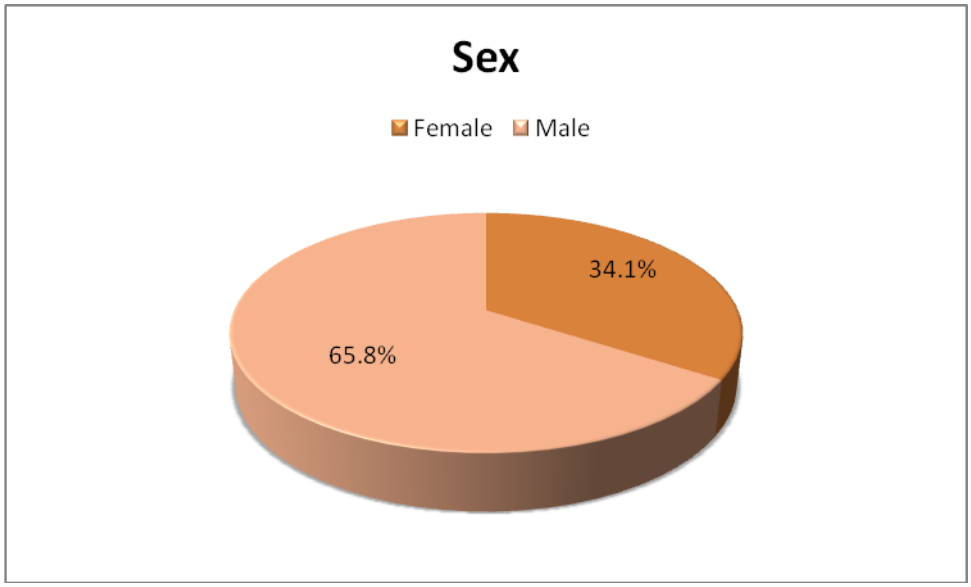
**Gender distribution:** Among 82 patients, 54 (65.8%) were males and 28 (34.1%) were females.

Table 5 and Figure 2 presents the gender distribution of the patients with type 2 diabetes mellitus included in the study.

**TABLE 5**

| Gender | No. of patients | Percentage |
|---|---|---|
| Female | 28 | 34.1 |
| Male | 54 | 65.8 |
| Total | 82 | 100.0 |

**FIGURE 2**



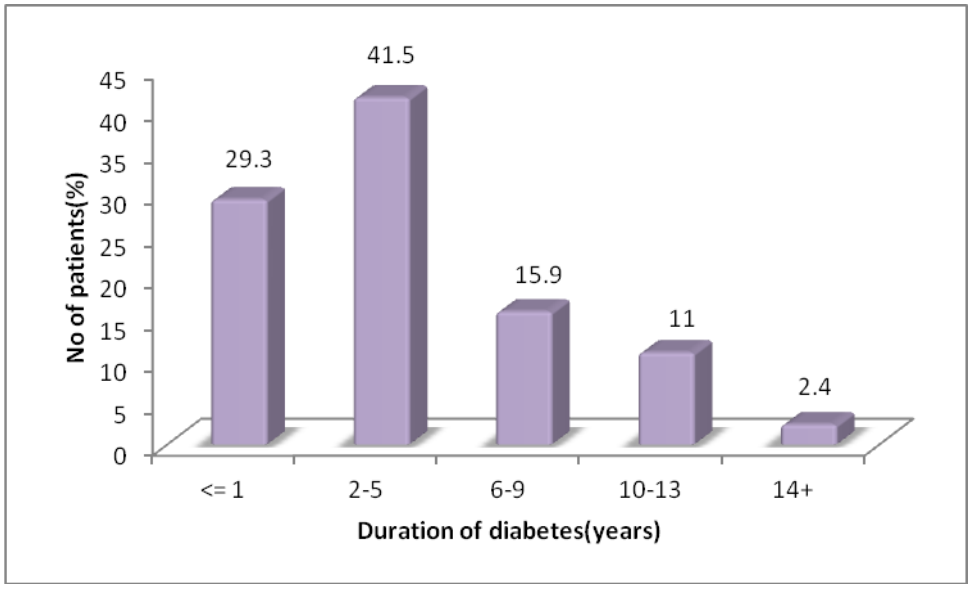
**Duration of diabetes:**

The duration of diabetes was found to highest between 2 to 5 years which consisted of 34 (41.5%) patients, followed by 24 (29.3%) patients with less than 1 year duration,13 (15.9%) patients with 6-9 years, 9(11%) patients with 10-13 years and 2(2.4%)patients with more than 14 years duration. Table 6 and Figure 3 represents the duration of type 2 diabetes mellitus included in the study.

**TABLE 6**

| **Duration of diabetes(years)** | | Frequency | Percent |
|---|---|---|---|
| Valid | <= 1 | 24 | 29.3 |
| | 2 – 5 | 34 | 41.5 |
| | 6 – 9 | 13 | 15.9 |
| | 10 - 13 | 9 | 11.0 |
| | 14+ | 2 | 2.4 |
| | Total | 82 | 100.0 |

**FIGURE 3:**



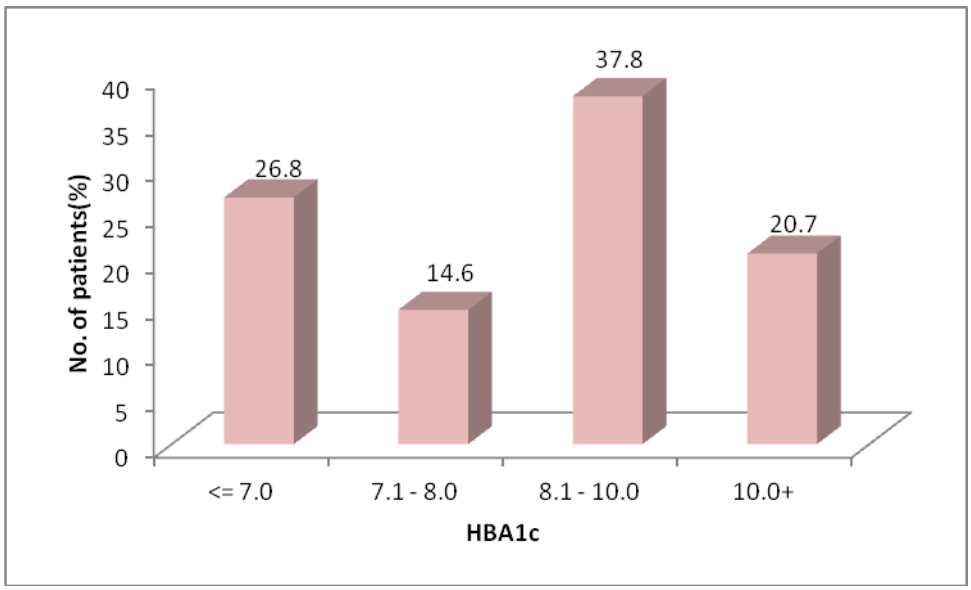
**HbA1c levels**: Patient clustering with HbA1c of 8.1-10% were of 31(37.8% )patients followed by less than 7% in 22(26.8%) , more than 10% in 17 (20.7%) patients and between 7.1-8.0% in 12(14.6%) patients.

Table 7 and Figure 4 represents the HbA1c levels in patients with type 2 diabetes mellitus included in the study.

**TABLE 7:**

| HbA1C | | Frequency | Percent |
|---|---|---|---|
| Valid | <= 7.0000 | 22 | 26.8 |
| | 7.0001 - 8.0000 | 12 | 14.6 |
| | 8.0001 - 10.0000 | 31 | 37.8 |
| | 10.0001+ | 17 | 20.7 |
| | Total | 82 | 100.0 |

FIGURE 4:



**NFC changes:**

The nail fold capillaroscopic changes in patients with type II diabetes mellitus was present in 51 (62.2%)patients, absent in 25(30.5%) patients and nail fold was pigmented in 5(6.1%).

The different types of NFC changes like Tortusity was seen in 24 (29.3%)patients, microhemorrhage in 1 (1.2%) patient, avascular area in 17(20.7%) patients, Bizzare capillaries found in 2 (2.4%) patients, capillary ectasia in 1 (1.2%) megacapillary or dilated loops were present in 40(48.8%) patients and no patients had neoangiogenesis and extravasation.

Table 8 and Figure 5 represents the presence of NFC changes in patients with type 2 diabetes mellitus included in the study. Table 9 to Table 16 represent the frequency of different NFC changes.

**TABLE 8:**

| NFC | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 25 | 30.5 |
| | pigmented | 5 | 6.1 |
| | Present | 51 | 62.2 |
| | Total | 82 | 100.0 |

**FIGURE 5**

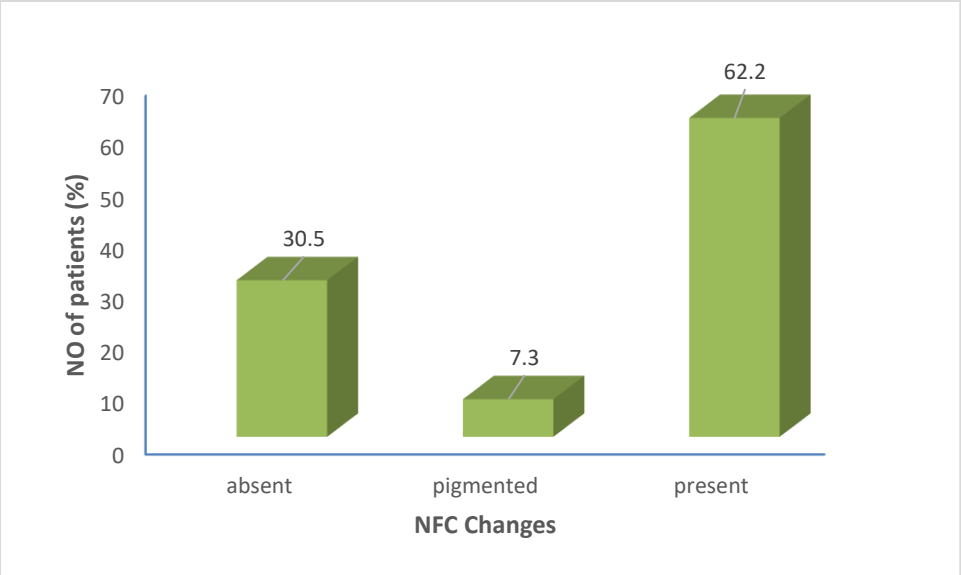


**TABLE 9:**

| Tortusity | | Frequency | Percent |
|---|---|---|---|
| Valid | | | |
| | absent | 58 | 70.7 |
| | present | 24 | 29.3 |
| | Total | 82 | 100.0 |

**FIGURE 6:**

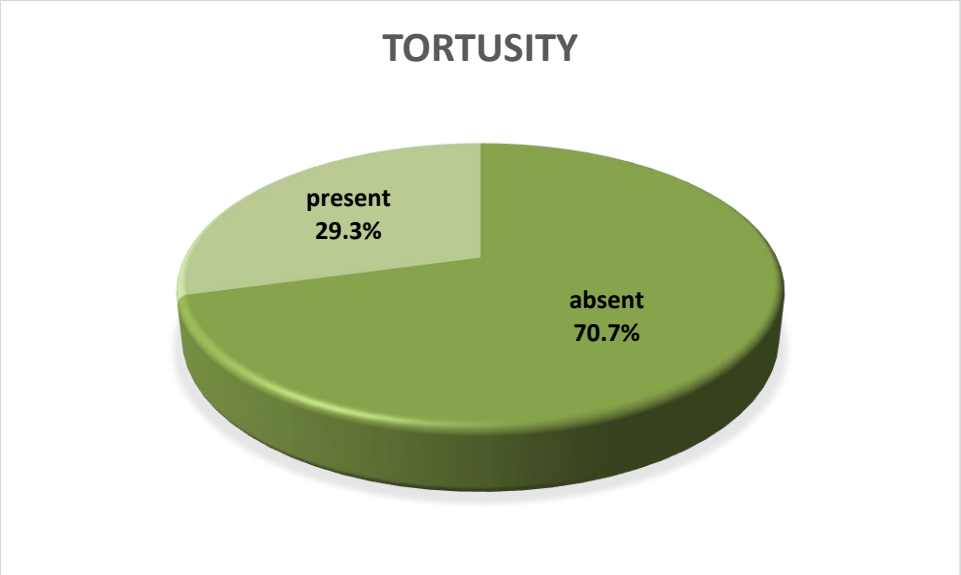



**TABLE 10**

| **Microhemorrhage** | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 81 | 98.8 |
| | Present | 1 | 1.2 |
| | Total | 82 | 100.0 |

**FIGURE 7:**

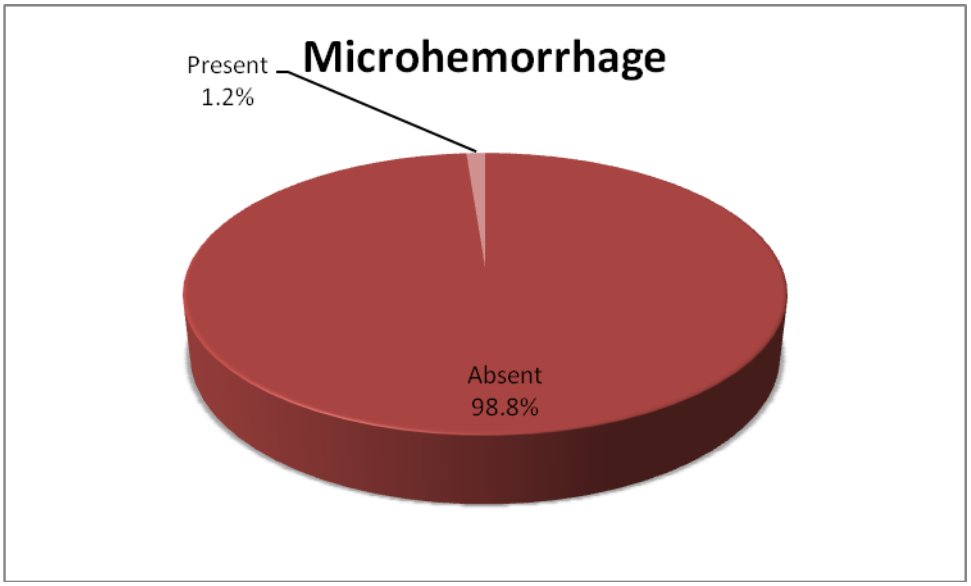



**TABLE 11:**

| Avascular area | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 65 | 79.3 |
| | Present | 17 | 20.7 |
| | Total | 82 | 100.0 |

