DISSERTATION ON

CORRELATION OF VASCULOPATHY IN NAIL FOLD WITH RETINOPATHY IN DIABETIC AND HYPERTENSIVE PATIENTS

Submitted to
The Tamil Nadu Dr. M.G.R. Medical University

In partial fulfillment of regulations for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH – I

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KILPAUK MEDICAL COLLEGE

CHENNAI – 10

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"CORRELATION OF VASCULOPATHY IN NAIL FOLD WITH RETINOPATHY IN DIABETIC AND HYPERTENSIVE PATIENTS"** is a bonafide work done by **Dr. KARTHIK.S.M.**, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under our guidance and supervision in partial fulfillment of the rules and regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D.Degree Branch I, (General Medicine)** during the Academic period from May 2010 to March 2013.

Prof.Dr.N.GUNASEKARAN,M.D.,D.T.C.D.,
Director and Superintendent,
Institute of Non-Communicable Diseases,
Professor and Head of Department,
Department of General Medicine,
Kilpauk Medical College,
Chennai – 10.

Prof.Dr. R.SABARATNAVEL, M.D.,
Chief -Medical Unit III,
Department of General Medicine,
Government Royapettah Hospital,
Chennai – 14.

Prof.Dr.P.RAMAKRISHNAN,M.D.,D.L.O.,
Dean,
Kilpauk Medical College,
Chennai – 10.

DECLARATION

I, solemnly declare that the dissertation entitled "**CORRELATION OF VASCULOPATHY IN NAIL FOLD WITH RETINOPATHY IN DIABETIC AND HYPERTENSIVE PATIENTS"** is done by me at Kilpauk Medical College, Chennai – 10 during May 2010 to March 2013 under the guidance and supervision of **Prof.Dr.R.SABARATNAVEL, M.D.,** to be submitted to **The Tamilnadu Dr.M.G.R.Medical University** towards the partial fulfillment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH – I.**

Place: Chennai
Date:

Dr. KARTHIK.S.M.,
Post Graduate Student,
M.D. General Medicine,
Department of General Medicine,
Kilpauk Medical College,
Chennai – 10.

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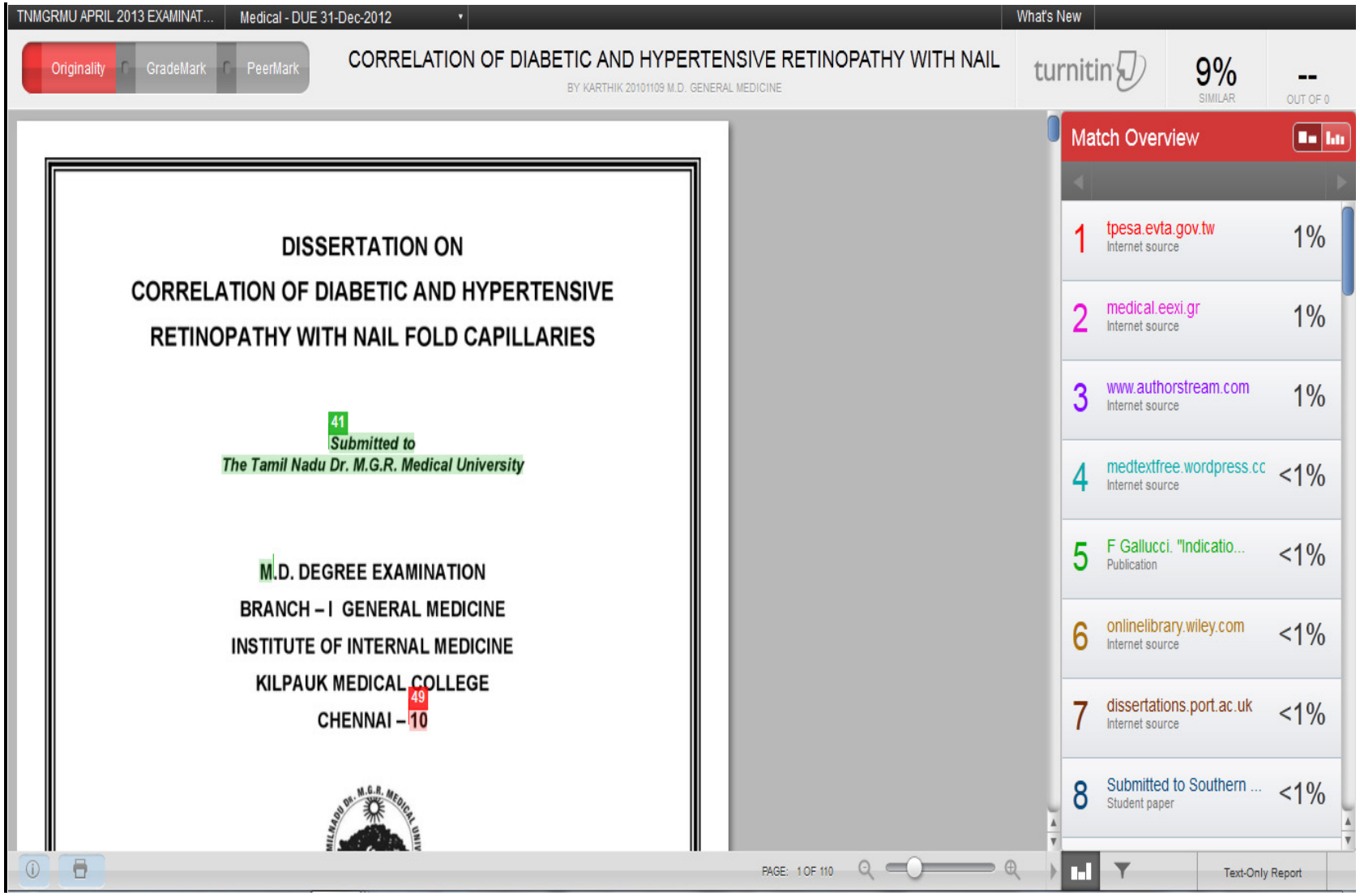
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ABSTRACT

INTRODUCTION

Diabetes and Hypertension are the commonest diseases that have major impact on morbidity and mortality. Early detection of end organ complications may reduce the morbidity substantially.

AIM OF THE STUDY

To investigate whether there is any correlation between nail fold capillaries and diabetic and hypertension retinopathy.

MATERIALS AND METHODS

Patients with diabetic and hypertensive retinopathy were recruited from outpatient department and medical wards. A total of 100 patients who met inclusion and exclusion criteria were inducted into the study. They were assigned randomly to attend dermatology or ophthalmic department where they were assessed regarding nail fold changes and fundal changes. The study and control group were then compared statistically.

OBSERVATIONS AND RESULTS

There was correlation between age and nail fold capillary changes in both diabetics ($p=0.020$) and hypertensives ($p=0.010$). While there was significant correlation between duration of diabetes and nail fold changes ($p=0.015$), degree of retinopathy had no relation with duration of diabetes ($p=0.590$). In hypertensives, duration of the disease had no correlation with

either nail fold capillary changes (p=0.238) or degree of retinopathy (p=0.450). In both diabetics (p=0.002) and hypertensives (p=0.001), there was highly significant correlation between retinopathy and nail fold changes.

CONCLUSION

In this study, there is significant correlation between degree of retinopathy and vasculopathy in nail fold in both diabetics and hypertensives. Hence, assessing the nail fold capillaries, pending further larger study, would help predict degree of retinopathy in both diseases.

CONTENTS

INTRODUCTION

If eyes can be compared to the input devices of the CPU the brain then fingers can well be called the finest output devices.

While vision has helped humans to conceive great missions and visions, fingers have helped in giving shape to the dreams to become the wonders in the field of science as well as art. Diabetes Mellitus and Hypertension unleash profound devastating effects in all the organs including eyes and fingers.

A hypothesis was conceived and evaluated to find a cheaper, easier, handy, quick and reliably reproducible diagnostic method for the correlation of the vasculopathy in nail fold capillaries with retinopathy in patients with diabetes mellitus and hypertension.

AIMS AND OBJECTIVES

The primary aim of this study was to evaluate whether there was any correlation between the degree of retinopathy in diabetes and hypertension and pattern of capillary changes in nail fold.

The secondary objectives were to

i. Identify specific pattern in nail fold that correlates with specific abnormality in fundus.
ii. Know any relation between duration of the diabetes and hypertension and nail fold changes.
iii. Possibly predict the renal involvement by nail fold examination.

REVIEW OF THE LITERATURE

Veins which by the thickening of their tunicles in the old restrict the passage of blood, and by this lack of nourishment destroy their life without any fever, the old coming to fail little by little in slow death.

—Leonardo da Vinci (1452–1519)

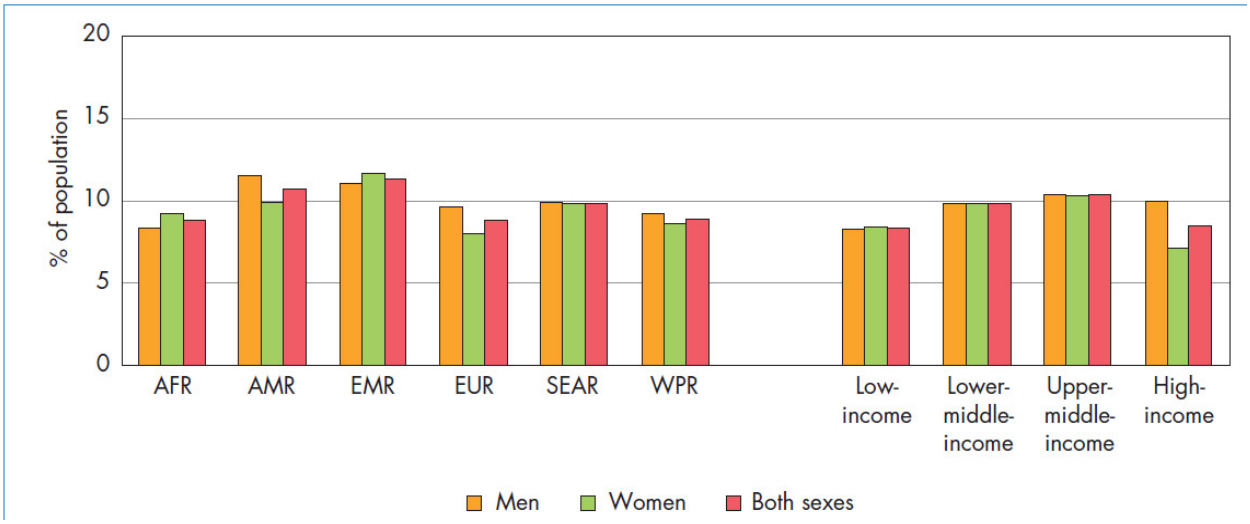
Impaired fasting glucose and impaired glucose tolerance are indicators of high risk categories for diabetes and cardiovascular disease development. Diabetics of certain age groups have twice the risk of stroke when compared to normal individuals. Throughout the world, diabetes is the primary cause of renal failure. When compared to non-diabetic individuals, lower limb amputations in diabetics are at least ten times common. Diabetes also leads the list in preventable blindness category in developed countries. Diabetics consume a minimum of thrice the health-care resources in comparison with non-diabetics and accounts up to 15% of health care budgets. Apart from all these, tuberculosis is three times common in people with diabetes.[1]