**FIGURE 9:**

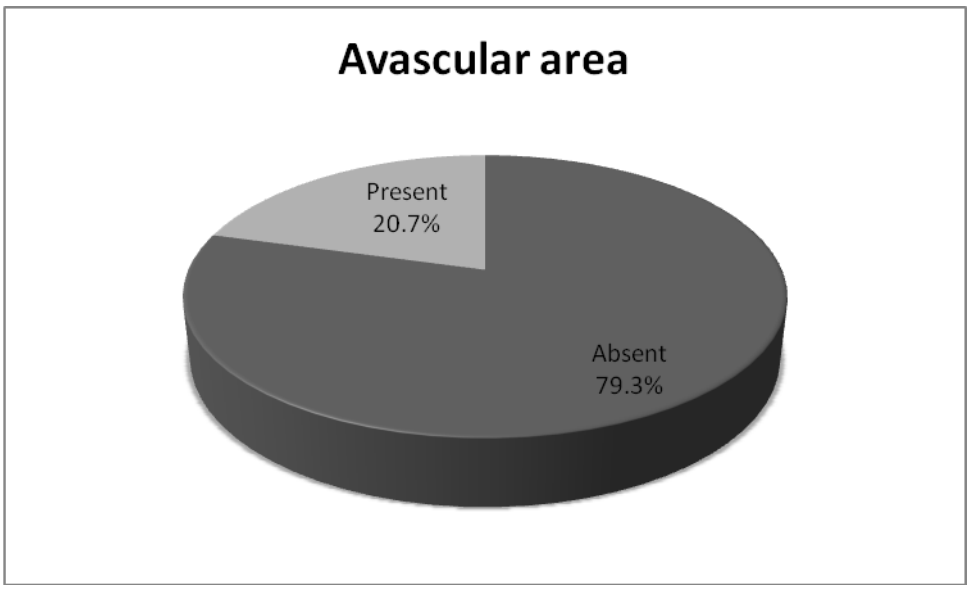


**Table 12:**

| Bizarre capillary | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 80 | 97.6 |
| | Present | 2 | 2.4 |
| | Total | 82 | 100.0 |

**FIGURE 10:**

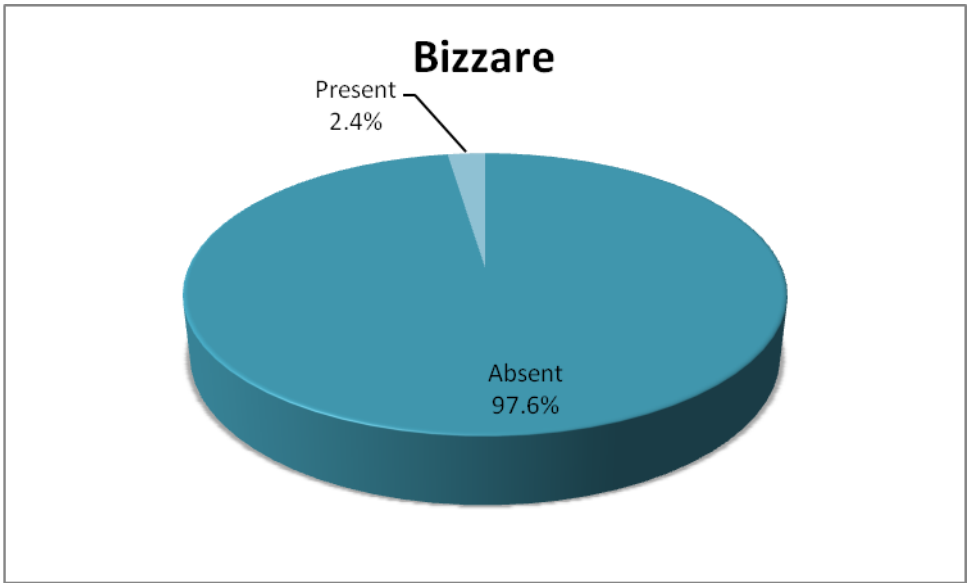



**TABLE 13:**

| Capillary ectasia | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 81 | 98.8 |
| | Present | 1 | 1.2 |
| | Total | 82 | 100.0 |

**FIGURE 11:**

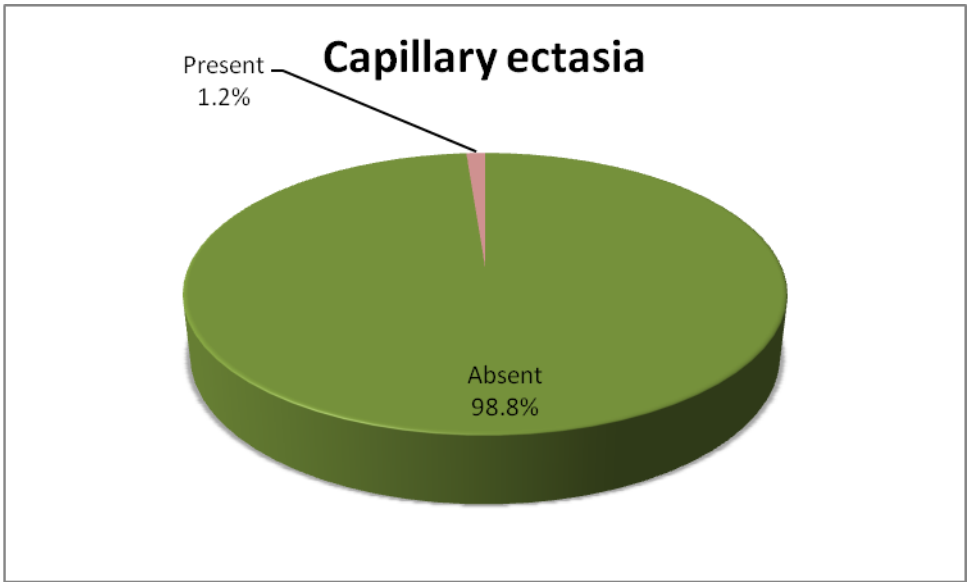



**TABLE 14:**

| **Megacapillary/Dilated loops** | | Frequency | Percent |
|---|---|---|---|
| Valid | Absent | 42 | 51.2 |
| | Present | 40 | 48.8 |
| | Total | 82 | 100.0 |

**FIGURE 12:**

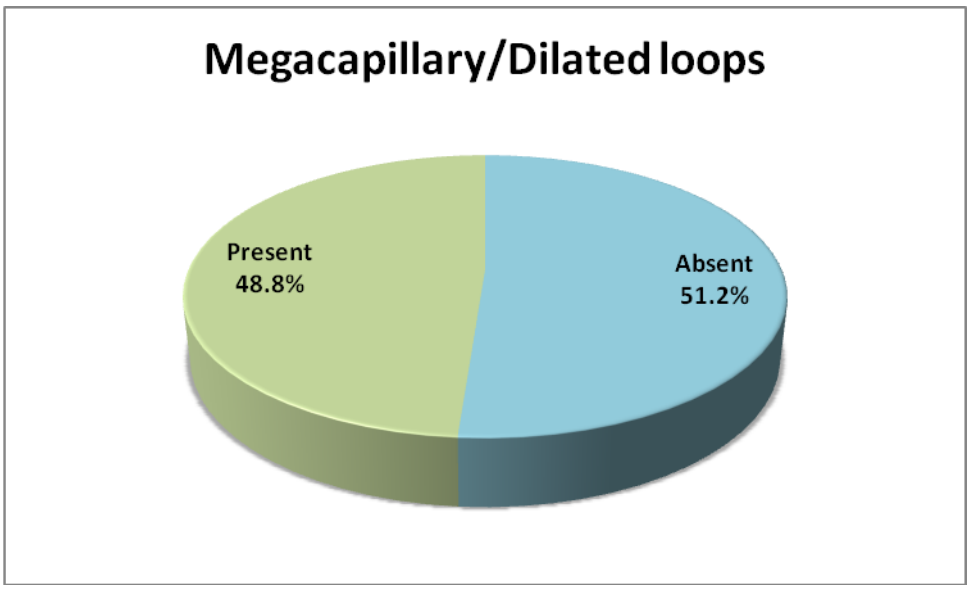


**TABLE 15:**

| **neoangiogenesis** | Frequency | Percent |
|---|---|---|
| Absent | 82 | 100.0 |

**TABLE 16:**

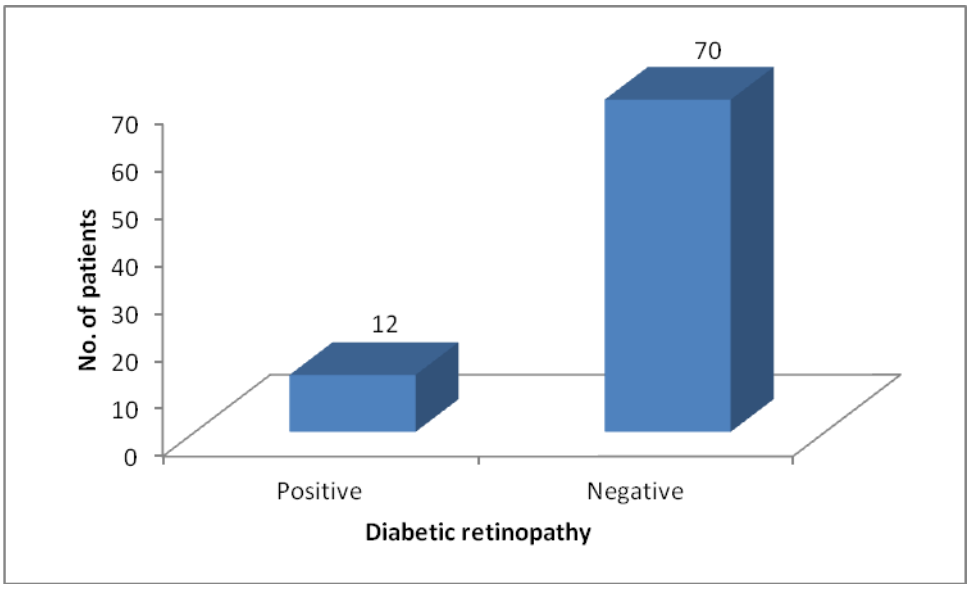
| **Extravasation** | Frequency | Percent |
|---|---|---|
| Absent | 82 | 100.0 |

**Diabetic retinopathy** : Out of 82 patients with type 2 diabetes mellitus, 12 (14.6%) patients had diabetic retinopathy and 70 (85.4%)patients did not have diabetic retinopathy. Table 17 and figure 14 represent the presence and absence of DR.

**TABLE 17:**

| **Diabetic Retinopathy** | | Frequency | Percent |
|---|---|---|---|
| Valid | Negative | 70 | 85.4 |
| | Positive | 12 | 14.6 |
| | Total | 82 | 100.0 |

**FIGURE 13**

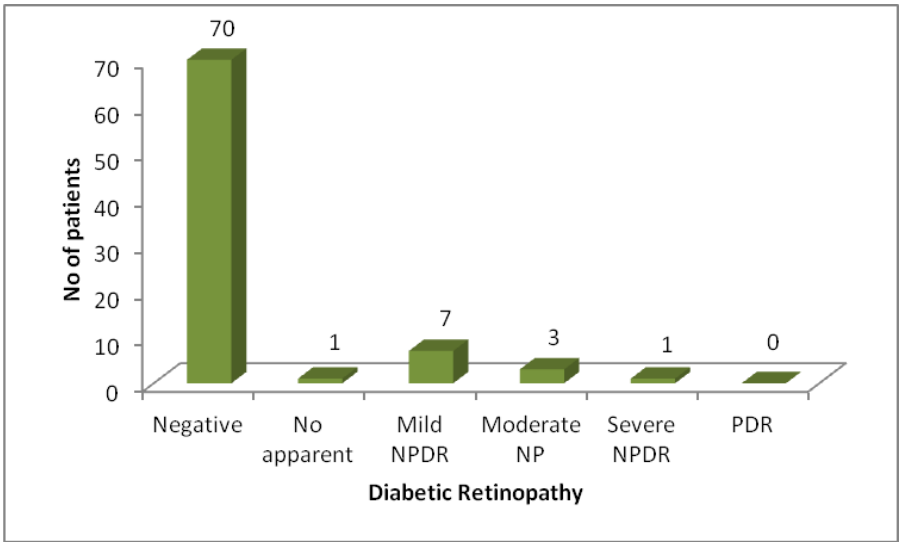


**Grades of DR :** Out of 12 patients with DR , 7 (8.5%) patients had mild NPDR, 3 (3.7%) patients had Moderate NPDR, 1(1.2%) patient had no apparent DR, and 1(1.2%) patient had severe DR. Table 18 and figure 15 represent the presence and absence of DR.

**TABLE 18:**

| Severity of DR | Frequency | Percent |
|---|---|---|
| Mild NPDR | 7 | 8.5 |
| Moderate NPDR | 3 | 3.7 |
| Negative | 70 | 85.4 |
| No apparent | 1 | 1.2 |
| Severe NPDR | 1 | 1.2 |
| Total | 82 | 100.0 |

**FIGURE 15**

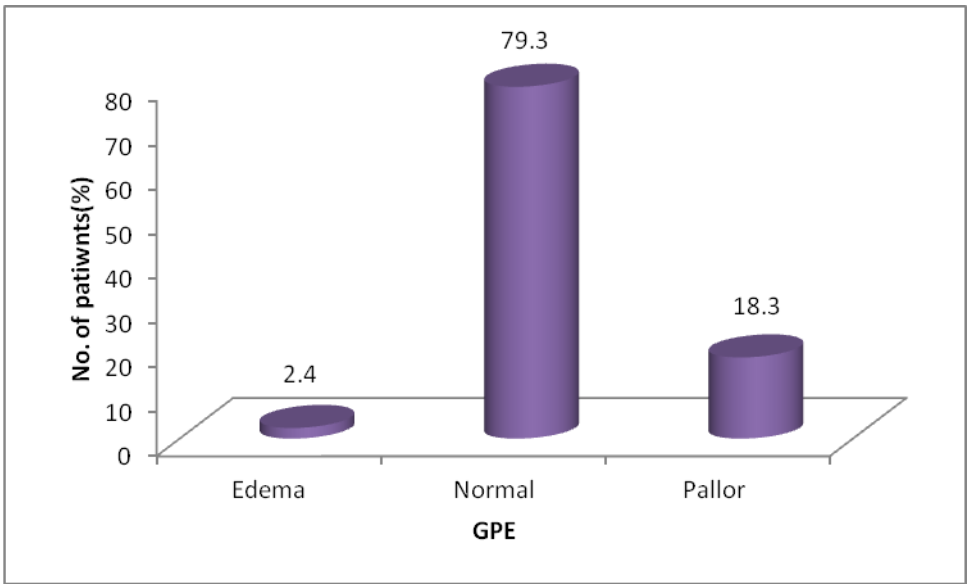


**GPE** : Out of 82 patients, 2 (2.4%)patients had edema, 15(18.3%) patients had pallor and rest 65(79%) were normal. Table 19 and figure 16 represent the general physical examination.

**TABLE 19:**

| GPE | | Frequency | Percent |
|---|---|---|---|
| Valid | Edema | 2 | 2.4 |
| | Normal | 65 | 79.3 |
| | pallor + | 15 | 18.3 |
| | Total | 82 | 100.0 |

**FIGURE 16**

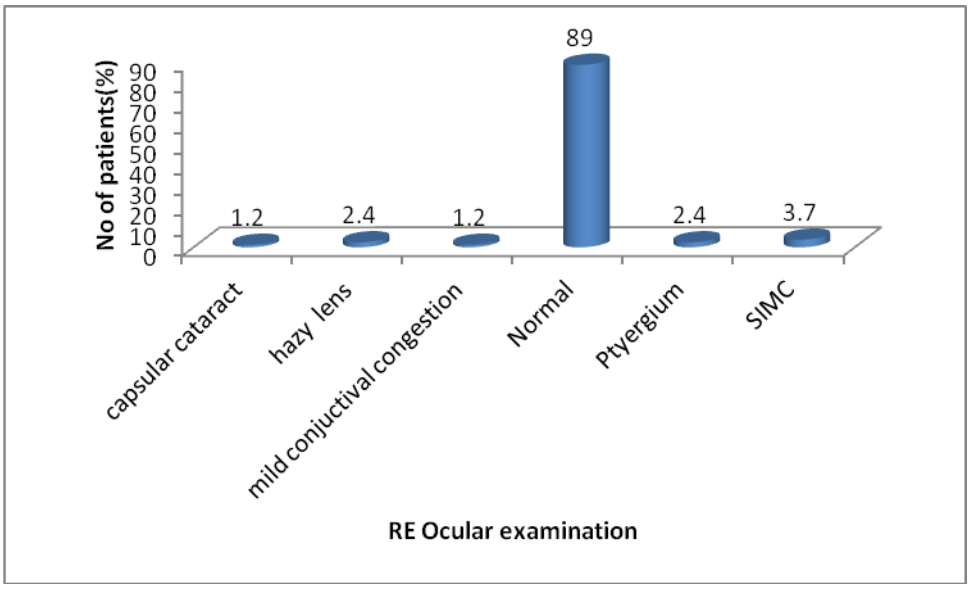


**RE Ocular examination**: 1(1.2%) patient had capsular cataract , 2(2.4%) had hazy lens, 1(1.2%) patient had mild conjunctival congestion , 2(2.4%) had ptyergium, 3(3.7%) had SIMC and the rest 73(89%) were normal. Table 20 and figure 17 represent the RE ocular examination.