Throughout the world, hypertension directly and indirectly results in 7.5 million deaths (12.8% of the total) - which estimates to 57 million disability adjusted life years (DALY) (3.7% of total DALYs). The most important determinant of ischemic, hemorrhagic stroke and coronary heart disease is elevated blood pressure and there is a proportional increment of risk with raised blood pressure. From 115/75 mmHg onwards there is doubling of risk of coronary heart

disease for every 20/10 mmHg rise in blood pressure. Other complications include renal failure, heart failure, retinal disease, peripheral vascular disease. Achieving and maintaining the blood pressure at or below 140/90 mmHg would substantially reduce the cardiovascular and cerebrovascular complications.[1]

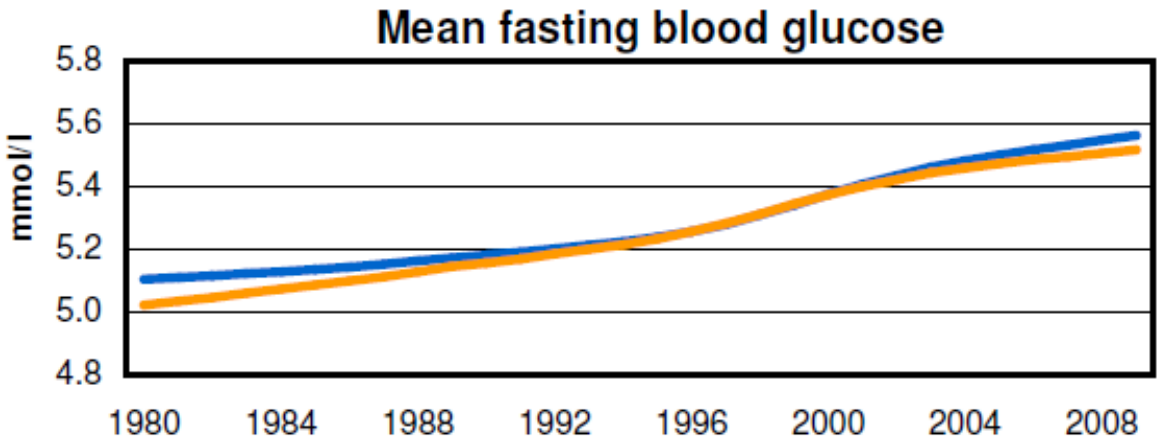
PREVALENCE

Age-standardized prevalence of diabetes in adults aged 25+ years, by WHO Region and World Bank income group, comparable estimates, 2008

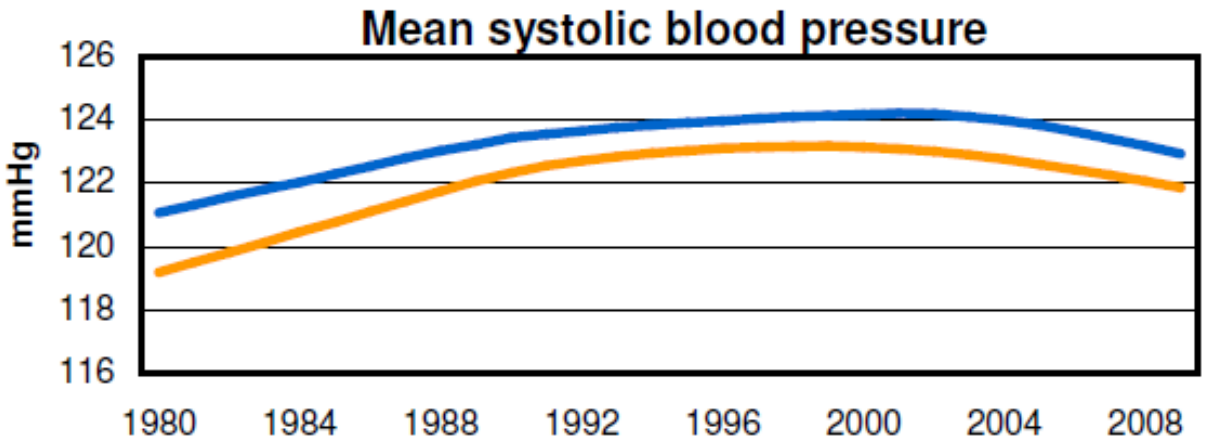


The varied prevalence of diabetes and hyperglycemic complications stem from the fact that, different organizations use different criteria for epidemiological surveys. In India, the estimated prevalence of diabetes is about 10.3% of population and approximately 10.8% are men and 9.67% are women.[2] In the city of Chennai approximate prevalence is 8%.There is no disparity between urban and rural population or between income groups. In most of the surveys

carried out until now, there is exclusion of these two entities – impaired fasting glucose and glucose tolerance, which if included would increase the burden exponentially!



In the statistical analysis, it is noted that high blood pressure was taken as systolic ≥ 140 mm Hg and diastolic ≥ 90 mm Hg and pre-hypertensive's were excluded. In India, the prevalence of hypertension in adults according to above stated definition was around 32.5% in 2008 with males being 33.2% and females 31.7%. Though the percentage of the total population with hypertension and/or uncontrolled hypertension saw a downward trend for two decades from 1980, the absolute number of people with hypertension has risen primarily due to increased longevity. Even in hypertensive's there were no gross changes in the proportion across income groups or area of residence.[1]



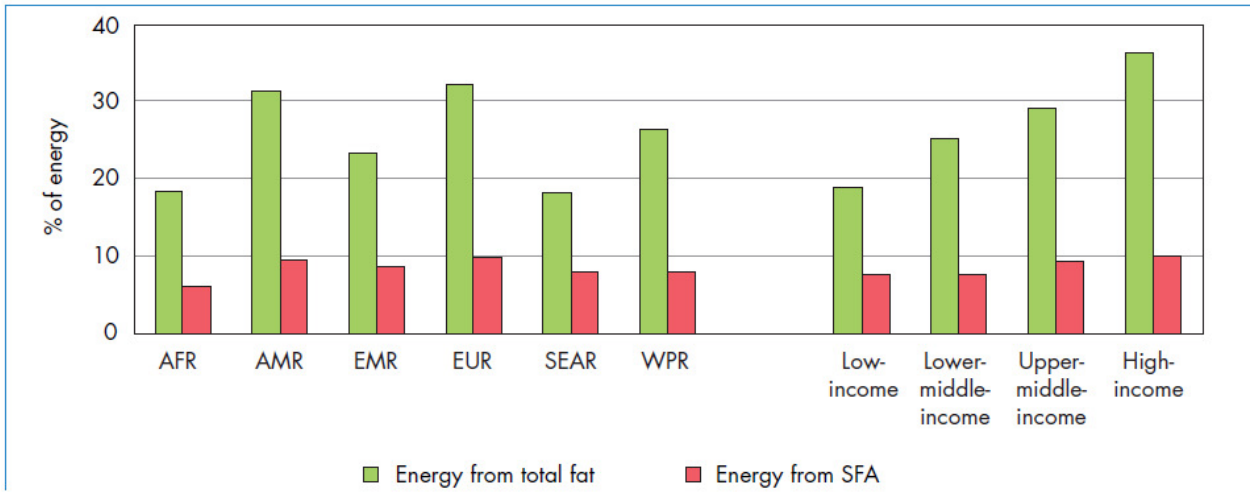
Age-standardized prevalence of raised blood pressure in adults aged 25+ years, by WHO Region and World Bank income group, comparable estimates, 2008

RISK FACTORS - Unhealthy diet

Consumption of high caloric, processed food promotes obesity and overweight when compared to low caloric fruits and vegetables. Dietary salt is an important determinant of cardiovascular risk and predictor of response to anti-hypertensive. A salt intake of ≤ 5 grams/person/day is recommended by World

Health Organization for reduction of cardiovascular complications. But the majority of people consume very high level of salt.[1] Saturated and trans fat elevate the cardiovascular risk profile. Mono saturated and/or polyunsaturated fat has substantially reduced the same risk. Current recommendation is high fiber diet, foods with low glycemic index, fruits and vegetables and consume whole-grain to minimize unhealthy fat consumption to <1% of total energy or eliminate it.[3]

Availability of total fat and saturated fatty acids (SFA) (as % dietary energy supply) for 2005–7, by WHO Region and World Bank income group[6]

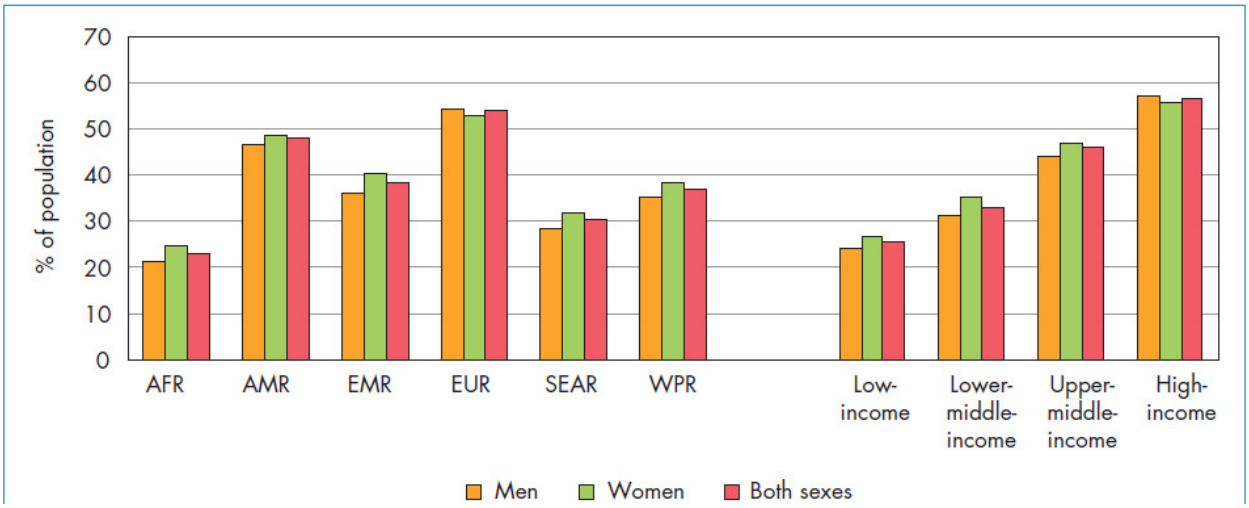


Cholesterol

A high level of cholesterol is an important predictor of cardiovascular mortality and increases the risk of stroke progressively. 10% reduction of total cholesterol values has resulted in 50% reduction in coronary artery disease and

acute coronary syndrome in middle aged men over next 5 years while in elderly aged men, the same amount of reduction in serum cholesterol has resulted approximately 20% reduction over subsequent 5 years.[1] Cholesterol levels measured early in life influence long-term cardiovascular risk. AHA recommends to reduce the saturated fat content to <7% of energy and cholesterol <300 mg, include oily fish, for a minimum of 2 days in a week and to minimize trans fat consumption to <1% of total energy or eliminate for cardiovascular disease prevention.[3]

Age-standardized prevalence of raised total cholesterol in adults aged 25+ years, by WHO Region and World Bank income group, comparable estimates, 2008