**TABLE 20:**

| RE Ocular examination | Frequency | Percent |
|---|---|---|
| capsular cataract | 1 | 1.2 |
| hazy lens | 2 | 2.4 |
| mild conjuctival congestion | 1 | 1.2 |
| Normal | 73 | 89.0 |
| Ptyergium | 2 | 2.4 |
| SIMC | 3 | 3.7 |
| Total | 82 | 100.0 |

**FIGURE 17:**

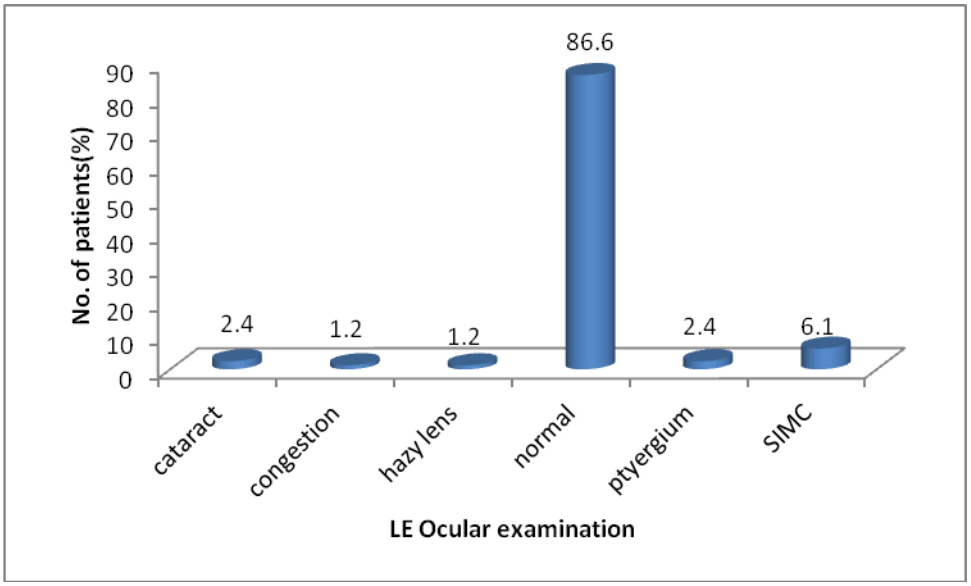


**LE Ocular examination**: 2(2.4%) patient had cataract , 1 (1.2%) had hazy lens, 1(1.2%) patient had conjunctival congestion , 2(2.4%) had ptyergium, 5 (6.1 %) had SIMC and the rest 71 (86.6%) were normal. Table 21 and figure 18 represent the LE Ocular examination.

**TABLE 21:**

| LE Ocular examination | Frequency | Percent |
|---|---|---|
| Cataract | 2 | 2.4 |
| Congestion | 1 | 1.2 |
| hazy lens | 1 | 1.2 |
| Normal | 71 | 86.6 |
| Ptyergium | 2 | 2.4 |
| SIMC | 5 | 6.1 |
| Total | 82 | 100.0 |

**FIGURE 18:**

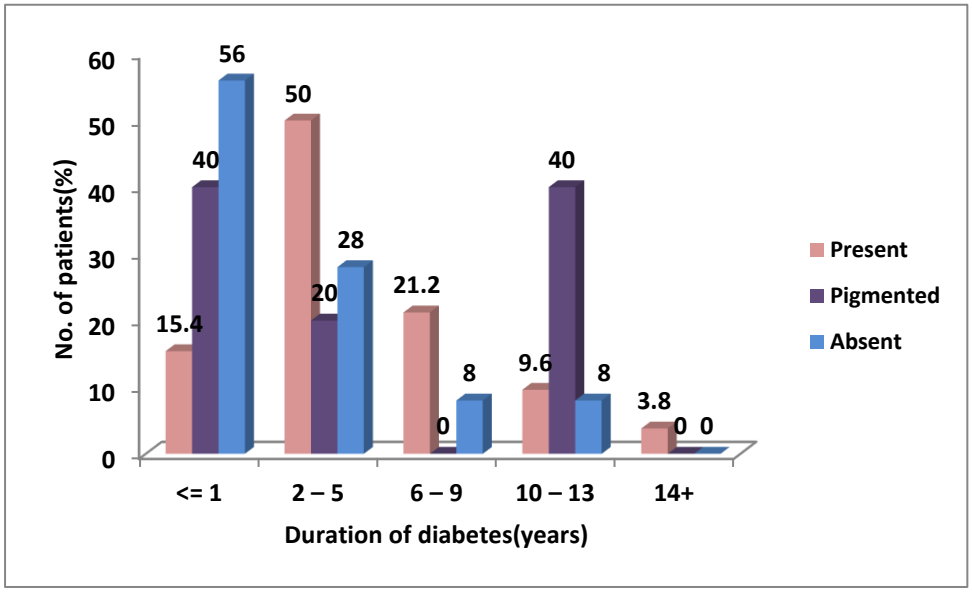


**Association between NFC changes and duration of diabetes :** The P value was 0.009 which is statically significant hence suggesting that there is a positive correlation between NFC changes and duration of diabetes mellitus. Table 22 and figure 19 represent the association between NFC changes and duration of diabetes

**TABLE 22:**

| **Duration of diabetes(years)** | NFC changes | | | | Chi square test | P value |
|---|---|---|---|---|---|---|
| | Present | Pigmented | Absent | Total | | |
| <= 1 | 8 | 2 | 14 | 24 | 20.255 | 0.009* |
| % | 15.4 | 40.0 | 56.0 | 29.3 | | |
| 2 – 5 | 26 | 1 | 7 | 34 | | |
| % | 50.0 | 20.0 | 28.0 | 41.5 | | |
| 6 – 9 | 11 | 0 | 2 | 13 | | |
| % | 21.2 | 0.0 | 8.0 | 15.9 | | |
| 10 – 13 | 5 | 2 | 2 | 9 | | |
| % | 9.6 | 40.0 | 8.0 | 11.0 | | |
| 14+ | 2 | 0 | 0 | 2 | | |
| % | 3.8 | 0.0 | 0.0 | 2.4 | | |
| Total | 52 | 5 | 25 | 82 | | |
| | 100.0% | 100.0% | 100.0% | 100.0% | | |
| *:Statistically significant | | | | | | |

**FIGURE 19**:

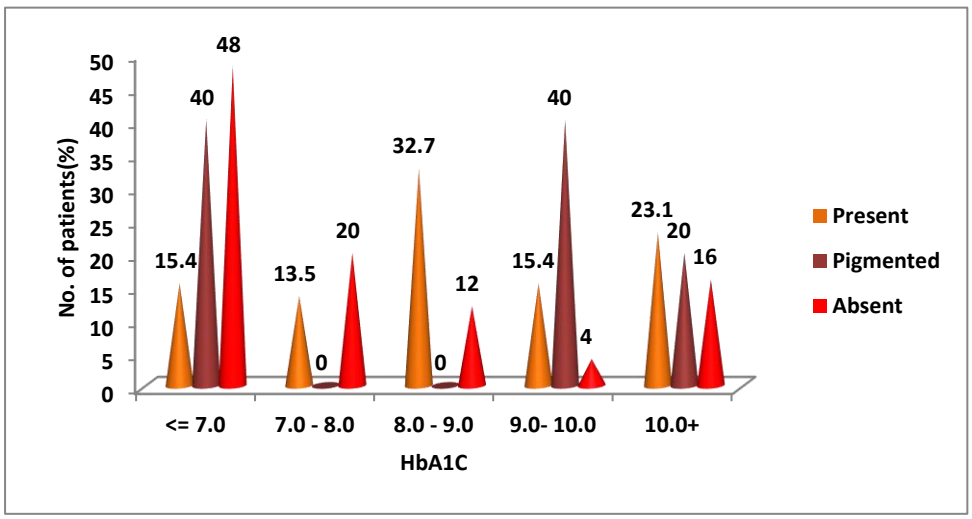


**Association between NFC changes and HbA1c level**: The P value was found to be 0.026 which is statistically significant hence stating that there is a positive correlation between NFC changes and HbA1c levels. Table 23 and figure 20 represent the association between NFC changes and HbA1c levels.

**TABLE 23:**

| hbA1C | NFC changes | | | | Chi square test | P value |
|---|---|---|---|---|---|---|
| | Present | Pigmented | Absent | Total | | |
| <= 7.0000 | 8 | 2 | 12 | 24 | 17.419 | 0.026* |
| % | 15.4 | 40.0 | 48.0 | 29.3 | | |
| 7.0001 - 8.0000 | 7 | 0 | 5 | 34 | | |
| % | 13.5 | 0.0 | 20.0 | 41.5 | | |
| 8.0001 - 9.0000 | 17 | 0 | 3 | 13 | | |
| % | 32.7 | 0.0 | 12.0 | 15.9 | | |
| 9.0001 - 10.0000 | 8 | 2 | 1 | 9 | | |
| % | 15.4 | 40.0 | 4.0 | 11.0 | | |
| 10.0001+ | 12 | 1 | 4 | 2 | | |
| % | 23.1 | 20.0 | 16.0 | 2.4 | | |
| Total | 52 | 5 | 25 | 82 | | |
| % | 100.0% | 100.0% | 100.0% | 100.0% | | |
| *:Statistically significant | | | | | | |

**FIGURE 20:**

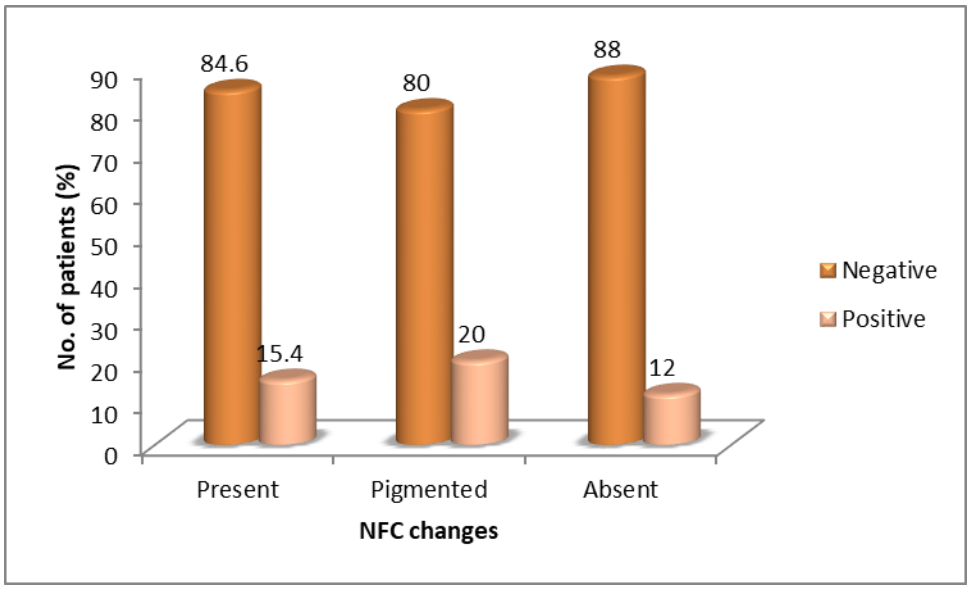


**Association between NFC changes and DR**: The P value was found to be 0.870 which is not statistically significant hence stating there is no correlation between NFC changes and DR. Table 24 and figure 21 represent the association between NFC changes and DR

**TABLE 24:**

| DR | NFC changes | | | | Chi square test | P value |
|---|---|---|---|---|---|---|
| | Present | Pigmented | Absent | Total | | |
| Negative | 44 | 4 | 22 | 70 | .278 | 0.870 |
| % | 84.6 | 80.0 | 88.0 | 85.4 | | |
| Positive | 8 | 1 | 3 | 12 | | |
| % | 15.4 | 20.0 | 12.0 | 14.6 | | |
| Total | 52 | 5 | 25 | 82 | | |
| % | 100.0% | 100.0% | 100.0% | 100.0% | | |
| *:Statistically significant | | | | | | |

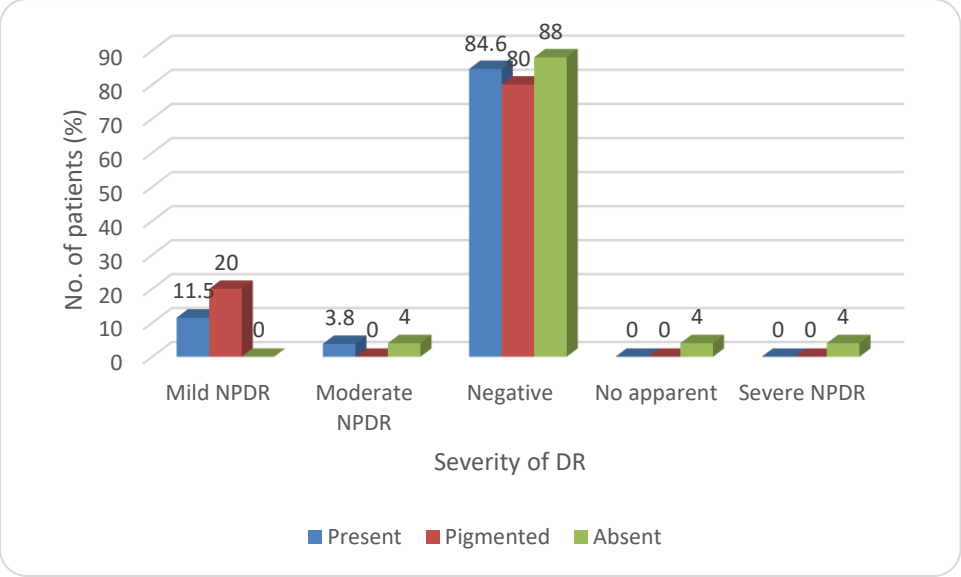
**FIGURE 21:**



**Association between NFC changes and severity of DR**: The P value was found to be 0.410 which is not statistically significant hence stating there is no correlation between NFC changes and severity of DR. Table 25 and figure 22 represent the association between NFC changes and severity of DR.

**TABLE 25:**

| **Severity of DR** | NFC changes | | | | Chi square test | P value |
|---|---|---|---|---|---|---|
| | Present | Pigmented | Absent | Total | | |
| Mild NPDR | 6 | 1 | 0 | 7 | 8.248 | .410* |
| % | 11.5 | 20.0 | 0.0 | 8.5 | | |
| Moderate NP | 2 | 0 | 1 | 3 | | |
| % | 3.8 | 0.0 | 4.0 | 3.7 | | |
| Negative | 44 | 4 | 22 | 70 | | |
| % | 84.6 | 80.0 | 88.0 | 85.4 | | |
| No apparent | 0 | 0 | 1 | 1 | | |
| % | 0.0 | 0.0 | 4.0 | 1.2 | | |
| Severe NPDR | 0 | 0 | 1 | 1 | | |
| % | 0.0 | 0.0 | 4.0 | 1.2 | | |
| Total | 52 | 5 | 25 | 82 | | |
| % | 100.0% | 100.0% | 100.0% | 100.0% | | |
| *:Statistically significant | | | | | | |


No. of patients (%)
90
80
70
60
50
40
30
20
10
0
11.5
20
0
3.8
0
4
84.6
80
88
0
0
4
0
0
4
Mild NPDR
Moderate NPDR
Negative
No apparent
Severe NPDR
Severity of DR
Present
Pigmented
Absent

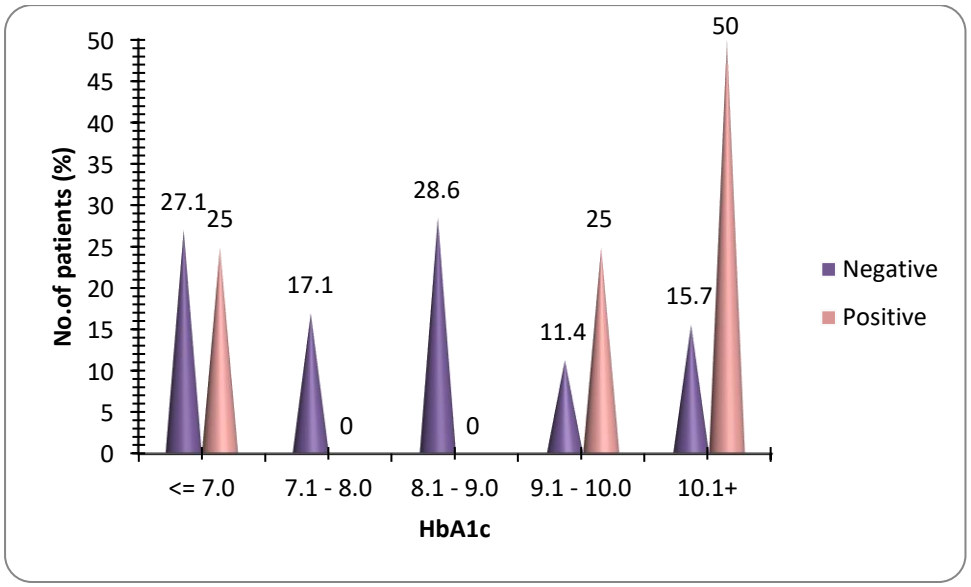
**Association between HbA1C and DR**: The P value was found to be 0.013 which is statistically significant hence stating there is correlation between HbA1c and DR.

Table 26 and figure 23 represent the association between HbA1c and DR

**TABLE 26:**

| **HBA1C** | Diabetic retinopathy | | | Chi square test | P value |
|---|---|---|---|---|---|
| | Negative | Positive | Total | | |
| <= 7.0 | 19 | 3 | 22 | 12.718 | .013* |
| % | 27.1 | 25.0 | 26.8 | | |
| 7.1 - 8.0 | 12 | 0 | 12 | | |
| % | 17.1 | 0.0 | 14.6 | | |
| 8.1 - 9.0 | 20 | 0 | 20 | | |
| % | 28.6 | 0.0 | 24.4 | | |
| 9.1 - 10.0 | 8 | 3 | 11 | | |
| % | 11.4 | 25.0 | 13.4 | | |
| 10.1+ | 11 | 6 | 17 | | |
| % | 15.7 | 50.0 | 20.7 | | |
| Total | 70 | 12 | 82 | | |
| % | 100.0% | 100.0% | 100.0% | | |
| *:Statistically significant | | | | | |

**FIGURE 23:**




As both the duration of DM and HbA1c level correlate with Diabetic retinopathy, there is a association between duration od DM , Hba1c and DR.

Patient with 2 years duration of DM , with HbA1c 13.5% with NFC changes and no diabetic retinopathy

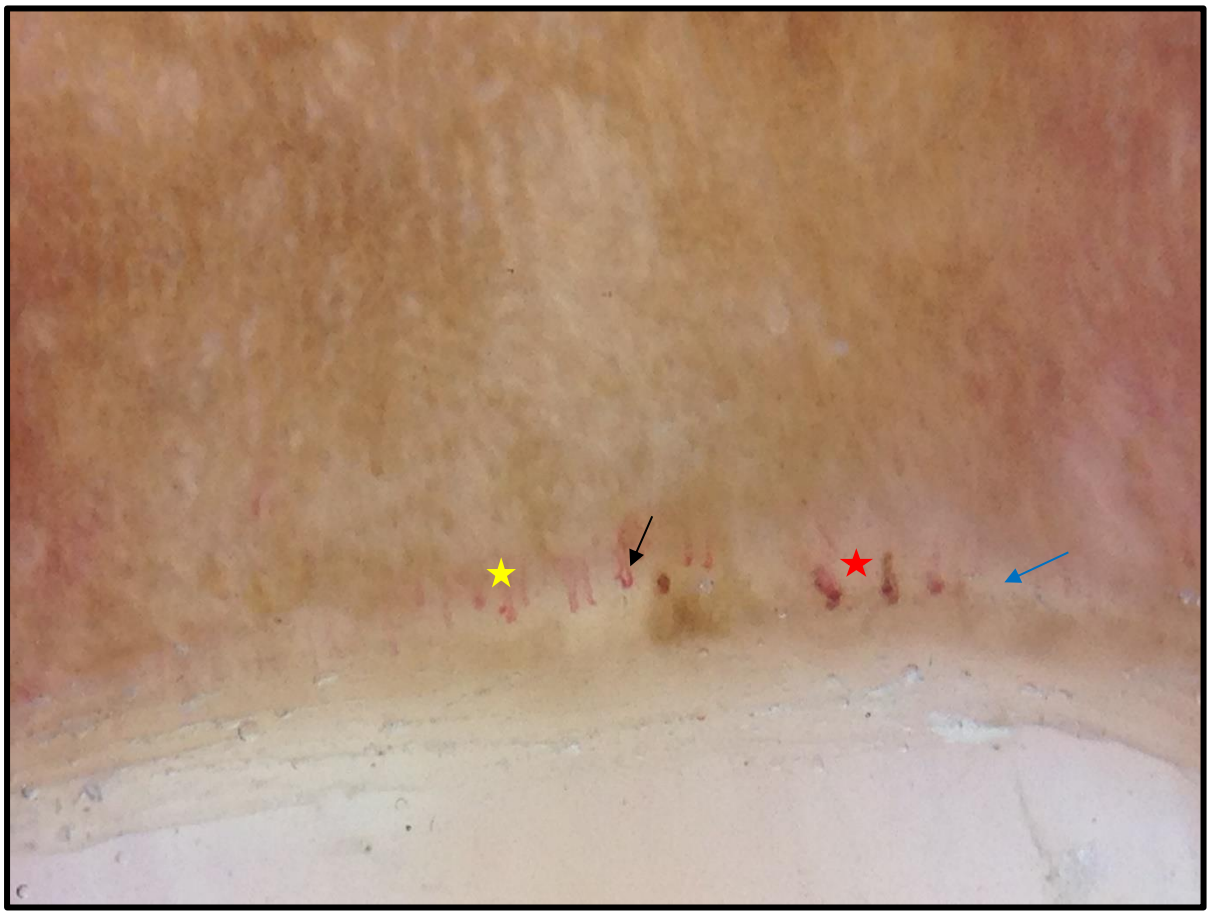


**FIGURE 24:Yellow star represent Multiple tortuous capillaries , avascular area by blue arrow, capillary ectasia by red star, dilated capillaries by black arrow are seen.**

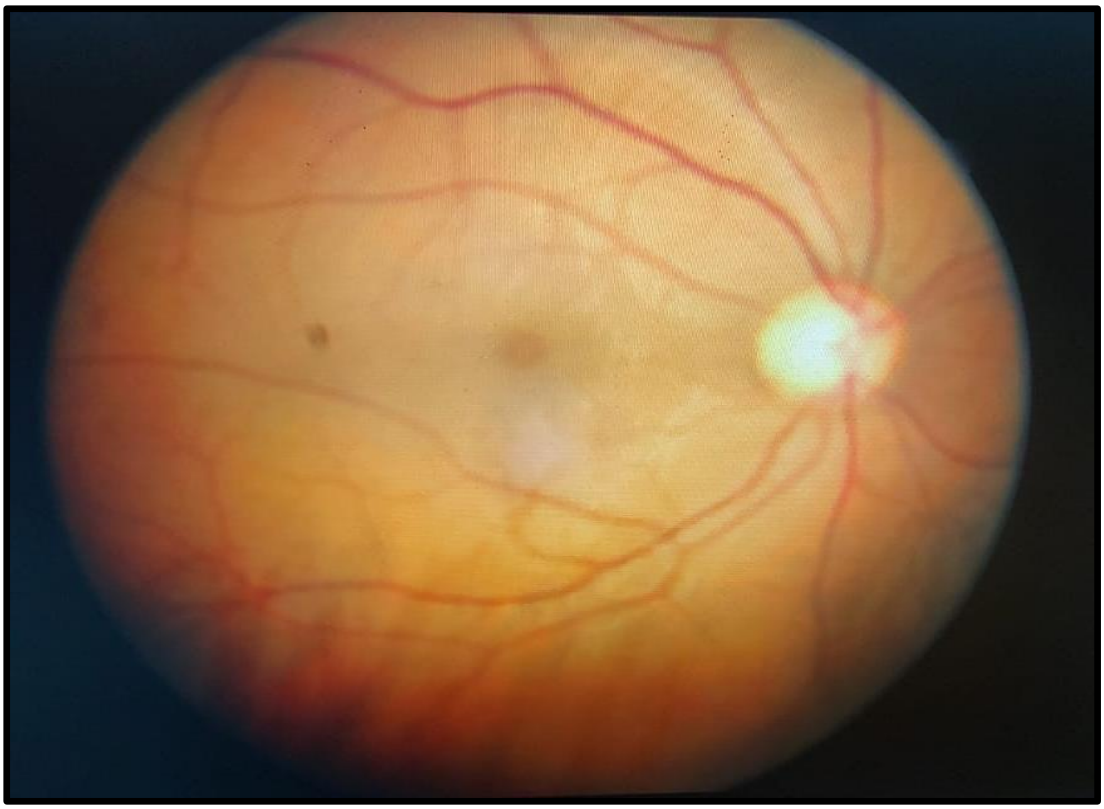


**IMAGE 2: Fundoscopy showing no diabetic retinopathy changes.**

Patient with 1 year duration of DM with HbA1c level 10.1%

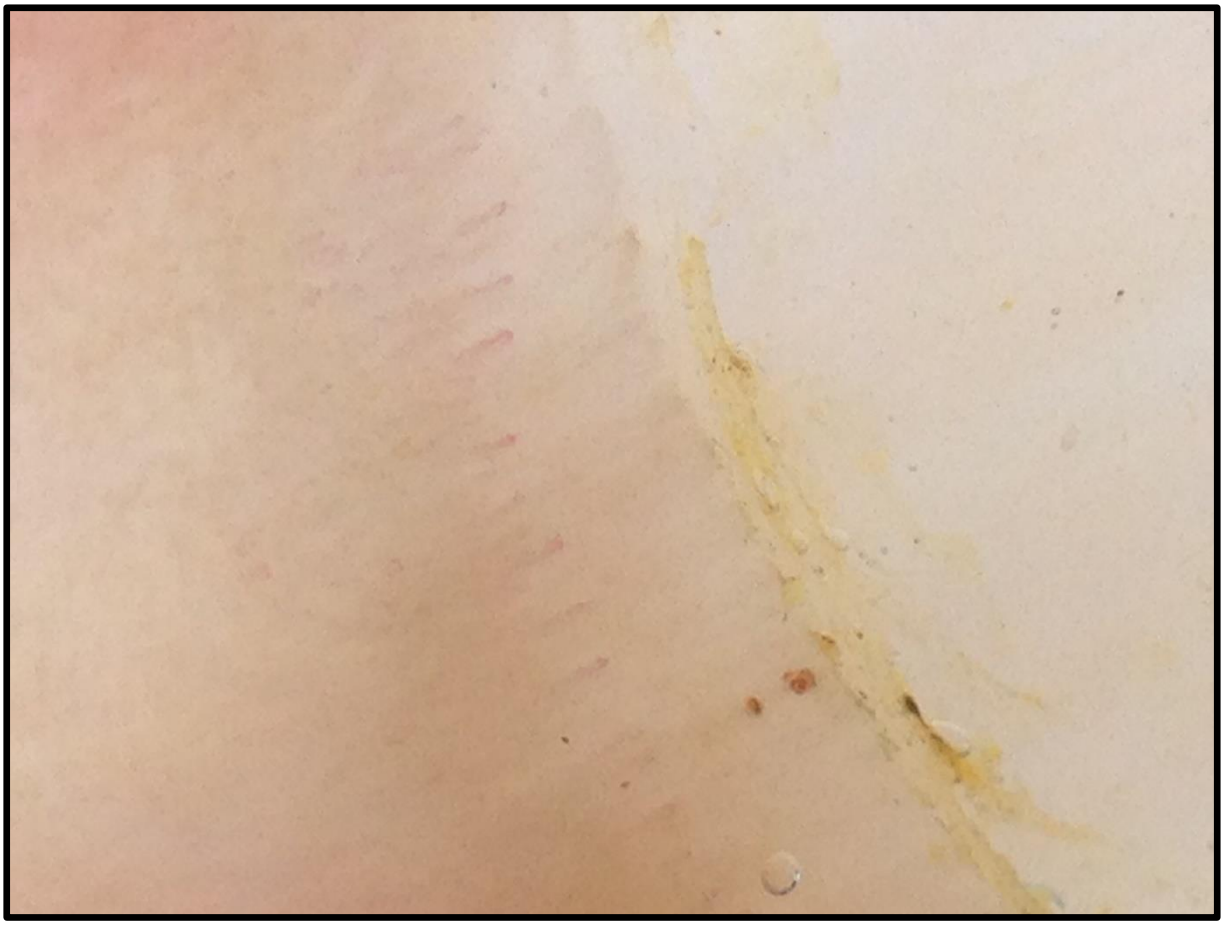
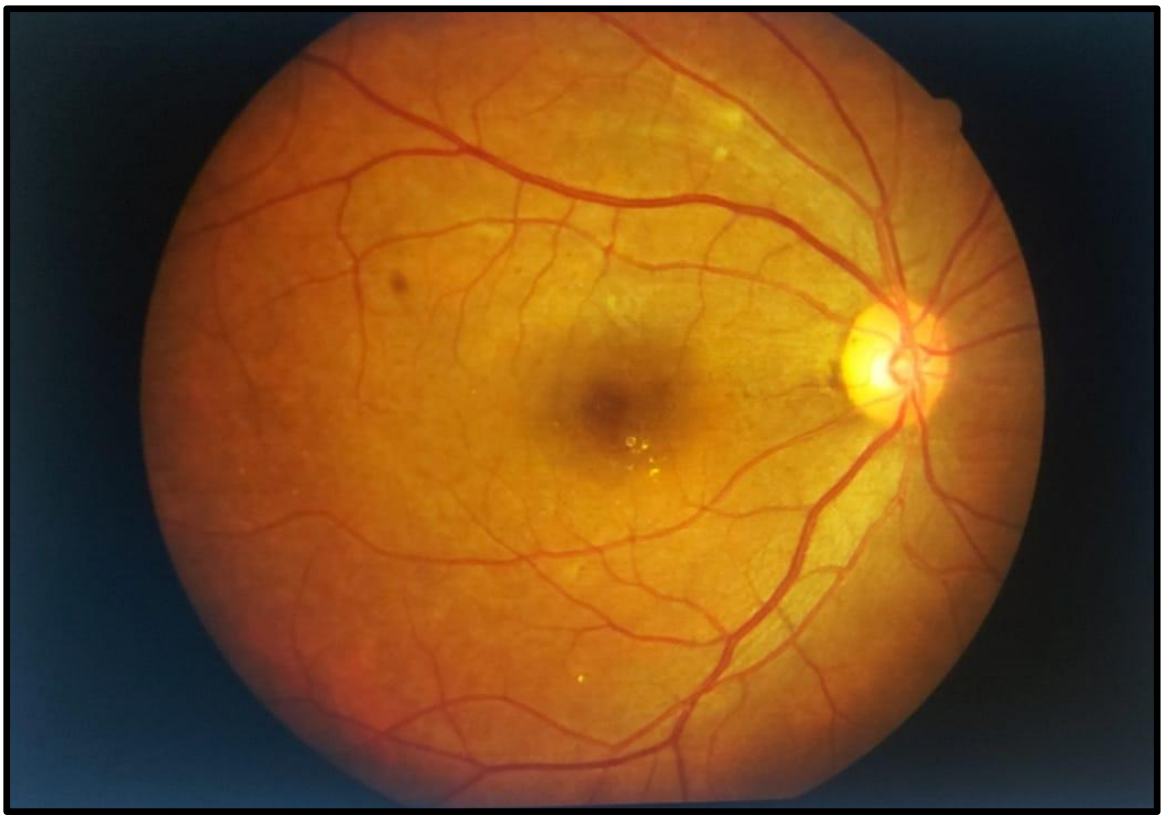