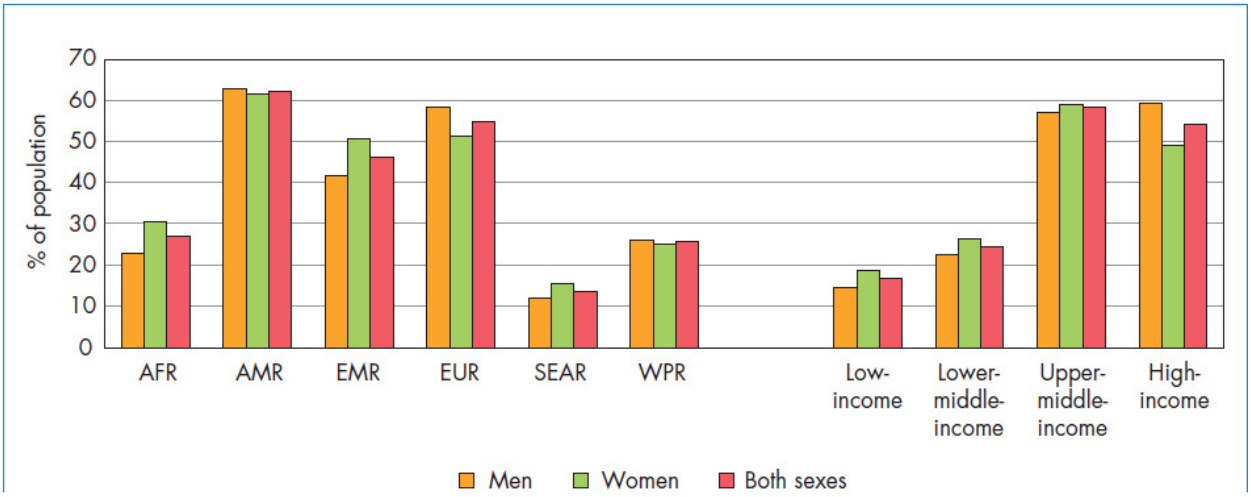


Obesity

Overweight and obesity leads not only to elevated blood pressure, dyslipidemia but also to insulin resistance. With progressive increase in body mass index (BMI), there is proportionate increase in risk of atherosclerotic coronary

artery disease, diabetes and stroke. Educational status has been correlated inversely with BMI and obesity in both sexes. With adoption of western culture in developing nations, there has been fast spreading of this pandemic of obesity. While upper middle class was noted to have high prevalence of obesity/overweight, lower middle class showed fastest rise in the incidence.[1] Specifically, metabolic syndrome is associated with a greater risk for diabetes mellitus, subclinical atherosclerosis and subsequent CV events, especially among individuals classified as low risk by the Framingham risk score .[3]

Age-standardized prevalence of overweight in adults aged 20+ years, by WHO Region and World Bank income group, comparable estimates, 2008

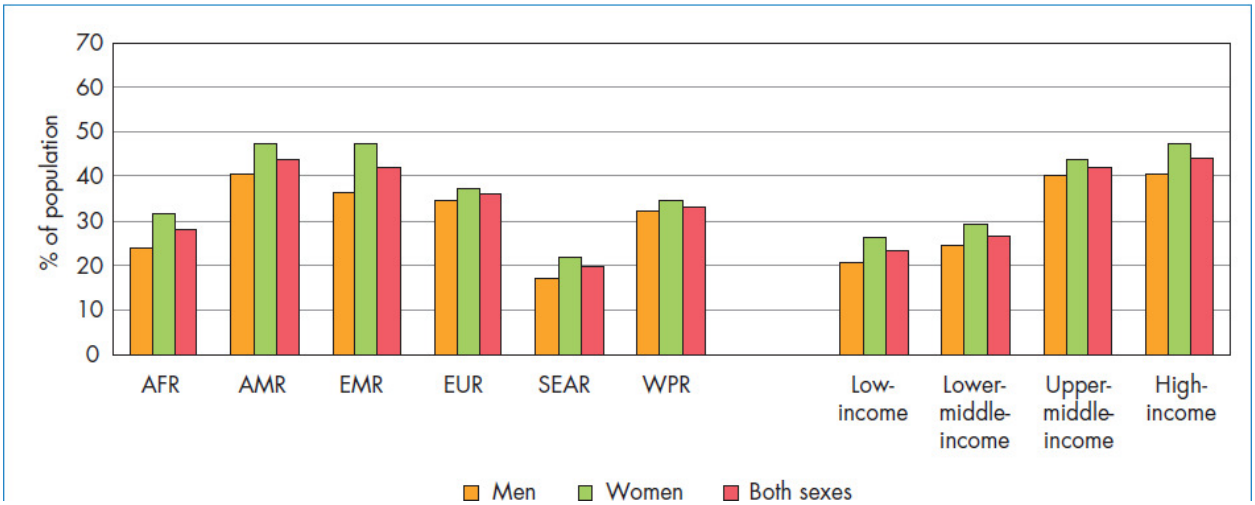


Physical inactivity

Globally and in India, men were more active than women. Every alternate woman in high income class was physically inactive. The reason for this disparity has been said to be due to the physical activity associated with low and

middle income group. Industrialization of work and home based remedies through internet has resulted in reduced activity in high income groups.[1] In both men and women, exercise levels achieved with as little as 30 minutes of walking daily provide major cardiovascular benefits and accumulated episodes of exercise, even if brief, have further demonstrated benefit, suggesting that risk reduction does not require prolonged vigorous work.[4] Aerobic exercise is associated with a reduction of mean blood pressure of 5 mm Hg in hypertensive participants, a level comparable with that of many drug interventions.[3]

Age-standardized prevalence of insufficient physical activity in adults aged 15+ years, by WHO Region and World Bank income group, comparable estimates, 2008



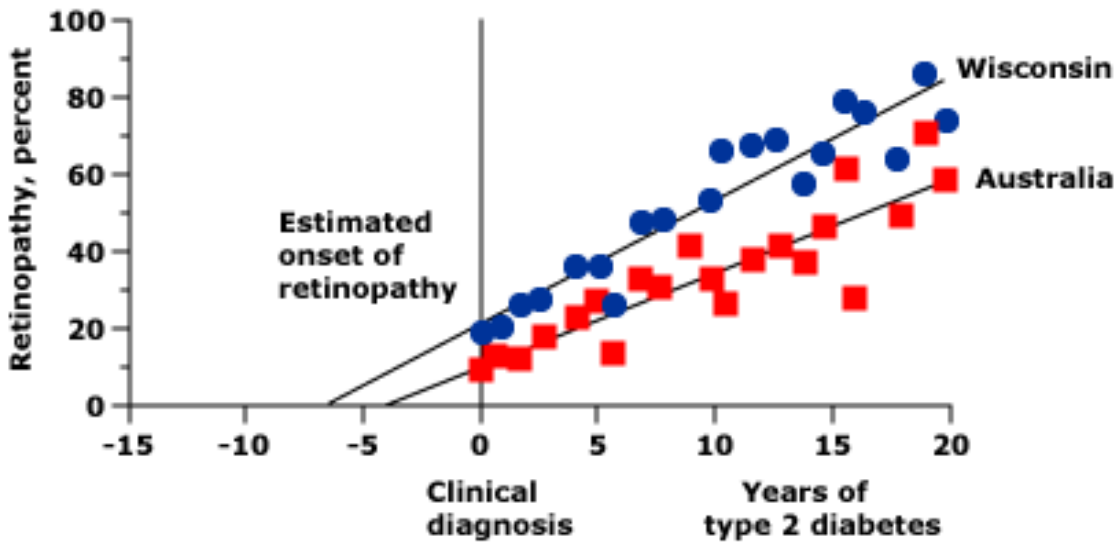
DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the primary cause of vision loss and visual impairment in young and economically productive age group. Visual loss from diabetic retinopathy, which is usually sudden, is due to retinal detachment,

hemorrhage due to neo-vascularisation, macular edema (edema and retinal thickening importantly in the macula) and neo-vascular glaucoma.

Majority of diabetic patients remain asymptomatic for a very long duration and by the time the diagnosis of retinopathy is made, it is usually very late for intervention. Hence, early detection during supposedly asymptomatic phase would result in reducing the morbidity of the disease. Even if found out during late stages some amount of vision could be salvageable if macula is not involved. This justifies periodic screening of DR to reduce complications subsequently.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy[5] is one of the most comprehensive studies documenting the natural history of retinal disease in diabetic patients. The reported prevalence of DR varies substantially between studies, even amongst contemporary diabetic populations in the same country, but is probably up to 40%. It is very common in type 1 diabetics than in type 2 and sight-threatening disease is present in up to 10%. Proliferative diabetic retinopathy (PDR) affects about 5–10% of diabetics; type 1 diabetics have an incidence of about 60% after 30 years.



Prevalence of DR at clinical diagnosis.[5]

Classification of diabetic retinopathy[6]

DR is of two major groups by the presence or absence of new vessels in any quadrant of retina: non-proliferative (NPDR) characterized by the absence of new vessels and proliferative (PDR) characterized by the presence of new vessels.

DR can be further sub classified according to severity and these sub classifications have been standardized globally for international comparisons and evaluation of treatment strategies. But what has to be remembered is the fact that

each patient has an independent rate of progression and therapies have to individualize in order to achieve the goal – to preserve vision.

Nonproliferative Diabetic Retinopathy (NPDR)

Very mild NPDR:

- ✓ Micro aneurysms only

Mild NPDR:

Any or all of:

- ✓ micro aneurysms,
- ✓ retinal haemorrhages,
- ✓ exudates,
- ✓ cotton wool spots, up to the level of moderate NPDR.

Moderate NPDR:

Any of the following:

- ✓ Severe retinal haemorrhages in 1–3 quadrants *or* mild intraretinal micro vascular abnormalities (IRMA),
- ✓ Significant venous beading can be present in no more than 1 quadrant,
- ✓ Cotton wool spots commonly present.

Severe NPDR:

One or more of:

- ✓ Severe hemorrhages in all 4 quadrants
- ✓ Significant venous beading in 2 or more quadrants
- ✓ Moderate IRMA in one or more quadrant

Very severe NPDR:

- ✓ Any two or more of criteria for severe NPDR

Proliferative Diabetic Retinopathy (PDR)

Mild to moderate PDR:

- ➢ New vessels on the disc (NVD) or new vessels elsewhere (NVE),
- ➢ Insufficient to meet the high-risk criteria

High-risk PDR:

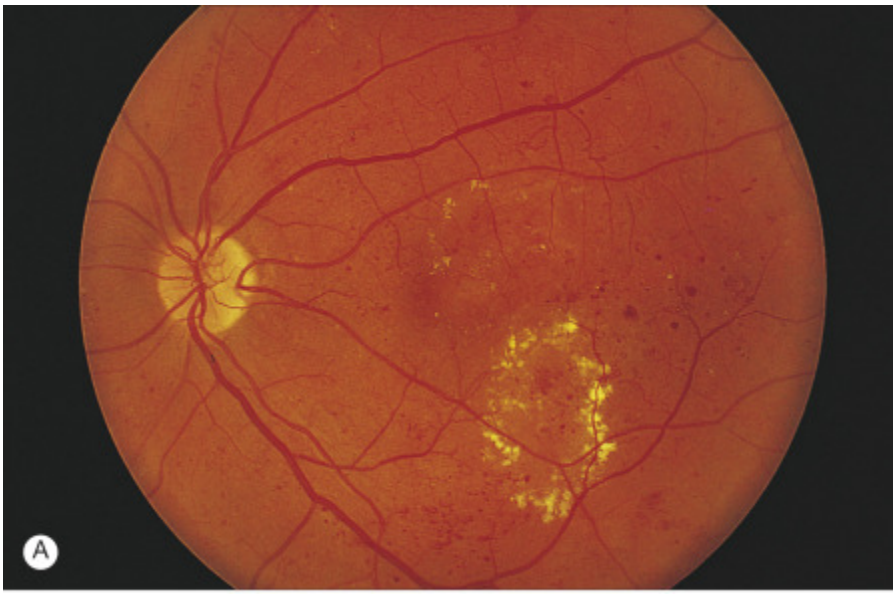
- ➢ New vessels on the disk ≥ 1/3-1/2 disk area OR
- ➢ New vessels on the disk with preretinal and/or vitreous hemorrhage OR
- ➢ New vessels elsewhere ≥ 1/2 disk area AND vitreous or preretinal hemorrhage