IMAGE 3: Multiple dilated capillaries are present



Fundoscopy of right eye showing moderate NPDR

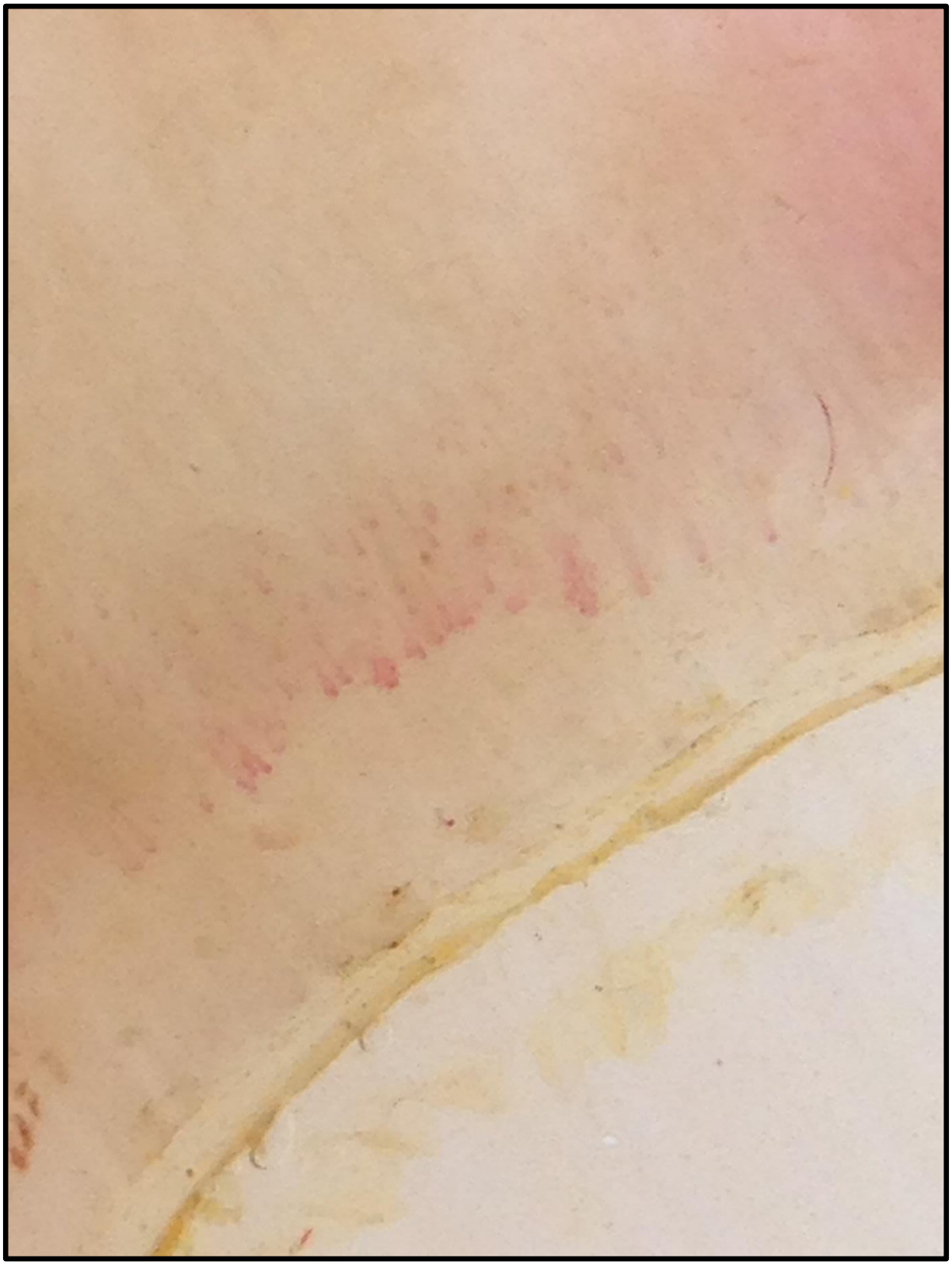


IMAGE 5: Multiple tortuous and megacapillaries present.

- A patient with 7 years duration of DM with HbA1C : 12.7% and NFC changes showing tortusity, dilated capillaries with mild NPDR

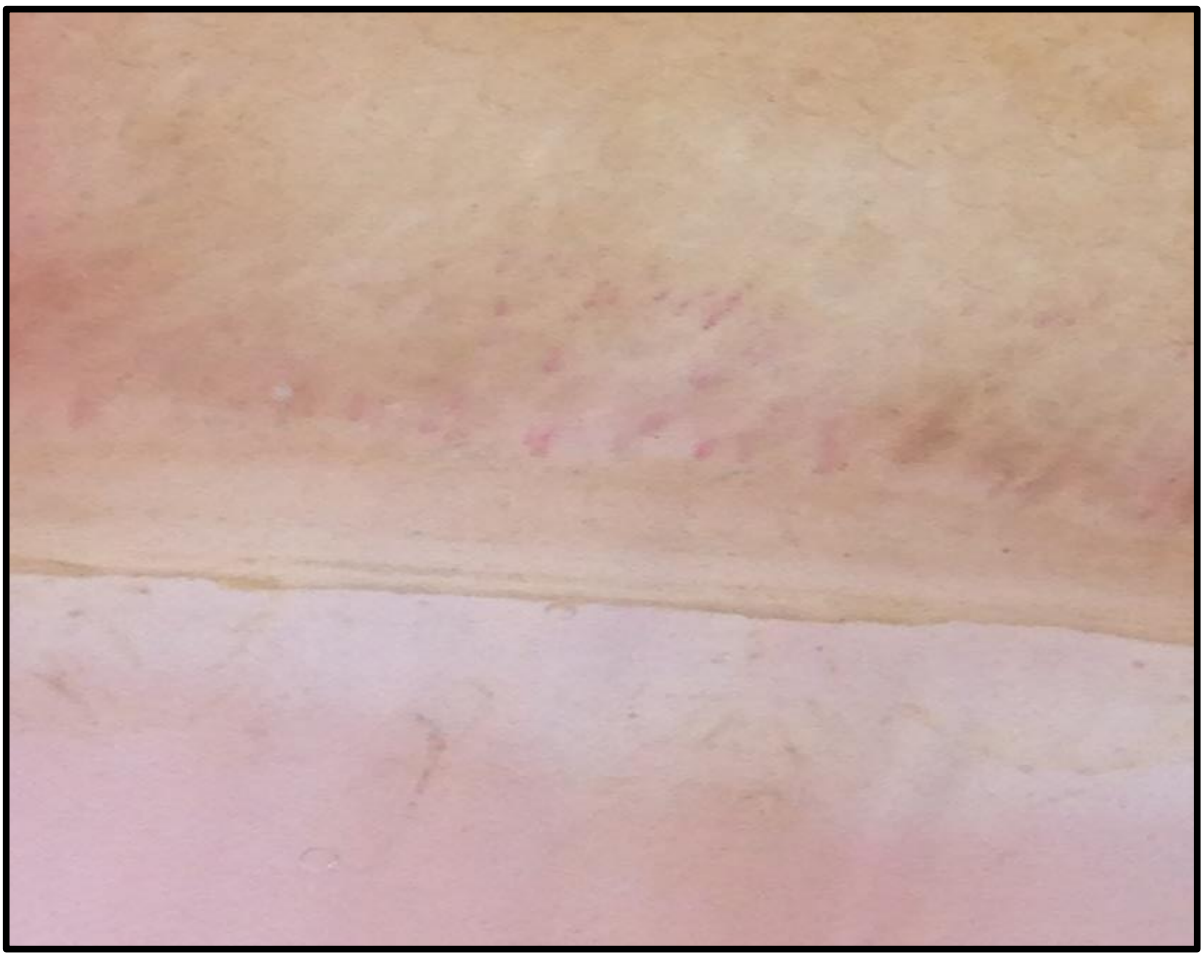


**IMAGE 6: NFC changes showing dilated capillaries**

**IMAGE 7: NFC changes showing tortuous capillaries**

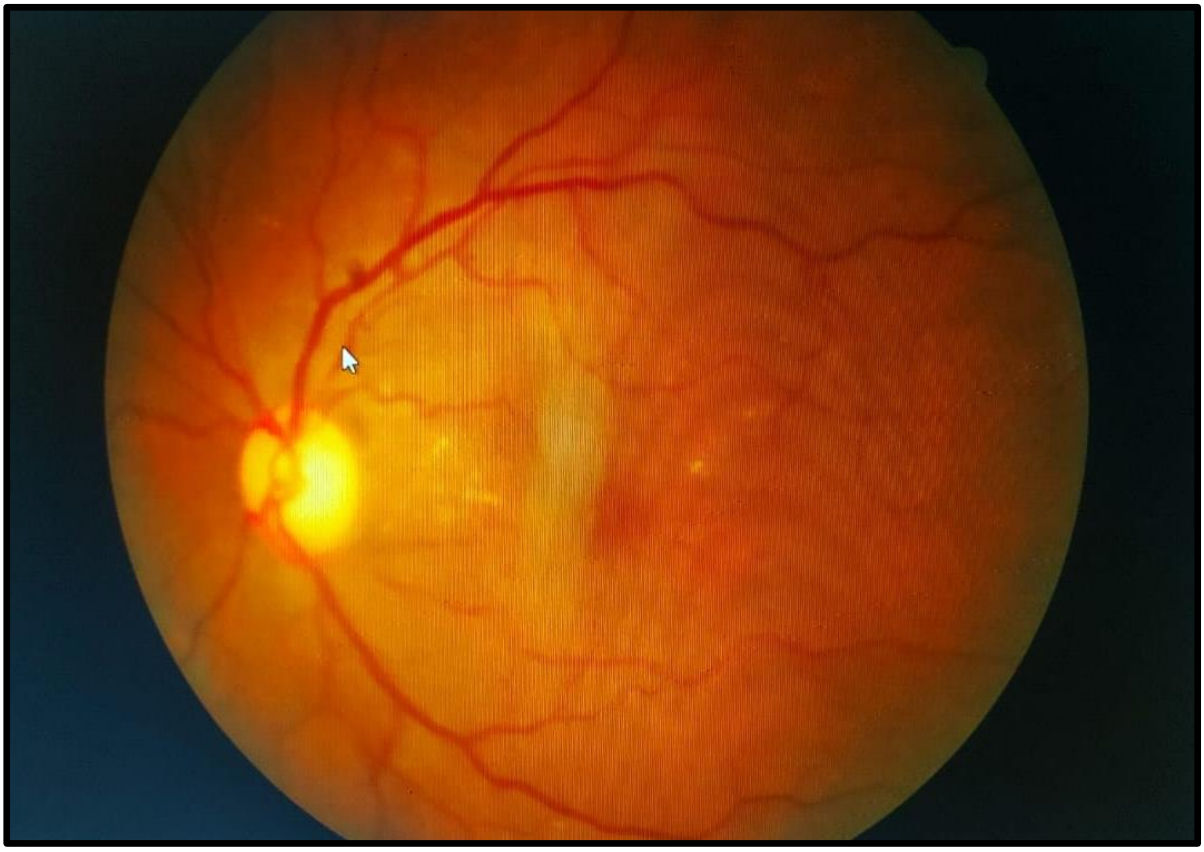


**IMAGE 8: Fundoscopy showing mild NPDR**

**A DR negative patient with 8 years duration of DM with HbA1C 6.9% having tortous and dilated NFC changes .**

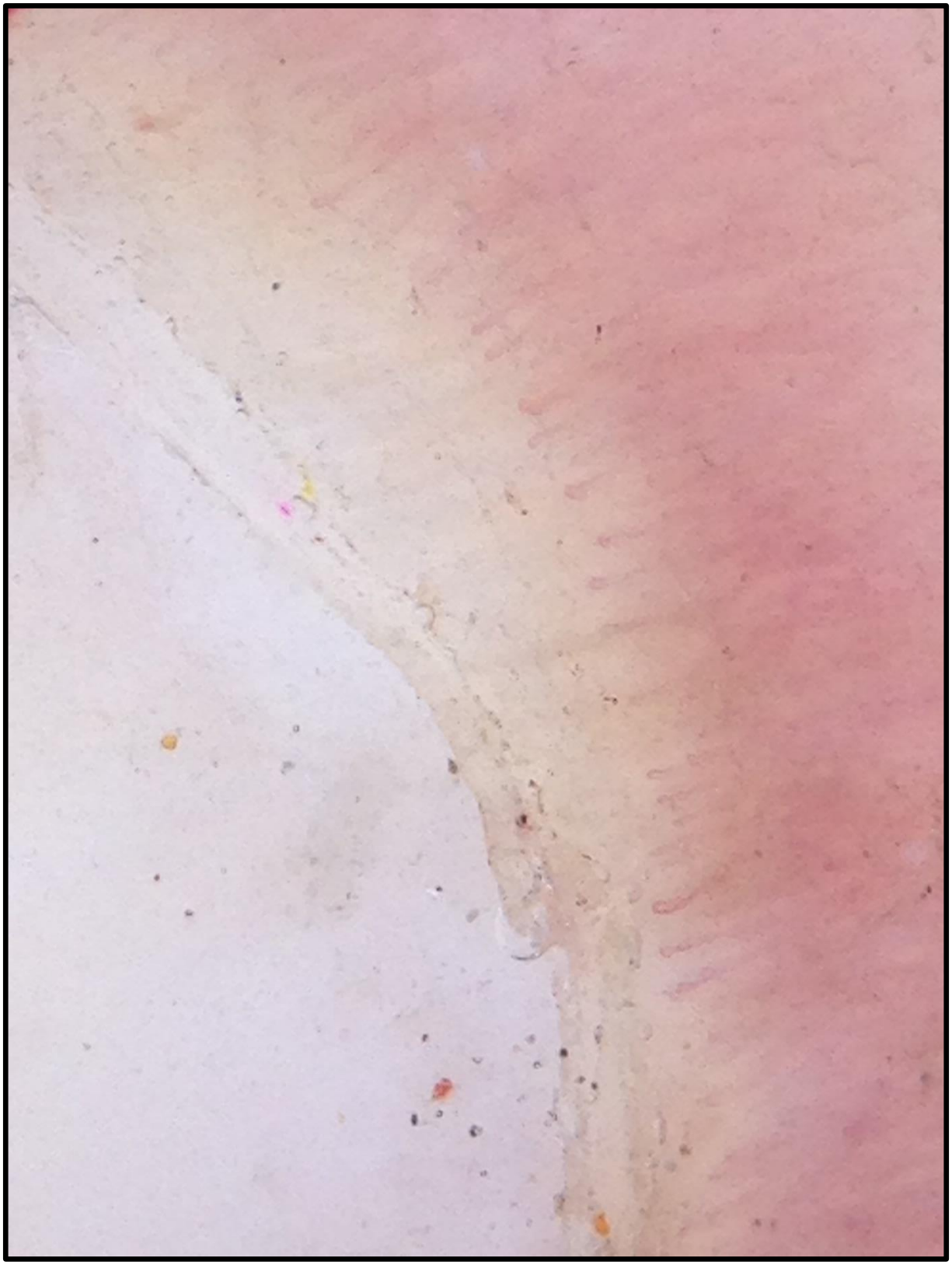


**IMAGE 9: NFC showing tortuous capillaries**

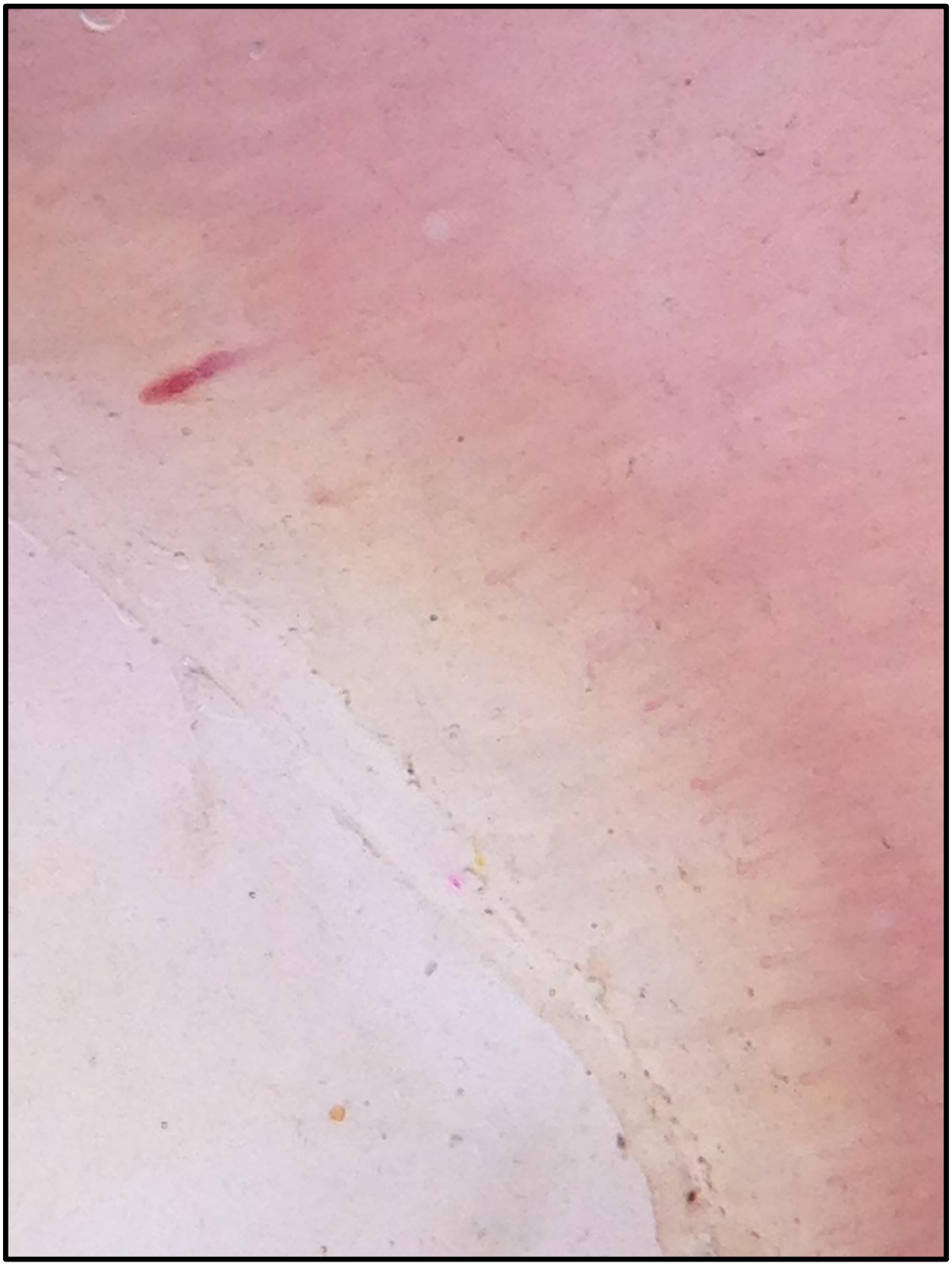


IMAGE 10: NFC showing dilated and tortuous capillaries

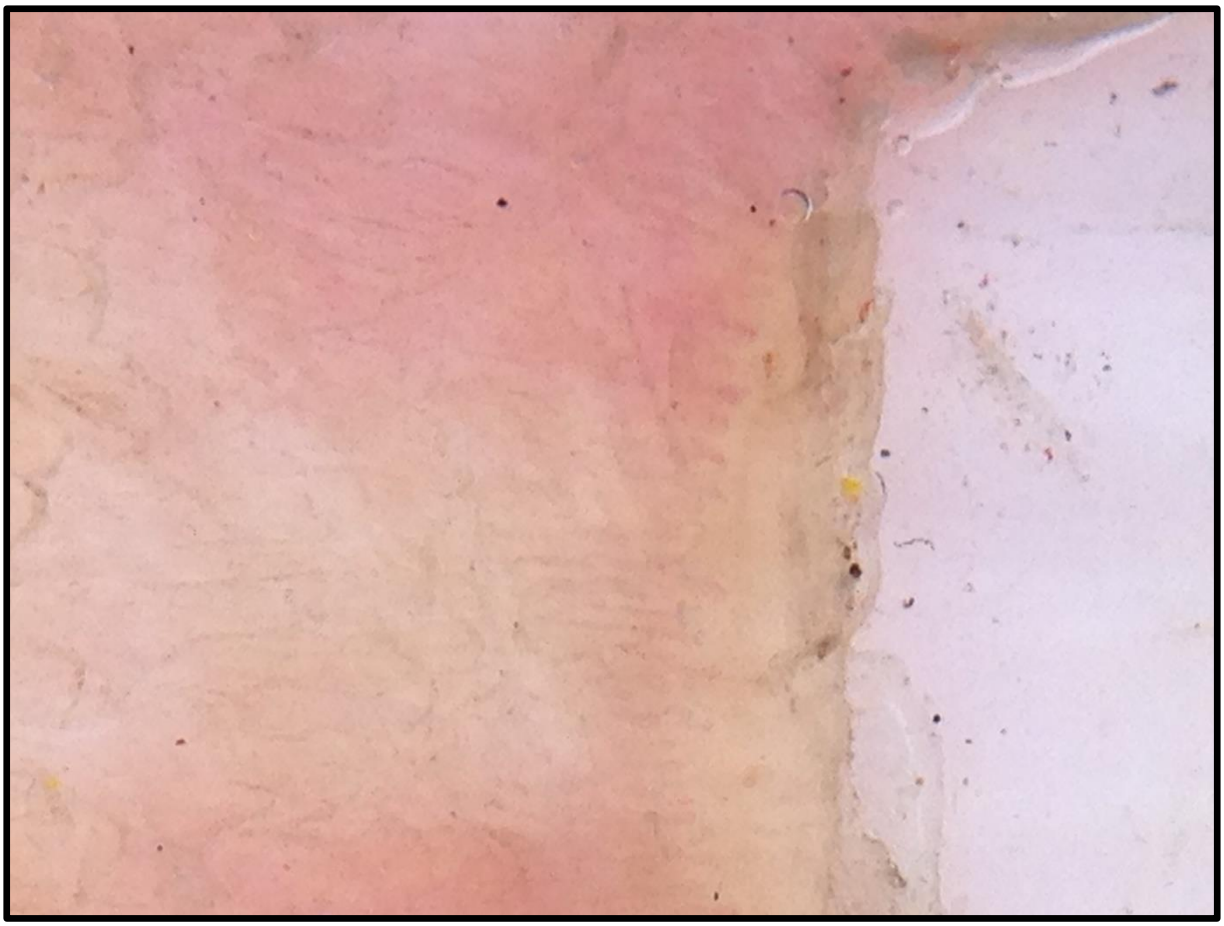


**IMAGE 11: NFC showing dilated capillaries**

**IMAGE 12: Fundoscopy : normal**

- A patient with 1 month duration of DM  with HbA1C : 8.7% and NFC changes showing tortusity, globular dilated capillaries with no DR

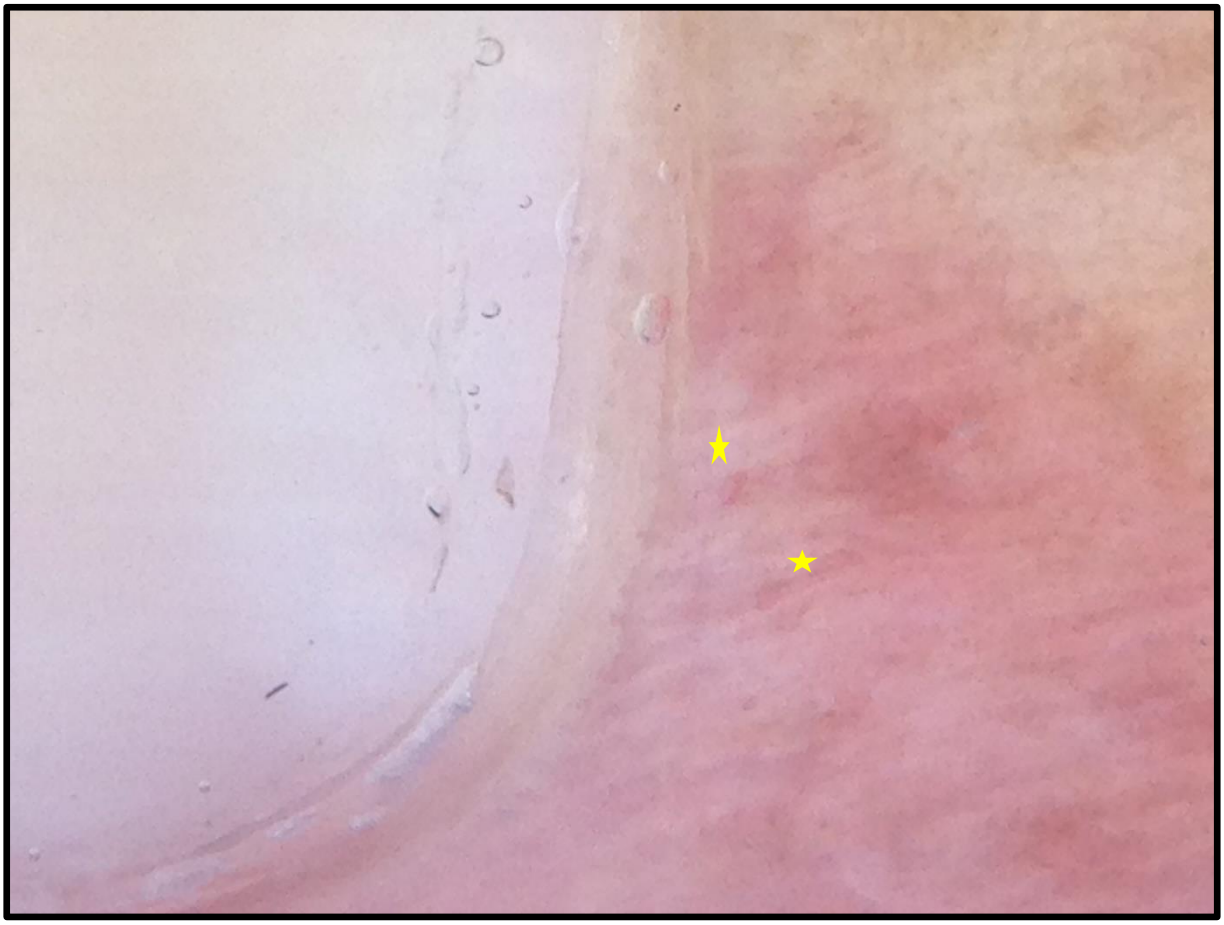


**IMAGE 12: yellow star represents globular dilated capillaries**

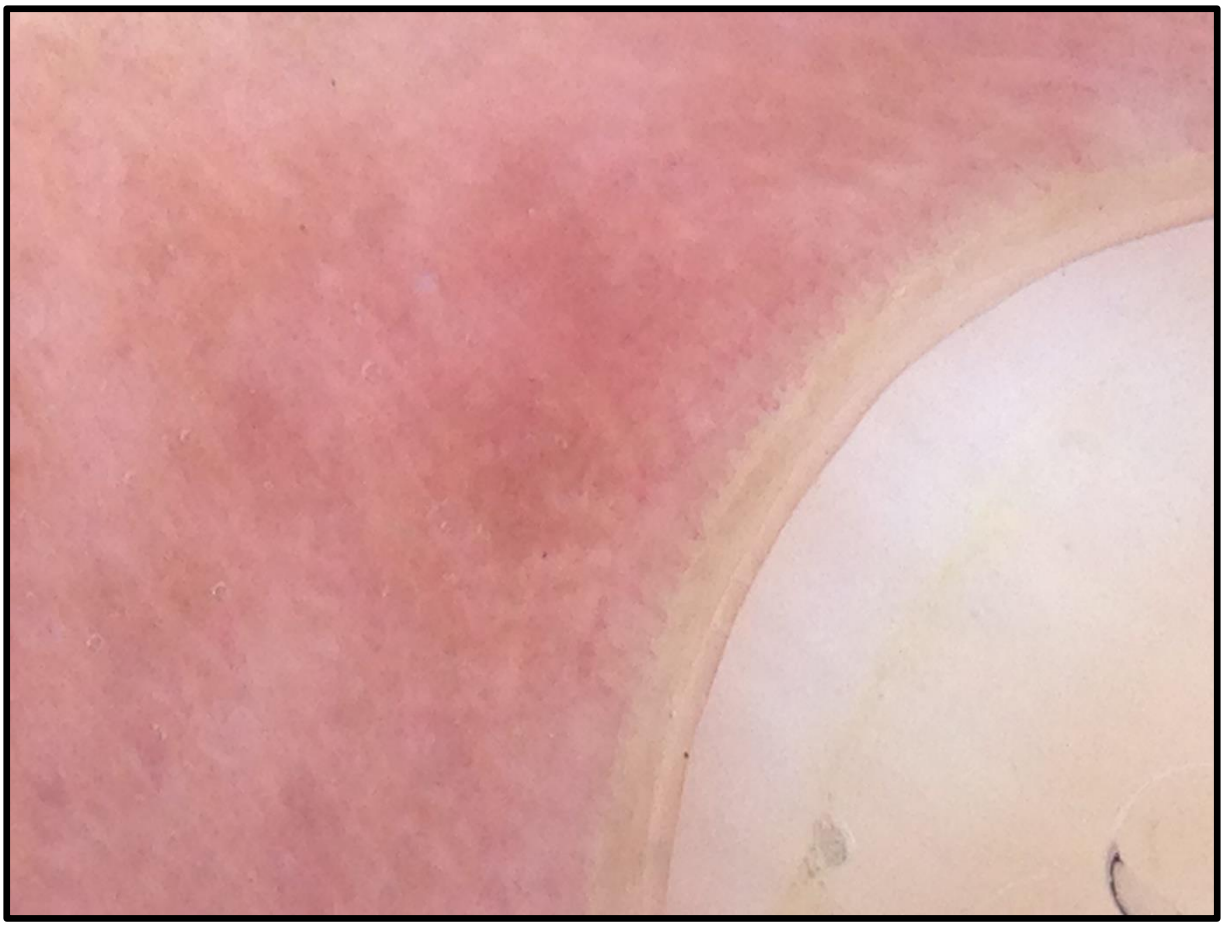


**IMAGE 13: NFC showing tortous capillaries**

- A patient with 10year duration of DM with HbA1C : 12.1% and NFC changes showing tortusity with no DR