Severe PDR:

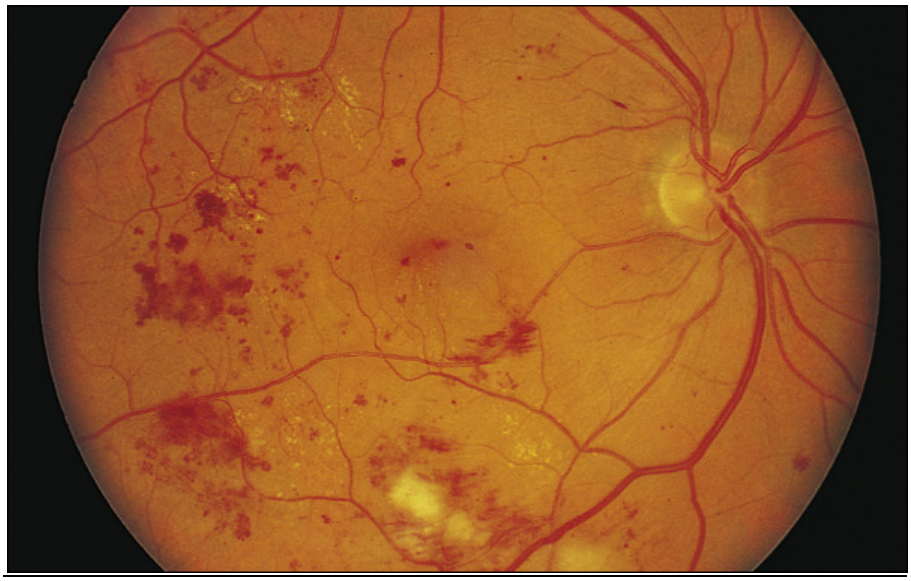
- ➢ Vitreous or preretinal hemorrhage OR
- ➢ Detachment of center of macula.

Clinically Significant Macular Edema (CSME)

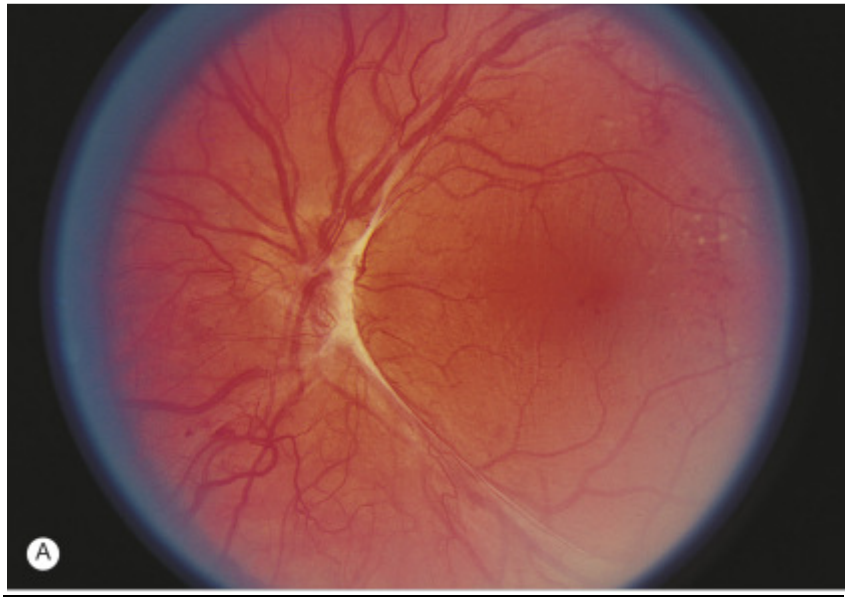
- Retinal thickening within 500 µm of the centre of the macula OR
- Exudates within 500 µm of the centre of the macula, if associated with retinal thickening OR
- Retinal thickening one disc area 1500 µm or larger, any part of which is within one disc diameter of the centre of the macula.



Mild NPDR[17]



Severe NPDR[17]



High risk PDR[17]

Ophthalmological consequences

Patients might have certain symptoms depending upon the type of eye problem (e.g., a falling curtain associated with a vitreous bleed, floaters during their resolution and reduced visual acuity that may or may not be recover associated with macular edema).

The development of clinical DR is complex and is the result of many interrelated factors, which cause two basic changes within the retinal vessels, namely: abnormal permeability and vascular occlusion with ischemia and subsequent neovascularization.

The retina is undoubtedly the most relentlessly active tissue amongst our tissue systems and is particularly susceptible to substrate imbalance or ischemia. Retinal pericytes and endothelial cells are the earliest to be lost in diabetes.[7] Retinal basement membrane getting thickened is another early change in DR, a finding similar to that seen in glomeruli. Hence, the loss of retinal pericytes and endothelial cells and the abnormality of basement membrane function are associated with micro aneurysm formation and enhanced endothelial permeability. Micro aneurysms (hyper cellular outpouchings of retinal capillaries with weakened walls owing in part to pericyte loss) and the leakage of lipid and proteinaceous material ("hard" exudates) are the initial clinical signs of diabetic retinopathy.[8]

The earliest stage of cell death and increased capillary permeability may be followed by cycles of renewal and further cell death, leading to progressive micro vascular obliteration and ischemic injury with the subsequent release of vasoproliferative factors (such as vascular endothelial growth factor (VEGF), erythropoietin, and many others) in the ischemic retinal area. These diffusible factors incite the development of new vessels (neovascularization) from the adjacent retinal vessels, in an abortive attempt to revascularize the diseased tissue.

Although PDR can be diagnosed by fundus examination, fluorescein angiography (a photographic study in which the transit of intravenously-injected fluorescein dye is recorded by photography with a special camera) is useful to document capillary nonperfusion and leakage from new blood vessels.

New vessels are categorized by four variables: presence; location; severity; and associated hemorrhagic activity. In PDR, the vessels initially grow along the plane of the retina, under the posterior hyaloid or outermost layer of the vitreous body, but as the vitreous gradually pulls away and detaches from the retina, the new vessels grow out from the retina plane and into the vitreous cavity. The consequences of neovascularization are extremely severe, because the fragile new vessels invariably rupture with the development of intraocular (usually vitreous) hemorrhage. Alternatively, they can create a fibro vascular overgrowth of

the retina that can cause distortion of the retina and retinal detachment, especially if forward growing vessels have attached to the posterior pole of the vitreous body and pull the retina anteriorly when they contract.

Capillary leakage is associated with retinal thickening and edema. If treatment is not initiated, loss of visual acuity can ensue if this occurs near the macula (macular edema). Macular edema is bound to occur at any stage of retinopathy. It manifests as an insidious onset of visual blurring of distant and near objects in patients with other evidence of retinopathy such as peri-macular micro aneurysms.

The yellow exudates typically seen in association with macular edema in diabetic retinopathy represent a residuum of more copious leakage that has been principally reabsorbed leaving behind the least soluble lipid components. This "circinate" exudate has an arc-like appearance because of demarcation of areas of damaged retinal vessels from those adjacent more normal areas that are capable of reabsorbing the edema. In advanced edema, widespread or diffuse leakage is present, and the macula becomes generally thickened and even cystic without the presence of visible yellow exudates, given that no normal vessels remain to resorb the leaked fluid. Patients with diffuse or cystoid edema will typically have the most profound visual decrease, yet the fundus exam may appear unremarkable unless

specialized techniques (fluorescein angiography and optical coherence tomography) are used.[9]

Neovascularisation occurring on the surface of iris is called rubeosis and may also occur in the anterior chamber. The latter change can obstruct the flow of aqueous humor from the ciliary body, leading to acute glaucoma.

Rationale for screening

As already described, majority of the patients remain asymptomatic until the terminal stage of vision loss either due to macular edema or proliferative DR. Through several clinical randomized trials, the efficacy of laser photocoagulation in delaying and/or prevention severe visual impairment has been established. But at the same time, one has to remember that reversing the visual loss is virtually impossible. Hence, it is very much justified in early screening and referring the patients before complete visual impairment ensues.

Methods of screening

Now arises an important question regarding the method of screening. For ages ophthalmoscope has been used by ophthalmologists but when a primary care physician performs fundus evaluation, he/she is liable to miss many findings. Seven field stereoscopic fundus photography is a gold standard method but

requires both an experienced technician and a doctor for its interpretation. If examined by an experienced optometrist, ophthalmic technician or ophthalmologist, ophthalmoscopy has favorable results in comparison with fundus photography.[10]

The presence of retinal photography allows for re examination by experts in case of doubt, record of the state of retinopathy and getting the opinion in less privileged areas. This method hardly takes about 10 – 15 minutes. Digital imaging (three fields) has an excellent specificity and sensitivity for diagnosing diabetic retinopathy when compared to fundus evaluation or gold standard seven field photography.[11] Currently fundus photographs are preserved in digital format that results in easy retrieval and comparison.

For the initial screening examination, evaluation by an ophthalmologist or optometrist who is experienced with diagnosing and treating diabetic retinopathy is required. In certain settings (e.g., when previous exams have been normal or when there is a shortage of eye care specialists), subsequent examinations can be done with retinal photographs if there is a trained photographer and reader. A comprehensive exam is required for follow-up of abnormalities detected on retinal photographs. These recommendations are consistent with ADA guidelines.[12]

Ophthalmologic examination schedule[13]

PATIENT GROUP	RECOMMENDED FIRST EXAMINATION	MINIMUM ROUTINE FOLLOW-UP
Type 1 diabetics	Within 5 years after diagnosis of diabetes once patient is age 10 years or older	Yearly
Type 2 diabetics	At time of diagnosis of diabetes	Yearly
Pregnant diabetics	Prior to conception and during first trimester. Counsel on the risk of development and/or progression of retinopathy.	Close follow-up throughout pregnancy and for one year postpartum.

HYPERTENSIVE RETINOPATHY

Hypertensive retinopathy implies the morphological and hemodynamic changes taking place in retina, choroid and optic nerve (the latter two during prolonged duration and/or severity of the disease) due to systemic arterial hypertension. Malignant hypertension is an extremely different entity with changes evident in all three above mentioned layers. But essential hypertension has predominant retinal changes due to slow evolution of pathology. With rising population afflicted with hypertension in both developed and developing countries, hypertensive retinopathy would be encountered on routine basis by primary care physicians.