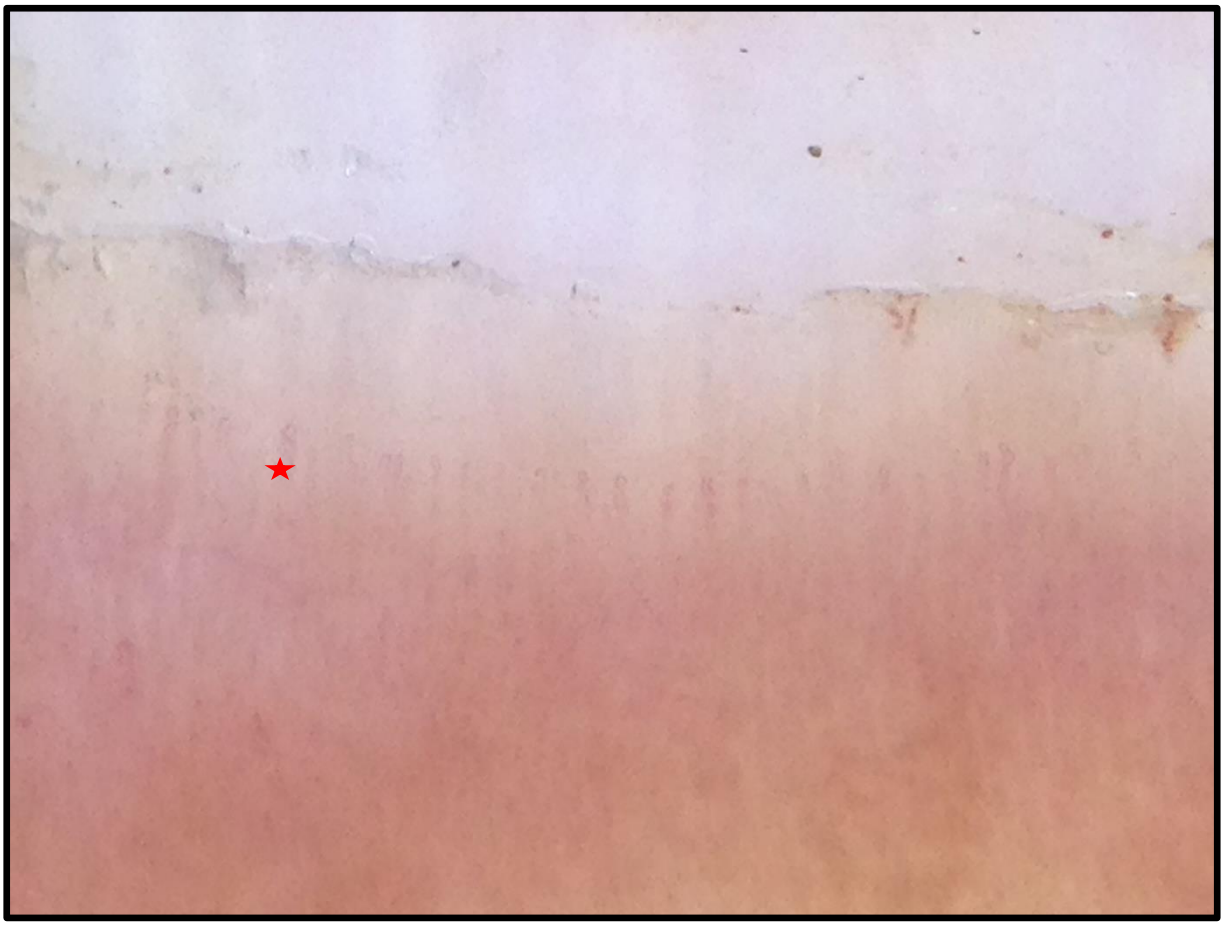


**IMAGE 14: NFC showing multiple tortuous capillaries.**

## DISCUSSION

The goal is to detect clinically severe retinopathy before vision is endangered, as DR is the major cause of blindness. Early detection of people at risk of DR progression and treatments can help prevent vision loss and lower the costs of maintaining more advanced illness. NVC has been utilised to examine microvascular structure, particularly in rheumatic disease and other extrarheumatic diseases, and there have been numerous studies evaluating capillaroscopic findings in various conditions. As a result, capillaroscopic studies in diabetic patients began in the 1960s.However, because to the complex nature of retinopathy, which gives findings on NVC, there is minimal evidence in the literature on this subject, particularly in relation to T2DM, and there have been numerous studies analysing capillaroscopic findings in various disorders.

Nailfold capillaroscopy (NFC) is an easy, noninvasive, safe and useful diagnostic tool to assess the microvascular structure of the nailfold. The use of dermoscope to assess the nail fold capillaries to evaluate diabetic microvascular involvement and to determine any correlation between nailfold capillaroscopic findings ,retinopathy, duration of DM and glycosylated hemoglobin ($HbA_{1c}$) levels is the highlight of the current study.

In this cross-sectional study, we report findings in 82 patients with type II diabetes mellitus. The age of the patients enrolled in the study ranged from 18 years to 76 years.Among 82 patients, 54 (65.8%) were males and 28 (34.1%) were females. The most common diabetes duration was found to be between 2 and 5 years, with 34 (41.5%) patients in this category, followed by 24 (29.3%) patients with less than 1 year, 13 (15.9%) patients with 6-9 years, 9 (11%) patients with 10-13 years, and 2 (2.4%) patients with more than 14 years. Patients with HbA1c of 8.1-10% were clustered in 31 (37.8%) patients, with less than 7% in 22 (26.8%), greater than 10% in 17 (20.7%) patients, and between 7.1-8.0 percent in 12 (14.6%) patients.

In our study, 12 (14.6 percent) of 82 patients with type 2 diabetes mellitus had diabetic retinopathy, while 70 (85.4 percent) did not. 7 (8.5 percent) of the 12 individuals with DR had mild NPDR, 3 (3.7 percent) had moderate NPDR, 1 (1.2 percent) patient had no apparent DR, and 1 (1.2 percent) patient had severe DR.

**NFC changes:**

In patients with type 2 diabetes mellitus in our study, the nail fold capillaroscopic changes were evident in 51 (62.2%) patients, absent in 25 (30.5%) patients, and pigmented in 5 patients (6.1 percent ).

Tortusity was seen in 24 (29.3%) patients, microhemorrhage in 1 (1.2%) patient, avascular area in 17 (20.7%) patients, bizarre capillaries in 2 (2.4%) patients, capillary ectasia in 1 (1.2%) patient, megacapillary or dilated loops in 40 (48.8%) patients, and no patients had neoangiogenesis and extravasation. Capillaroscopic features such as tortuosity, bushy capillaries, neoformation, and capillary ectasia were also considerably higher in patients with proliferative DR than in patients with nonproliferative DR and without DR, according to a study by Uyar S et al. In our study, type 2 Diabetes Mellitus patients had considerably more dilated capillaries, tortusity, and avascular area. Meyer et al. looked at the density, sizes, and shape of nailfold capillaries in 16 T1DM and 19 T2DM patients. Using NVC, they discovered tortuous and dilated capillaries that could indicate microangiopathy.

Furthermore, according to a research by Barchetta et al., NVC was capable of detecting changes in 50 percent of patients with diabetes who did not have retinopathy.

Out of 82 individuals, 2 (2.4 percent) had edoema, 15 (18.3%) exhibited pallor, and the remaining 65 (79%) were normal. The general physical examination is depicted in Table 18 and Figure 16.

RE Ocular Examination: 1 (1.2%) patient had capsular cataract, 2 (2.4%) had cloudy lens, 1 (1.2%) patient had mild conjunctival congestion, 2 (2.4%) had ptyergium, 3 (3.7%) had SIMC, and the remaining 73 (89%) were normal. LE Ocular examination revealed that 2 (2.4%) of the patients had cataracts, 1 (1.2%) had hazy lenses, 1 (1.2%) had conjunctival congestion, 2 (2.4%) had ptyergium, 5 (6.1%) had SIMC, and the remaining 71 (86.6%) were normal. The LE Ocular Examination is depicted in Table 20 and Figure 18.

**Association between NFC changes and duration of diabetes :** The P value was 0.009 which is statically significant hence suggesting that there is a positive correlation between NFC changes and duration of diabetes mellitus.

Uyar S et al study analysed the median diabetes years of patients with tortuosity, aneurysm, bizarre capillary, and microhemorrhage by the presence of DR, and found that patients with DR had considerably longer diabetes years than those without DR. Regardless of retinopathy, diabetic individuals with tortuosity, bushy capillary, aneurysm, neoformation, and odd capillary had longer diabetes years than diabetic patients without these characteristics. Although these data do not indicate when microvascular alterations develop, the Uyar S et al investigation found a significant correlation between diabetes years and capillaroscopic findings. Early discovery of tortuosity, aneurysms, unusual capillaries, and microhemorrhage could be a sign of DR. Chang et al. and Meyer et al. showed a positive link between capillaroscopic findings and diabetes duration, however Barchetta et al. discovered that NVC findings were unrelated to diabetes duration. On the other hand, study done by Hsu Po-Chi et al reported that there was no significant difference in NVC characteristics and scores according to disease duration.

**Association between NFC changes and HbA1c level**: The P value was determined to be 0.026, which is statistically significant, indicating that there is a positive link between NFC alterations and HbA1c levels. Table 22 and Figure 20 depict the relationship between NFC modifications and HbA1c levels. Patients with >8 percent HbA1c who had NFC changes were 37(71.2 percent) in our study, with 8-9 percent being the highest with 17(32.7 percent) patients, followed by more than 10 percent in 12 patients (23.1 percent), 9-10 percent in 8 (15.4 percent), and less than 7 percent in 8 (15.4 percent) patients, and the least in 7 patients with HbA1c levels of 7 - 8 percent (13.5 percent ).

Hsu Po-Chi et al evaluated the NVC characteristics in individuals with type 2 diabetes based on the duration of their diabetes and their HbA1c level. The findings demonstrated that in people with HbA1c 7%, the frequency of capillary abnormalities was increased, and the NVC score was substantially higher than in subjects with HbA1c 7%. Nailfold capillary anomalies were linked to vascular damage in patients with type 2 diabetes and poor glycemic control, according to the findings.[4]

Capillaroscopy was used by Hosking et al. to detect microvascular alterations in the paediatric population and adolescents with type I diabetes mellitus using a non-invasive technique. Avascular zones and microhemorrhages were the most common changes identified, and they were correlated to elevated HbA1c levels (p=0.03), indicating that capillaroscopy is a reliable approach for detecting microvascular damage.[6]

Patients with poor metabolic control and systemic involvement had moderate to severe aberrant capillaroscopic findings, according to Kuriliszyn-Moskalet et al.[2]

**Association between HbA1C and DR**: The P value was found to be 0.013 which is statistically significant hence stating there is correlation between HbA1c and DR.

Table 25 and figure 23 represent the association between HbA1c and DR.

As both the duration of DM and HbA1c level significantly correlate with Diabetic retinopathy, there is an association between duration DM , Hba1c and DR.

**Association between NFC changes and DR**: The P value was found to be 0.870 which is not statistically significant hence stating there is no correlation between NFC changes and DR. Table 23 and figure 21 represent the association between NFC changes and DR.

Chang et al. found a link between DR and tortuous capillaries, bushy capillaries, and capillary hypertrophy, with these changes occurring more frequently in patients with severe DM [23]. Uyar et al., on the other hand, compared DR-positive patients to healthy controls and found that DR-positive patients have a higher rate of tortuous, bushy, and dilated capillaries, that there is a significant correlation between capillaroscopic findings and DR, and that NVC can detect microvascular changes in T2DM patients without clinically apparent retinopathy [(2)]

DR-positive patients had a higher rate of tortuous, ectatic, and large capillaries, bleeding regions, and areas of neo-angiogenesis than DR-negative patients, according to Bakirci S et al's study, which did not reach statistical significance.

According to a research by Barchetta et al., NVC was able to detect changes in nearly half of diabetic patients without retinopathy [(1)]

**Association between NFC changes and severity of DR**: The P value was found to be 0.410 which is not statistically significant hence stating there is no correlation between NFC changes and severity of DR. Table 24 and figure 22 represent the association between NFC changes and severity of DR.

Whereas, capillaroscopic characteristics such as tortuosity, bushy capillary, neoformation, and capillary ectasia were also considerably higher in patients with proliferative DR than in individuals with nonproliferative DR and without DR, according to a study by Uyar et al. Chang et al. compared 20 healthy controls to 35 diabetic patients (10 without DR, 10 with background DR, and 15 with proliferative DR). Tortuosity was the most common finding in the proliferative DR group (68 % )

**Correlation of Capillaroscopic Findings with HbA1c and DR:**

As there is no significant correlation bewtwwen NFC and DR, no correlation could be assessed with NFC, HbA1c And DR.

# CONCLUSION

The goal is to detect clinically severe retinopathy before vision is endangered by DR, which is the major cause of blindness. Early detection of people at risk of DR progression and treatments can help prevent vision loss and lower the costs of maintaining more advanced illness.

The goal of this study was to see if using NVC could aid in the early detection of DR. Several investigations have identified convoluted, cross-linked capillaries, microhemorrhagic, and avascular regions as typical capillaroscopic patterns in diabetic individuals who have NVC results, and there have been several research evaluating capillaroscopic findings in various conditions.

NFC (nailfold capillaroscopy) is a simple, noninvasive, safe, and effective diagnostic method for determining the microvascular anatomy of the nailfold. NFC has been utilised to investigate microvascular structure, particularly in rheumatic and extrarheumatic disorders. Any condition that affects the vascular structures can cause NFC results. As a result, it can be utilised to evaluate diabetic microvascular involvement in the nail fold capillaries.

The following conclusions were drawn from the study:

1. Our data have showed that there is a significant correlation with nailfold capillaroscopic changes and duration of type II diabetes mellitus and hence NFC can detect microvascular changes in T2DM patients without clinically apparent retinopathy.
2. In consistence to other investigations, Capillaroscopic findings including tortuosity, dilated capillary, and avascular area were significantly linked with a longer DM duration patients in our study.

3. The current study revealed that NFC score was positively correlated with level of HbA1c .NFC identified high frequencies of microcirculation abnormalities among subjects with higher HbA1c levels.
4. No statistically significant difference was found between capillaroscopic findings and DR- positivities in our study.
5. No statistically significant difference was found between capillaroscopic findings and severity of DR- positivities in our study.

Our observations show NFC changes appear to correlate with the duration of DM and HbA1c levels and hence NFC changes can possibly be early markers for the detection of microvascular involvement.

Further studies are required with appropriate size and study design to validate our observations.

## LIMITATIONS OF THE STUDY

- The desired number of subjects could not be enrolled because of the limited attendance to hospital due to the COVID-19 pandemic.

- The majority of the study population consisted of Fitzpatrick skin type 4 and 5 who had increased pigmentation of the nail fold which in some cases lead to hinderance to the visualization of the nail fold capillaries.

- Absence of controls.

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## ANNEXURES

### ETHICAL CLEARANCE CERTIFICATE

IEC/NO-131/2019
22-11-2019

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

**INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE**

The ethical committee of this college met on 13-11-2019 at 3-15 pm to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

**Title:** A hospital based cross Sectional study to determine the correlation between the nailfold capilloroscopy and retinal microvascular changes in type II Diabetes mellitus in a tertiary care centre

**Name of PG student:** Dr Poojita B S , Department of Dermatology,

**Name of Guide/Co-investigator:** Dr Keshavmurthy Adya, Associate Professor , Department of Dermatology,

DR RAGHVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103

**Following documents were placed before Ethical Committee for Scrutinization:**

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

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**B.L.D.E.U's SHRI B M PATIL**

**MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,**

**VIJAYAPURA-586 103**

**RESEARCH INFORMED CONSENT FORM**

**TITLE OF THE PROJECT:-** A HOSPITAL BASED CROSS SECTIONAL STUDY TO DETERMINE THE CORRELATION BETWEEN THE NAILFOLD CAPILLAROSCOPY AND RETINAL MICROVASCULAR CHANGES IN TYPE II DIABETES MELLITUS IN A TERTIARY CARE CENTRE

**PG GUIDE** **:-** DR. KESHAVMURTHY ADYA

**PG STUDENT** **:-** DR. POOJITA B S

**PURPOSE OF RESEARCH:**

I have been informed that this project will assess the correlation between the nailfold capillaroscopy and retinal microvascular changes in type II diabetes mellitus

**BENEFITS:**

I understand that my participation in this study will help the investigator to know the correlation of the nailfold capillaroscopy and changes in retinal microvascular in type II DM.

**PROCEDURE:-**

I understand that relevant history will be taken and I will undergo detailed clinical examination after which treatment will be given.

**RISK AND DISCOMFORTS:-**

I understand there is no risk involved and I will experience no discomfort during the clinical examination.

**CONFIDENTIALITY:-**

I understand that medical information produced by this study will become a part of my hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purposes no names will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, videotapes and hear the audiotapes before giving this permission.

**REQUEST FOR MORE INFORMATION:-**

I understand that I may ask more questions about the study at any time concerned. Dr. POOJITA BS is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which may influence my continued participation.

**REFUSAL OR WITHDRAWAL OF PARTICIPATION:-**

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that Dr Poojita BS may terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician, if this is appropriate.

**INJURY STATEMENT:-**

I understand that in the unlikely event of injury to me resulting directly from my participation in this study and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my participation in this study, I am not waiving any of my legal rights.

I have explained to (patient's / relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Investigator / P. G. Guide Date

I confirm that …….(Name of the PG guide / chief researcher) has explained to me the research, the study procedures that I undergo and the possible risks and discomforts as well as benefits that I may experience. I have read and I understand this consent form. Therefore, I agree to give my consent for my participation as a subject in this research project.

_____ _____

Participant / guardian Date

_____ _____

Witness to signature Date

**PROFORMA**

**Department of Dermatology, Venereology and Leprosy.**

**SCHEME OF CASE TAKING**

1. General information

Name: SL no:

Age:

Sex: Address:

Education:

Occupation: Contact no:

Out patient no: Date:

1. History

Duration of diabetes :

- General Physical Examination:

Weight: Pallor :

BP: Clubbing :

PR: Icterus :

Cyanosis :

Edema :

Lymphadenopathy:

Other findings:

- Systemic Examination

Cardiovascular system :

Respiratory system :

Central nervous system :

Abdominal examination :

HbA1C :

Ocular examination :

Nailfold capillaroscopy:

| | |
|---|---|
| Changes present | |
| No Changes | |

| ABNORMAL NAILFOLD CAPILLARY FINDINGS | |
|---|---|
| 1. Tortuosity | |
| 2. Neoangiogenesis | |
| 3. Microhemorrhage | |
| 4. Extravasation | |
| 5. Avascular area and neoformation | |
| 6. Bizarre capillary | |
| 7. Capillary ectasia | |
| 8. Megacapillary | |

| (DR POSITIVE) | (DR NEGATIVE) |
|---|---|
| | |

GRADE OF DR

| | |
|---|---|
| 1. No apparent retinopathy | |
| 2. Mild NPDR | |
| 3. Moderate NPDR | |
| 4. Severe NPDR | |
| 5. PDR | |

# KEY TO MASTER CHART

DR- Diabetic Retinopathy

NPDR- Non Proliferative Diabetic Retinopathy

PDR- Proliferative Diabetic Retinopathy

GPE- General Physical Examination

LE – Left eye

RE- Right eye

NFC – Nail fold capillaroscopy

SIMC- Senile immature cataract

B/L - Bilateral

| SL no | age I | year | sex | duration c | GPE | hbA1C | RE ocular | LE Ocular | NFC chang | tortusity | neoangio | microhem | extravasat | avascular | bizarre | cap ectasi | megacapil | DR | DR | | No appare | Mild NPDF | mod NPDF | sev NPDR | PDR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 65 | Male | 10 | Edema + | 6.5 | Normal | normal | absent | | | | | | | | | | positive | Positive | Moderate NPDR | | | present | | |
| 2 | 38 | Female | 1 | Normal | 9.3 | Normal | normal | absent | | | | | | | | | | positive | Positive | No appare | present | | | | |
| 3 | 68 | Male | 10 | Normal | 8.6 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 4 | 53 | Male | 1 | Normal | 6.5 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 5 | 51 | Male | 1 | Normal | 6.8 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 6 | 73 | Male | 2 | Normal | 6.9 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 7 | 53 | Female | 4 | Normal | 9.1 | mild conju | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 8 | 50 | Female | 6 | pallor + | 11.3 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 9 | 62 | Male | 10 | Normal | 6.5 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 10 | 62 | Female | 10 | Normal | 8.9 | Normal | cataract | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 11 | 37 | Male | 3 | Normal | 13.6 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 12 | 35 | Male | 1 | Normal | 9.1 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 13 | 42 | Male | 3 | pallor + | 9.1 | Normal | normal | present | present | | | | | | | | | negative | Negative | Negative | | | | | |
| 14 | 65 | Male | 10 | Normal | 9.3 | Normal | normal | **pigmented** | | | | | | | | | | positive | Positive | Mild NPDR | | present | | | |
| 15 | 58 | Male | 2 | pallor + | 12.3 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 16 | 65 | Male | 5 | Normal | 6.5 | SIMC | SIMC | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 17 | 55 | Male | 15 | Normal | 9.3 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 18 | 76 | Female | 5 | Normal | 8.9 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 19 | 38 | Male | 7 | Normal | 8.2 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 20 | 66 | Male | 5 | pallor + | 6.8 | Normal | normal | **pigmented** | | | | | | | | | | negative | Negative | Negative | | | | | |
| 21 | 68 | Female | 8 | pallor + | 8.9 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 22 | 65 | Female | 8 | Normal | 6.6 | Normal | SIMC | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 23 | 72 | Male | 1 | Normal | 13.8 | Normal | normal | **pigmented** | | | | | | | | | | negative | Negative | Negative | | | | | |
| 24 | 60 | Male | 7 | Normal | 12.7 | hazy medi | normal | present | present | | | | | | | | dilated lo | positive | Positive | Mild NPDR | | present | | | |
| 25 | 40 | Male | 6 | Normal | 14.8 | Normal | normal | present | present | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 26 | 55 | Male | 3 | pallor + | 6.8 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 27 | 60 | Female | 7 | Normal | 14.7 | hazy lens | hazy lens | present | present | | | | | present | | | | fundus-nc | Positive | Mild NPDR | | | | | |
| 28 | 68 | Male | 10 | Normal | 12.1 | Normal | normal | present | present | | | | | | | | | negative | Negative | Negative | | | | | |
| 29 | 38 | Female | 1 | Normal | 6.7 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 30 | 62 | Male | 2 | Normal | 7.8 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 31 | 70 | Female | 2 | pallor + | 12.1 | Normal | normal | present | present | | | | | | | | | positive | Positive | Mild NPDR | | mild | | | |
| 32 | 38 | Female | 1 | pallor + | 7.7 | Normal | normal | absent | | | | | | | | | | negative | Negative | Negative | | | | | |
| 33 | 56 | Male | 5 | Normal | 8.2 | Normal | normal | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 34 | 75 | Male | 1 | pallor + | 8.5 | SIMC | SIMC | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 35 | 59 | Male | 2 | Normal | 9.3 | SIMC | SIMC | present | | | | | | | | | dilated lo | negative | Negative | Negative | | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 36 | 68 | Male | 10 | Normal | 8.7 | Normal | normal | present | | | | | present | | | dilated lo | negative | Negative | Negative | | | | | |
| 37 | 61 | Female | 1 | Normal | 8.7 | Normal | normal | present | present | | | | | | | dilated lo | negative | Negative | Negative | | | | | |
| 38 | 57 | Male | 1 | Normal | 10.1 | Normal | normal | present | | | | | | | | dilated lo | positive | Positive | Moderate NPDR | | present | | | |
| 39 | 63 | Male | 1 | Normal | 6.6 | Normal | normal | absent | | | | | | | | | positive | Positive | Severe NPDR | | | present | | |
| 40 | 60 | Male | 2 | pallor + | 13.5 | Normal | normal | present | present | | | | present | | present | present | negative | Negative | Negative | | | | | |
| 41 | 78 | Male | 2 | Normal | 6.5 | Normal | normal | present | | | | | present | | | present | negative | Negative | Negative | | | | | |
| 42 | 48 | Male | 1 | Normal | 8.7 | Normal | normal | present | | | | | present | | | present | negative | Negative | Negative | | | | | |
| 43 | 61 | Male | 3 | B/L edem | 6.5 | Normal | normal | present | present | | | | present | | | present | negative | Negative | Negative | | | | | |
| 44 | 49 | Female | 4 | Normal | 6.9 | Normal | normal | present | present | | | | | | | present | negative | Negative | Negative | | | | | |
| 45 | 45 | Female | 1 | Normal | 8.1 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 46 | 67 | Male | 10 | Normal | 9.2 | Normal | normal | **pigmented** | | | | | | | | | negative | Negative | Negative | | | | | |
| 47 | 50 | Female | 15 | Normal | 9 | nasal ptye | nasal ptye | present | present | | | | | present | | present | negative | Negative | Negative | | | | | |
| 48 | 36 | Male | 1 | Normal | 7.4 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 49 | 51 | Male | 1 | pallor + | 6.9 | Normal | normal | present | | present | | | present | | | present | negative | Negative | Negative | | | | | |
| 50 | 38 | Female | 1 | Normal | 6.8 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 51 | 59 | Male | 5 | Normal | 10.1 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 52 | 65 | Female | 10 | Normal | 7.6 | Normal | normal | present | | | | | present | | | | negative | Negative | Negative | | | | | |
| 53 | 60 | Female | 2 | Normal | 12.1 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 54 | 18 | Male | 1 | pallor ,clu | 7.2 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 55 | 52 | Male | 2 | Normal | 8.1 | Normal | normal | present | present | | | | | | | present | negative | Negative | Negative | | | | | |
| 56 | 40 | Male | 3 | Normal | 6.2 | capsular c | capsular c | present | present | | | | present | | | | couldn't b | Positive | Mild NPDR | | | | | |
| 57 | 50 | Female | 1 | Normal | 7.9 | Normal | normal | present | | | | | | | | present | negative | Negative | Negative | | | | | |
| 58 | 65 | Male | 4 | Normal | 15 | Normal | normal | present | present | | | | | present, meandering | | present | positive | Positive | Mild NPDR | present | | | | |
| 59 | 60 | Male | 8 | Normal | 10.8 | Normal | normal | present | | | | | present | | | | negative | Negative | Negative | | | | | |
| 60 | 48 | Male | 6 | pallor + | 7.4 | Normal | normal | present | | | | | | | | present | negative | Negative | Negative | | | | | |
| 61 | 49 | Female | 2 | Normal | 7.5 | Normal | normal | present | | | | | present | | | | negative | Negative | Negative | | | | | |
| 62 | 52 | Female | 5 | Normal | 8.2 | Normal | normal | present | | | | | present | | | present | negative | Negative | Negative | | | | | |
| 63 | 56 | Female | 3 | Normal | 8.4 | Normal | SIMC | present | | | | | | | | present | negative | Negative | Negative | | | | | |
| 64 | 28 | Male | 6 | Normal | 7.2 | Normal | normal | present | present | | | | | | | present | negative | Negative | Negative | | | | | |
| 65 | 41 | Male | 1 | Normal | 6.8 | Normal | congestio | present | present | | | | | | | present | negative | Negative | Negative | | | | | |
| 66 | 40 | male | 1 | Normal | 6.7 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 67 | 60 | Male | 1 | Normal | 6.9 | Normal | normal | **pigmented** | | | | | | | | | negative | Negative | Negative | | | | | |
| 68 | 54 | Female | 6 | Normal | 7.3 | Normal | normal | present | present | | | | | | | | negative | Negative | Negative | | | | | |
| 69 | 55 | Male | 4 | Normal | 8.4 | ptyerigiun | ptyerigiun | absent | | | | | | | | | negative | Negative | Negative | | | | | |
| 70 | 48 | Male | 6 | Normal | 10.2 | Normal | normal | present | present | | | | | | | present | positive | Positive | Mild NPDR | present | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 71 | 52 | Male | 1 | Normal | 7.6 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | | |
| 72 | 55 | Female | 4 | pallor + | 9.8 | Normal | normal | present | present | | | | present | | | present | positive | Positive | Moderate NPDR | | present | | | | |
| 73 | 68 | Male | 1 | Normal | 8.8 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | | |
| 74 | 56 | Male | 3 | Normal | 8.4 | Normal | normal | present | | | | | present | | | present | negative | Negative | Negative | | | | | | |
| 75 | 48 | Male | 6 | Normal | 9.2 | Normal | normal | present | present | | | | present | | | | negative | Negative | Negative | | | | | | |
| 76 | 50 | Female | 3 | Normal | 7.2 | Normal | normal | present | | | | | | | | present | negative | Negative | Negative | | | | | | |
| 77 | 48 | Female | 1 | Normal | 6.8 | Normal | normal | absent | | | | | | | | | negative | Negative | Negative | | | | | | |
| 78 | 46 | Male | 3 | Normal | 6.7 | Normal | normal | absent | absent | | | | | | | | negative | Negative | Negative | | | | | | |
| 79 | 53 | Male | 3 | Normal | 8.4 | Normal | normal | present | present | | | | present | | | | negative | Negative | Negative | | | | | | |
| 80 | 65 | Female | 5 | pallor | 8.8 | Normal | normal | present | present | | | | | | | present | negative | Negative | Negative | | | | | | |
| 81 | 67 | Male | 4 | Normal | 9.4 | Normal | normal | present | present | | | | | | | | negative | Negative | Negative | | | | | | |
| 82 | 48 | Female | 3 | Normal | 10.8 | Normal | normal | present | present | | | | present | | | present | negative | Negative | Negative | | | | | | |