Though measuring blood pressure is one of the easiest bedside procedure, many patients remain undiagnosed and hence inadequately treated. The

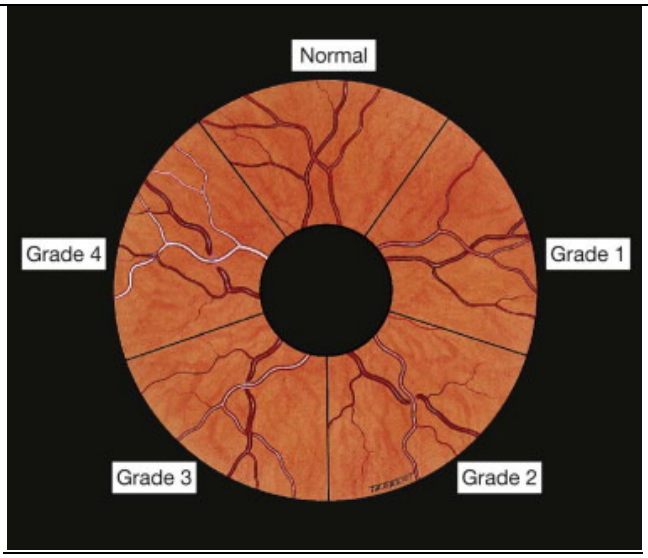
most significant confounding factor in the diagnosis of hypertensive retinopathy is the coexistent diabetes. In the Beaver Dam Eye Study,[14] that enrolled only patients with isolated hypertension without any other vascular disease, the total incidence of retinopathy in hypertensives was about 15%;of which only 8% showed the evidence of retinopathy, while 13% showed the evidence of diffuse arteriolar narrowing and 2% showed the evidence of peri discal arteriovenous nicking. Retrospectively, from the retinopathic findings, hypertension could be diagnosed only in 47 – 53% of patients. Most specific finding being arteriovenous nicking. Hence, the importance of recording blood pressure was reiterated. Retinopathic changes were obviously more common among those with poor blood pressure control.

Malignant hypertension – as the name suggests is the most dramatic form of hypertension characterized by a severe elevation of blood pressure, with the systolic pressure usually more than 200mmHg and/or the diastolic blood pressure usually greater than 140mmHg. Rather than the absolute value of the blood pressure what is important is the rate of rise of blood pressure, clinical findings and demonstration of end organ damage which could include cerebral, ocular, renal and cardiac injury. If left untreated, the patients would die within a duration of 6 months due to cardiac failure, stroke, renal failure and myocardial infarction.[15] Though there are several classification systems to stage hypertensive

retinopathy, the most widely acclaimed and the clinically more useful systems are the Keith-Wagener-Barker classification[16] and the Scheie classification. The Keith-Wagener-Barker scheme combines atherosclerosis with the clinical findings noted in chronic hypertension.

KEITH-WAGENER-BARKER CLASSIFICATION

Stage 1	Mild or moderate arteriolar narrowing or sclerosis
Stage 2	Moderate or severe arteriolar narrowing Focal and/or total arteriolar narrowing Light reflex enhancement, Arteriovenous changes
Stage 3	Narrowing of arterioles with constriction focally Edema, Cotton-wool spots Hemorrhage
Stage 4	As for stage 3, plus papilledema



Ophthalmic findings

Most of the patients with hypertensive retinopathic changes remain asymptomatic. The characteristic fundus findings are absence of the intra-vascular blood transparency, enhanced light reflex by arterioles, arteriolar tortuosity and arteriolar focal attenuation and post stenotic dilation. As already stated above, the *sine qua non* of chronic hypertensive retinopathy is arteriovenous changes.[17] The pathophysiology behind it is the common arteriovenous adventitial sheath that gets thickened with hypertensive changes. When the intercepting retinal vein is less prominent or if it entirely disappears on both sides of the artery, arteriovenous nicking is diagnosed. Sometimes the course of the vein becomes almost perpendicular to that of artery. When the sheath is constrictive, there is impediment of the blood flow and as a result post stenotic portion of the vein appears larger, darker and more tortuous. Apart from this, other signs of impedance to the blood flow are cotton-wool spots, macular edema and retinal hemorrhages. Development of veno-venous collaterals indicates that the obstruction is almost complete and long standing. Subsequently complications such as macro aneurysm formation, occlusive vascular disease and nonarteritic ischemic anterior optic neuropathy develop in the patients with chronic hypertension.[18]

The fundal picture in hypertensives is a direct consequence of absolute degree of blood pressure and rate of its rise.[17] The age of the patient also plays an important role in fundus findings. With ageing, there is some amount of replacement fibrosis (involutional) of the retinal vessels as a result of which, focal or diffuse constriction of arterioles never manifests which is not the case in young hypertensives. When there is superadded atherosclerosis, the retinal vessels become straight and exhibit some vasoconstriction without classical arteriovenous changes.[19] Almost always long duration of hypertension results in arteriosclerosis and accelerated atherosclerosis which is superimposed on ageing vessels – hence it can be difficult to recognize retinal changes exclusively due to hypertension.

Endogenous vasoconstrictors such as angiotensin II, epinephrine, and vasopressin mediate the hemodynamic changes of choroidopathy in systemic hypertension. Initially, there is delayed, discrete, patchy filling of choroidal vessels followed by leakage of fluorescein dye to sub retinal space from choroidal vessels.[20] Elschnig's spots are formed due to micro vascular occlusion resulting in atrophy of retinal pigment epithelium. In acute stages, angiographically, elschnig spots are visualized as tan white, punctate lesions due to disruption of blood-retinal barrier. Eventually, gradual accumulation of sub retinal fluid leads to formation of macular edema which is an important consequence of hypertensive choroidopathy. With increasing chronicity, there is mottled appearance of pigmentary epithelium

due to diffuse atrophy. Siegrist's streaks are horizontal pigmentation that is aligned along the choroidal arteries.[21] Ultra structurally, there is gradual attenuation of lumen of the arterioles due to thickening and sclerosis of the walls of the vessels. These changes are more appreciable with long duration of hypertension. However, it is important to note that the thickness of arterioles are much greater in choroidal vessels than in retinal vessels and they correlate with the systemic arteriolar changes.[22]

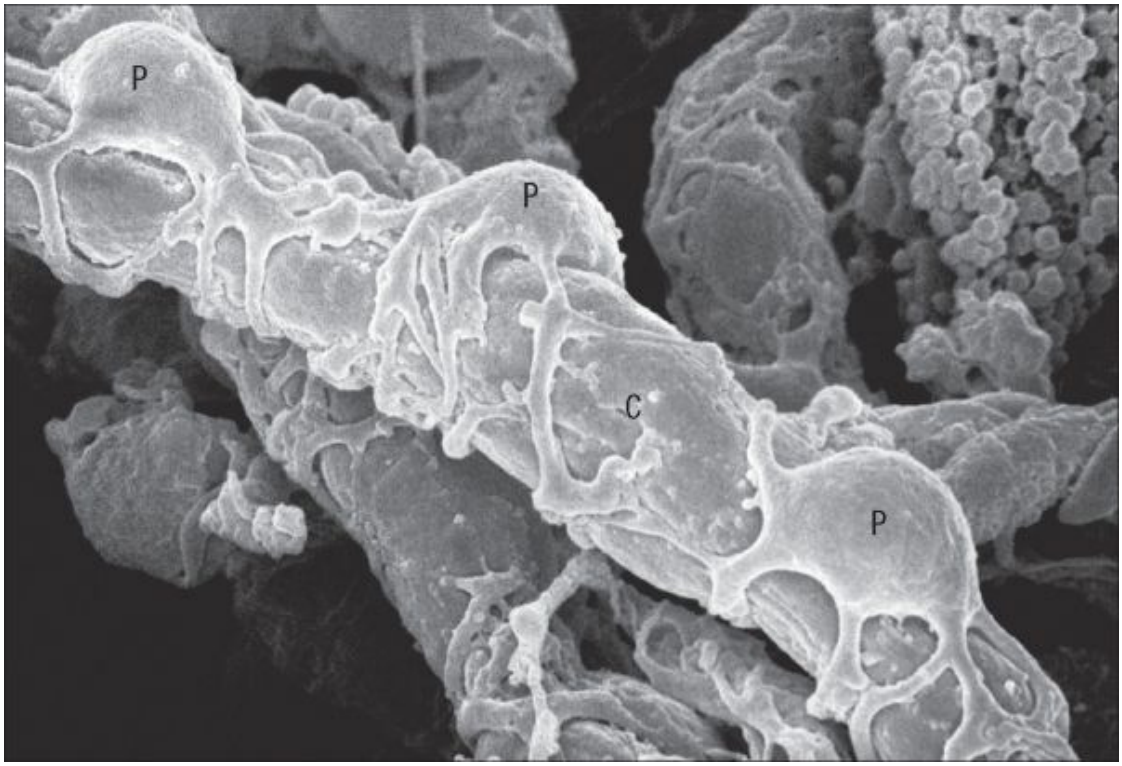
The presence of hypertensive retinopathy should serve as an additional stimulus to ensure adequate control of hypertension. With good control, retinopathy may regress, providing an easily obtained indicator of success. Hypertension increases the risk of a number of ocular diseases, with the most common being diabetic retinopathy. Other ocular diseases wherein hypertension serves as a risk factor include retinal venous and arterial occlusion, retinal emboli, retinal macro aneurysm, and anterior ischemic optic neuropathy.

Screening

From the prior discussions it is rather clear that hypertensive retinopathy is a clinical diagnosis in the background of elevated blood pressure. Fluorescein angiography, even if used, is not important in making the diagnosis. The characteristic angiographic findings described above are part of malignant and

not chronic hypertension. It is important to measure the blood pressure properly in order to rule out close differentials of hypertensive retinopathy.

ENDOTHELIUM



Capillaries and pericytes[23]

The endothelium which forms the most perplexing surface in our body is almost a complete barrier for blood products. However, there has been recent reappraisal of the fact that it is metabolically and functionally a more active surface and that it communicates with blood and tissues. One of the components of the virchow's triad - endothelial layer, balances the mechanisms of thrombogenesis

with anticoagulation. It also forms an integral part of immune system, regulates regional circulation, tone, growth and most importantly, in the current scenario plays a pivotal role in the origin, propagation and complication of atherogenesis. It is exposed to wide varieties of stresses and is subsequently influenced by the same.

Endothelial Cell Properties and Functions[24]

MAINTENANCE OF PERMEABILITY BARRIER
ELABORATION OF ANTICOAGULANT, ANTITHROMBOTIC, FIBRINOLYTIC REGULATORS
Prostacyclin Thrombomodulin Heparin-like molecules Plasminogen activator
ELABORATION OF PROTHROMBOTIC MOLECULES
Von Willebrand's factor Tissue factor Plasminogen activator inhibitor
EXTRACELLULAR MATRIX PRODUCTION (COLLAGEN, PROTEOGLYCANS)
MODULATION OF BLOOD FLOW AND VASCULAR REACTIVITY
Vasconstrictors: endothelin, ACE Vasodilators: NO, prostacyclin
REGULATION OF INFLAMMATION AND IMMUNITY
IL-1, IL-6, chemokines Adhesion molecules: VCAM-1, ICAM, E-selectin, P-selectin

Histocompatibility antigens
REGULATION OF CELL GROWTH
Growth stimulators: PDGF, CSF, FGF Growth inhibitors: heparin, TGF-β
OXIDATION OF LDL

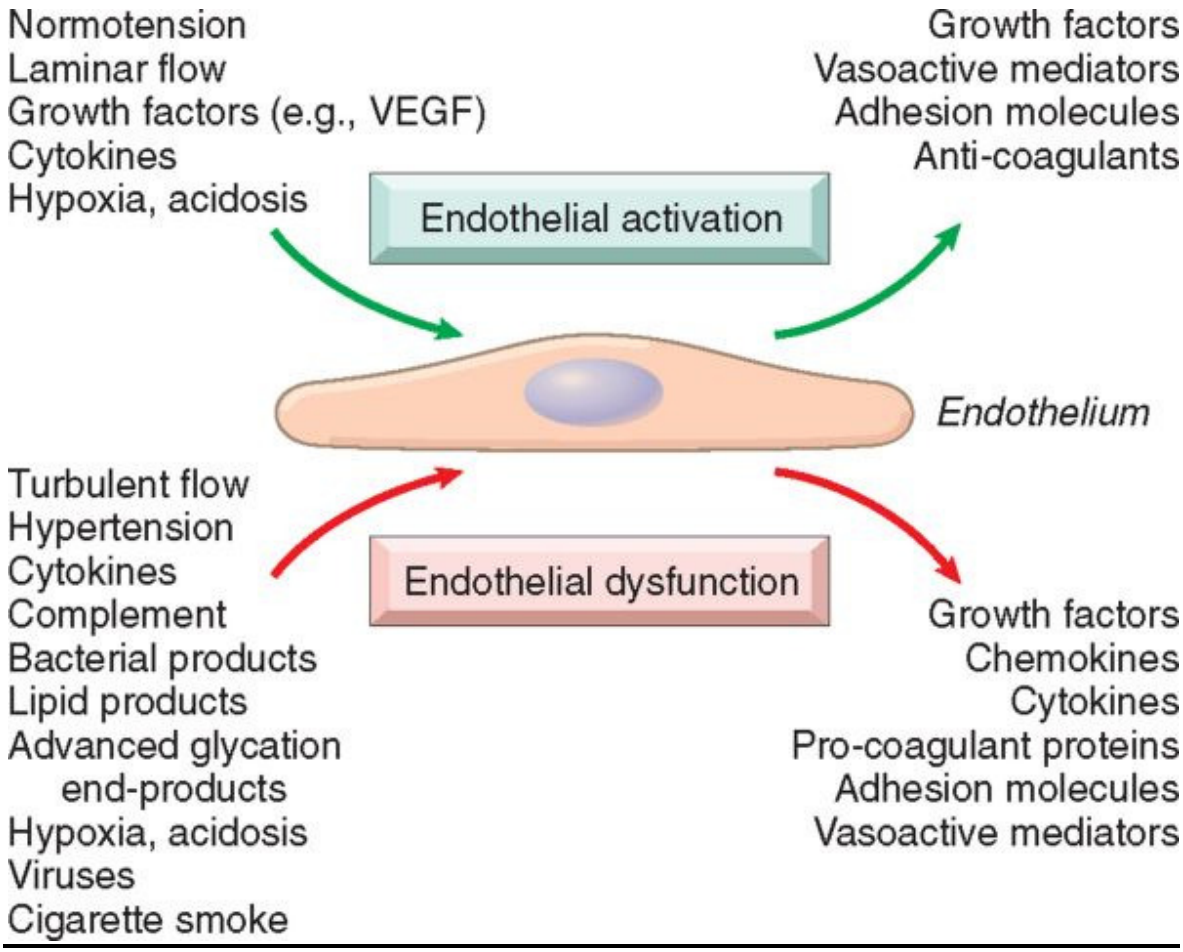
ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is a feature of innumerable disease conditions in addition to atherosclerosis which include cigarette smoking, heart failure, hypertension, hypercholesterolemia, aging and diabetes.Endothelial dysfunction is associated with high oxidative stress and fueled by oxidized low density lipoproteins (LDL), that causes adhesion, activation, and translocation of monocytes into the sub endothelial space, activation into macrophages, and subsequent transformation into foam cells. It has been observed that there is a definite correlation between plasma levels of adhesion molecules and endothelial dysfunction.[25]

The role of endothelial dysfunction (ED) in hypertension is as follows. In vitro studies demonstrate that normal endothelium responds to laminar and non turbulent flow by inducing antiatherogenic genes such as the antioxidant superoxide dismutase. Hemodynamic stress, hyperlipidemia, inflammation and other factors together result in dysfunctional endothelial cells culminating in an

altered pattern of gene expression, enhanced endothelial permeability and increased leukocyte adhesion. Arterioles show homogeneous, pink hyaline thickening with associated luminal narrowing. These changes stem from plasma protein leakage across injured endothelial cells and increased smooth muscle cell matrix synthesis in response to chronic hemodynamic stress. Although the vessels of elderly persons (either normo- or hypertensive) also frequently show hyaline arteriosclerosis, it is more generalized and severe in individuals with hypertension.[23]

In diabetes, the mechanism of ED is as follows. Hyperglycemia induced increased reducing equivalents (NADH and $FADH_2$) results in excessive pumping of protons across inner mitochondrial membrane and hence very high membrane potential. As a consequence of this, there is excessive inhibition of complex III which results in enhanced half life of intermediates coenzyme Q, that converts oxygen molecule to superoxide ion. As explained in forthcoming paragraphs, this central event results in four important pathogenic responses – increased aldose reductase activity, hexosamine formation, protein kinase-C activation and advanced glycation products formation.[26,27]



Endothelial cell responses to environmental stimuli [23]

CAPILLARIES – An overview

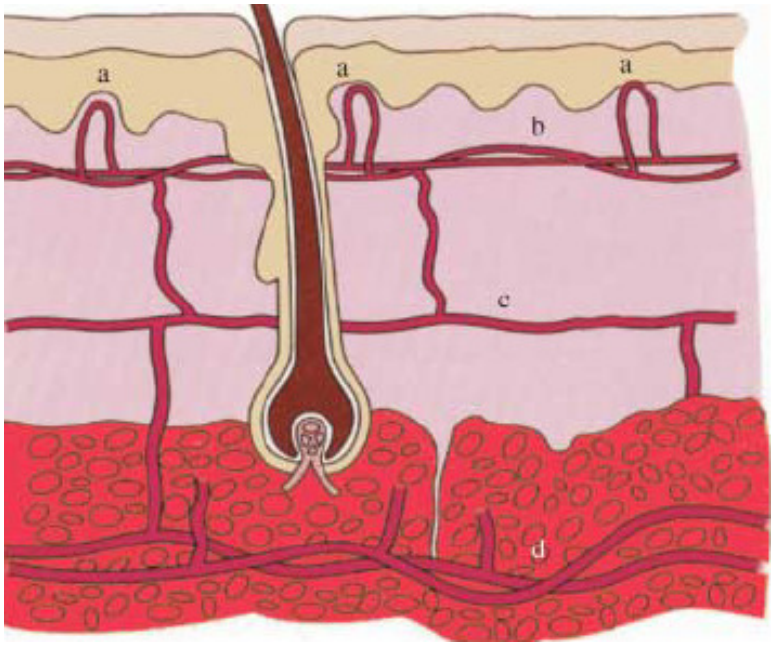
William Harvey was the first to describe capillaries as a tiny vessel which connects the venous and arterial tree.[28] The blood flow in these vessels was first visualized by Antonie van Leeuwenhoek.[29] Muller, in 1922, published a book in which, he displayed his findings of microscopic structure of skin capillaries as illustrations by artists.[30] The first measurement of capillary blood velocity was attempted by Basher in 1919.[31] A microscope combined with television system was

introduced by Zimmer and Demis in 1964 to study the dynamics of blood flow in human capillaries. A new microscopic system integrated with television was introduced in 1974 by Bollinger that helped to further clarify the capillary hemodynamics.[32] Carrier and Rehberg in 1923 measured capillary pressure by cannulation.[33] A paper on the methodology of measurement of capillary pressure and its influence by various physiological and drug interventions was published by Landis in 1930. In 1979, first dynamic pressure measurements were made by servonulling system.[34]

Only parts of the human body where there is direct access to the capillaries are – retina, conjunctiva, lips and most importantly nail fold. Of these, retinal manifestations of systemic diseases is well known and well studied for years. But here we focus upon nail fold capillaries with emphasis on anatomy and variation at different sites.

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

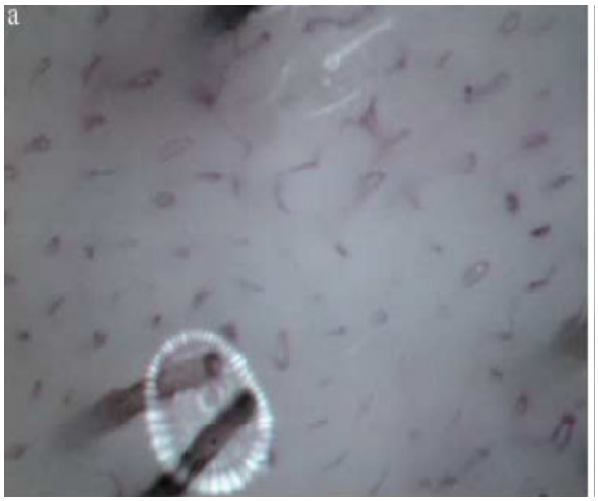
ridges. From these capillaries the blood is returned to venules that coalesce to intermediate plexuses. Thus, the cutaneous vasculature is rather elaborate and limited to the dermis, while the epidermis has no blood vessels.[35] Micro vessels in the papillary dermis range in size from 10 to 35 μm whereas those in the mid to deep dermis are 40-50 μm with an occasional arteriole as large as 100 μm being observed.[36]



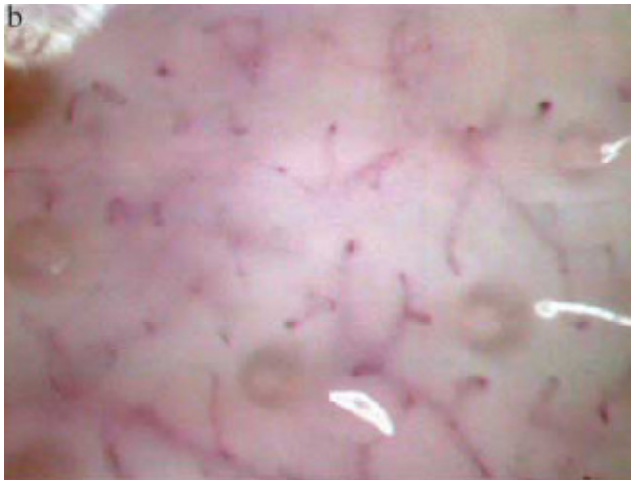
(a) Capillary loops, perpendicular to skin surface; (b) Horizontal capillary network; (c) deep dermal vascular plexus; (d) hypodermis vascular plexus.[45]

Different architectural frameworks of skin capillary network have been elaborated in detail. Parallel arrangement and regular meshes network – forehead, cheek ,chin, inner arm; parallel arrangement with irregular meshes

network- trunk, breast, arms, legs; perpendicular arrangement and regular dot line- fingertip, thenar & hypothenar eminence, tip of toes; perpendicular arrangement and irregular dot line- palm, back, foot, nipple; special pattern with parallel arrangement- fingernail, labial mucosa.[37]



Pattern in the palm[45]



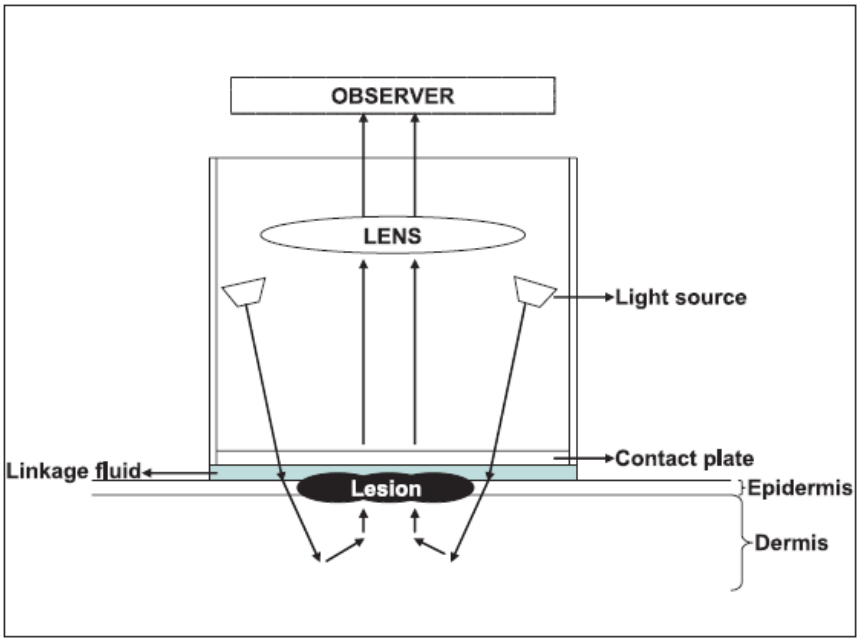
Pattern in the inner arm[45]

Basic physics of dermoscope and modern investigations

Natural light is reflected, scattered or absorbed by objects. Under normal conditions, most of the light is reflected by the skin surface because of the higher refractive index (RI) of the stratum corneum (1.55) compared with that of the air.

Reduction of the skin surface reflection allows the visualization of deeper epidermal and dermal structures. This reduction can be achieved by

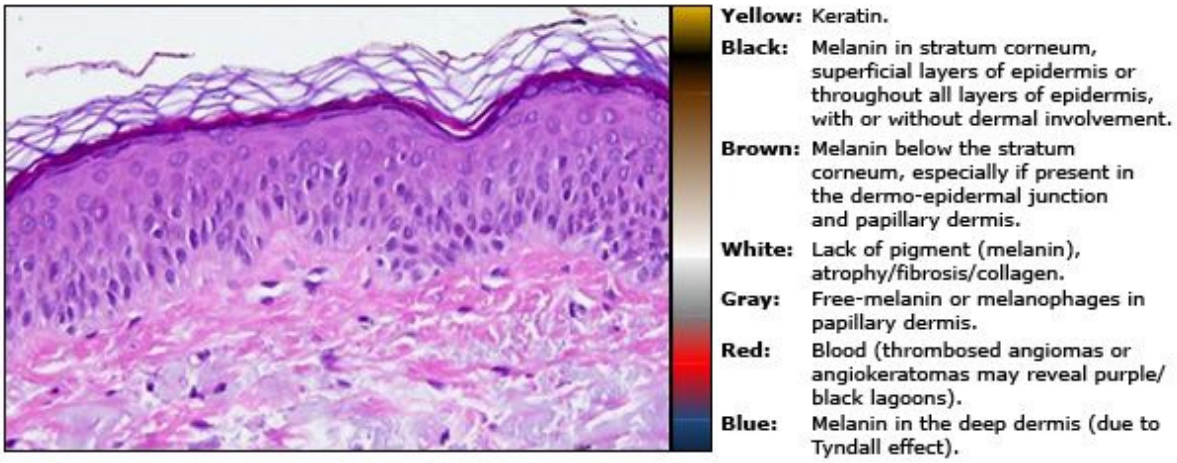
attaching a glass plate (RI: 1.52) to the stratum corneum (RI: 1.55) or by using a RI matched immersion fluid as an interface.[38]



Basic physics of dermoscope.[39]

Several immersion fluids have been used including water-soluble gels (ultrasound gel, cosmetic gels), water by itself, oils (mineral oil, immersion oil and olive oil) and alcohols (ethanol and isopropanol). Alcohols (in particular ethanol 70%) are the preferred immersion liquid due to their reduced viscosity, amphiphilic properties, disinfection properties and clarity of image. However, on some specific sites such as the mucosae and areas around the highly sensitive structures like eyes and nails, water-soluble gels are preferred over alcohol since

they are noncaustic and have higher viscosity.[38]

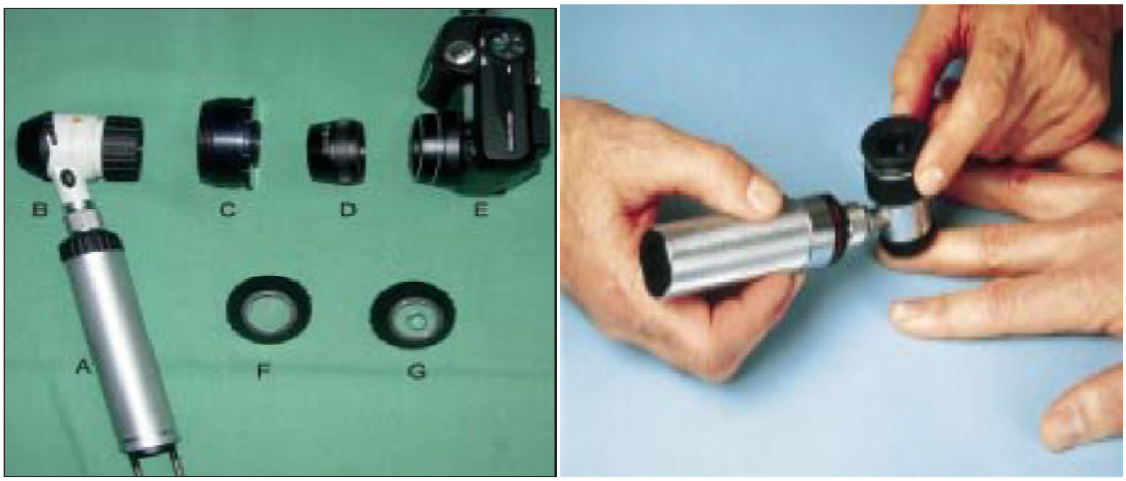


Colours seen under dermoscope.

Alternatively, reduction of the skin surface reflection can be obtained by using polarized light.[40] Polarized light dermoscopy utilizes two orthogonal filters in a process called cross-polarization. After reaching the skin surface, a part of the polarized light is reflected by the stratum corneum maintaining its polarization, whereas another part enters the skin and is scattered back from the deeper layers, losing its polarization. The light reflected by the skin surface, responsible for the glare of the skin, is blocked by the cross-polarized filter, since this light maintains its polarization. The backscattered light from the deeper layers passes through the cross-polarized filter since some of the polarized light has lost its angle of polarization. This makes the subsurface structures visible to the eye.[41,42]

The essential components of a dermoscope are:

- ✓ Achromatic lens: usually between 10 -20 times magnification.
- ✓ Inbuilt illuminating system: halogen bulb, LED light.
- ✓ Power supply: lithium ion battery, AA battery.



Hand held dermoscope.[39]

Three types of dermatoscopes are available:

- ➢ Contact and nonpolarized light
- ➢ Contact and polarized light
- ➢ Non contact and polarized light

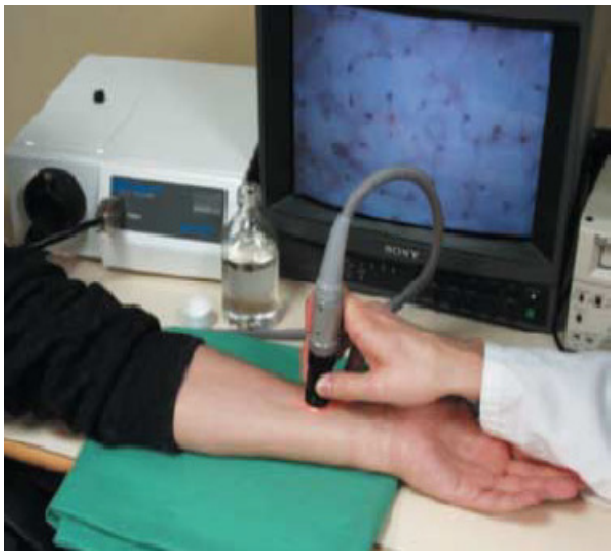
Noncontact dermoscopy can only be performed using polarized light. Although nonpolarized and polarized light dermoscopy are not equivalent, they appear to provide complementary information. For example, epidermal structures, such as comedo-like openings in seborrheic keratoses, are more conspicuous with

nonpolarized dermoscopy, whereas blood vessels, red color areas, white areas, or white shiny streaks are better visualized with polarized light dermoscopy.[43,44,45]

Noninvasive bioengineering techniques used to study skin microcirculation are -- *skin temperature measurements*; *direct photography* – ultraviolet, fluorescence, polarized light; *dynamic capillaroscopy with and without dye*- in vivo examination under high resolution microscope; *laser doppler flowmetry* - similar to doppler methods but uses laser light instead of sound waves*; isotope techniques* (^{133}Xenon); *transcutaneous measurement of partial oxygen pressure* - quantity of oxygen molecules transferred through skin; *iontophoresis* - single point probes; *laser doppler fluxmetry* ; *photopulse plethysmography*- pulsed light sequences detect the periodic variation of pressure in the tissue ; *infrared thermography*- works on the principle of heat transmission from the flowing column of blood; *colorimetry*- similar to pulse oximetry but with superior results.[46] "*CapiShape*" is a new method of evaluation of nail fold capillary hemodynamics that is semi automated method of analysis.[47]*High-resolution ultrasonography*- provides time gated tissue separation; *Magnetic resonance imaging*- variable proton concentration in each tissue gives different excitation pattern; *Optical coherence tomography*- interference pattern that resembles histological pattern of skin; *Terahertz pulse imaging*- particular wavelength excites intermolecular forces and differentiates various concentrations of water; *Profilometry* – mechanical,

laser, optical rely on reproduction of skin moulds by mathematical processing; *Confocal scanning laser microscopy*- allows visualization of skin in high resolution by different layers ; *Spectrophotometry and spectral imaging* – diuse reflectance, fluorescence , raman analyse the fluorophores emitted by skin are the other few techniques that are in research laboratories currently but may come into clinical use in future.[48]

Capillaroscope[46]



Contact videocapillaroscopy[46]

Office use of hand held dermoscope

Though traditional high magnifying dermatoscopes and videocapillaroscopes are very expensive and require good research setting for its existence, a simple ophthalmoscope with modification can serve us the purpose. Hand held dermoscope without modification can be used in clinical settings and in

resource poor settings for diagnosing scleroderma related disorders and the results are comparable with that of capillaroscope.[49] Also to note is the fact that ophthalmoscope and hand held dermoscope have similar performances for diagnostic ability in raynaud phenomenon evaluation.[50] With these evidences, it is evident that even an ophthalmoscope could be used for analyzing nail fold capillaries with immersion medium.

Uses of dermoscope

Main clinical uses of dermoscopy are in evaluation of melanoma, nevus, basal cell carcinoma, darier's disease, urticarial vasculitis, seborrheic keratosis, scabies, dermatofibroma, rosacea and erythrosis, venous insufficiency, psoriasis , peripheral arterial occlusive disease, keratosis, lichen planus, pediculosis, warts, in trichoscopy, hereditary hemorrhagic telangiectasia, connective tissue disorders, hair-shaft abnormalities, crohn's disease, acromegaly, psoriasis, hyperthyroidism, familial mediterranean fever, primary biliary cirrhosis and so on .[51,52,53,54] Of late it has been used to calculate the follicular density in the donor area before follicular unit hair transplantation and to monitor adverse effects of potent topical corticosteroids.

Normal and abnormal patterns of nail fold capillaries

The capillaries of the nail fold have autonomy and reflect precisely the haemodynamics of the microcirculation in the venules and arterioles. The arrangements of capillaries are in line with the surface of skin at the nail fold and hence both afferent and efferent portions of the capillary loop are easy to observe. The afferent (arterial) segment is thin and elongated (diameter of about 7 μm) when compared to that of efferent segments (diameter of about 9–10μm).[55]

In lower limb nail fold, the capillaries are perpendicular to the surface of skin and hence appear as dots or commas. The tonicity of the nail fold capillary bed can also be measured. The capillary density is around 30–50 per mm^2. As the terminal row of capillary loops is parallel to the skin surface both in fingers and toes, it is easier to visualize them. As one moves more proximal from fingers, orientation of capillaries changes from horizontal to oblique and vertical. For comparison purposes, Fagrell's classification is being used that characterizes the capillary structure using vital capillary microscopy.[56]

The usual capillary pattern is as follows:[57]

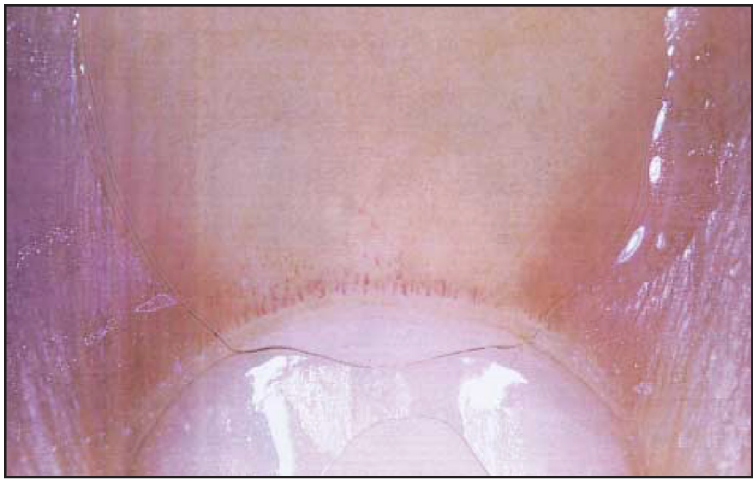
I. homogeneous and regular shape of small vessels;

II. one to three capillary vessels for each dermal papilla;

III. characteristic appearance resembling hairpin or upside down U;

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

V. mean length of the periungual capillary is approximately 400 μm.

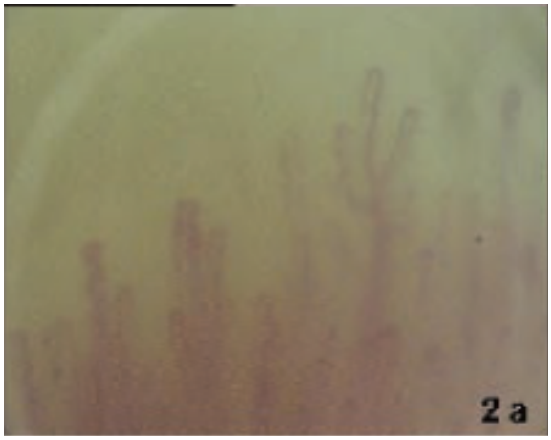


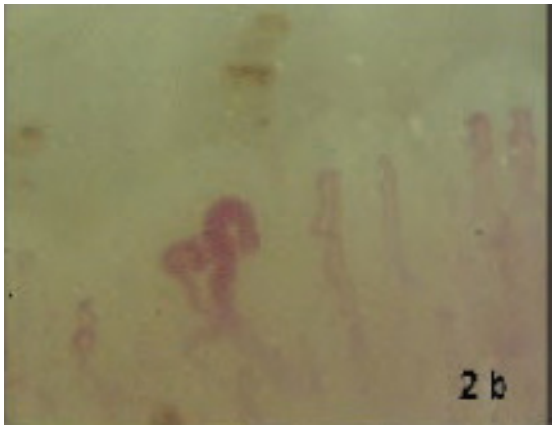
Normal nail fold capillaries

The main patterns of pathology are:[58,59,60]

- Architectural disarray – abnormal capillary distribution, inhomogeneous loops and misorientation.
- Enlarged loops- homogenous (mega capillaries if diameter > 50μm) or irregular.
- Capillary loss – avascular area if there are no capillaries for an area > 500 μm or loss of two contiguous capillaries.
- Angiogenesis – anastomosed loops ("ball" loops, "glomerular" loops, "bush" loops), branching ("trefoil" loops, "chandelier" loops, "antler" loops, "cactus" loops), tortuosity (single or multiple crossovers: "corkscrew" loops, "treble clef" loops, "8" loops).
- Micro bleeding/micro thrombosis.

- Reduced blood velocity.





Dilated homogenous capillary loops.[60] *Tortuous single loop.*[60]

Classification of capillary changes in the upper extremities - modified by Maricq et al.[61]

Type of nailfold capillaries	I Normal loops
	II Definitely enlarged capillaries with widening of arterial, apical and venous parts (micropools)
	III Giant capillaries
	IV Capillary haemorrhage
	V No blood field capillaries
Loss of nailfold capillaries	A No obvious avascular area
	B Small avascular areas
	C Moderate loss of capillaries
	D Extensive avascular zone along the edge

Micro vascular changes in other skin areas	O No significant capillaries
	U Enlarged and ramified capillaries surrounding ulcerations and atrophic white spots
	X Capillary telangiectasis
	Y Diffusely distributed enlarged capillaries
	Z Oedema of skin papilla

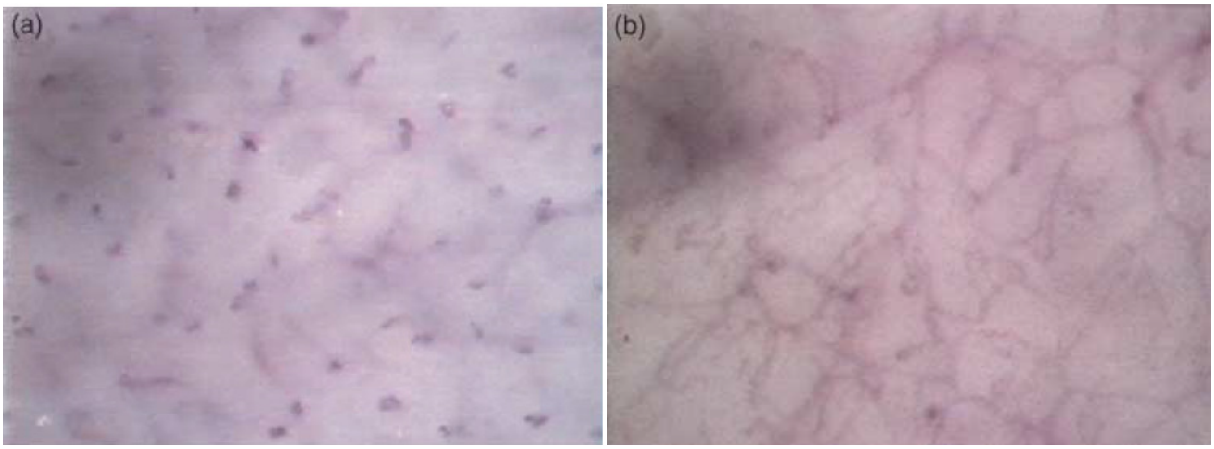
Traditional uses of nail fold capillaroscopy

It is useful in the characterization and diagnosis of micro vascular involvement in numerous rheumatic diseases especially systemic sclerosis and related disorders. Early pattern is recognized by giant capillaries, hemorrhages, loss of capillary density, regular architecture. In active disease, apart from regular pattern, ramifications may be present. Severe loss of capillaries, architecture signifies late pattern.[62,63] It is helpful to differentiate secondary forms of raynaud's disease from primary form.[64] Dermatomyositis, overlap syndromes, undifferentiated connective tissue diseases and mixed connective tissue disease have specific patterns in dermatoscopy.[65] Mixed cryoglobulinaemia, venous insufficiency, effects of topical cosmetics or chemical agents may also produce characteristic pattern changes.

Factors affecting nail fold patterns

With age, there is a gradual reduction of dermal capillary loop density and loss in dermal volume. The microvasculature in young individuals is regular with some horizontal vessels and orderly arranged capillary loops. It becomes irregular, twisted and thicker in older skins. Hence, visualization of parallel vasculature, papillary vascular plexus becomes easier as epidermis also undergoes atrophy. Similarly, dilated and thickened deep vessels may be seen. Elasticity of the arteries and endothelial function reduces with age. A higher prevalence of increase in capillary loop length (12% vs. 0%), arteriovenous sludge (36% vs 7%) and especially prominent sub papillary plexus (63% vs 12) was found in the geriatric group.[66]

Apart from age, other factors such as ethnicity, race and occupation impact the visualization of nail fold capillaries.



Forearm pattern in young age.[45] *Forearm pattern in old age.*[45]

Evidence of pattern changes in systemic disease

As diabetes and hypertension both are micro vascular diseases, we could expect the changes to occur throughout our body uniformly. Several articles have been published correlating various aspects of diabetes and hypertension to microvascular nail fold changes.

The mean functional capillary densities at rest, during post-occlusive hyperemia and during venous congestion responses were all significantly lower in patients with essential hypertension. The degree of rarefaction (reduced capillary density) ranges from 15.6% to 25.1%.[67] Capillary rarefaction supposedly co-exists rather than develop secondary to chronic hypertension. Hypertensives with reduced capillary density were younger and had a higher prevalence of hypertension in their family. A correlation between diastolic blood pressure and mean capillary density of fingers has also been found. The difference in capillary density was very highly significant only in the offspring of hypertensive parents.

The capillary loops are thin and elongated in the hypertensives as compared to the normotensives. In patients with isolated systolic hypertension, "flea bite" juxtacapillary micro hemorrhages, dilated and tortuous loops and arteriovenous sludge formation was noted probably due to atherosclerotic nature of the disease.[68] Reduced red blood cell velocity was found to be associated with capillary rarefaction and it does not revert with treatment. Although increases in

peripheral resistance develop in order to safeguard the capillaries from perturbation of systemic blood pressure, the compensatory increase in post capillary compliance and resistance probably contributes for the increase in the post capillary pressure and peripheral resistance.[69]

An observation was made in healthy individuals that higher fasting glucose correlates with capillary rarefaction and also results in high capillary blood flow velocity. There has been no correlation between insulin resistance and structural changes in dermal vessels.[70] In Type 1 diabetics, resting capillary blood velocity correlated inversely with capillary density. While, other studies have shown that mean capillary density had no correlation with age, gender or body mass.[71] The reduced capillary loop density in labial microcirculation, which was visualized with videocapillaroscope was correlating with peripheral microangiopathy. 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.[72]

In type 1 diabetics, capillary blood pressure was higher in patients with poor glycemic control and those with overt nephropathy.[73] In normoalbuminuric, normotensive type 2 diabetics, capillary pressure was normal. Dilated and slightly coiled loops, nodular apical elongation, reduced peak capillary

blood flow velocity and longer time to peak velocity of cutaneous microcirculation have been reported in both type 1 and type 2 diabetics with long standing disease.[74] These changes correlated with the degree of retinopathy, being more pronounced in the cases of proliferative retinopathy and also with the duration of disease but not with the glycemic control. In type 2 diabetics capillary apex diameter correlated with capillary peak velocity. Abnormal capillary perfusion was more marked in the feet than in the hands. Finger and toe dorsum skin blood flow in the patients with retinopathy were significantly lower than in patients without retinopathy. Proteinuria was associated with reduced skin blood flow at the toe dorsum.[75] Width of capillaries and arterial limb diameter correlated inversely with duration of the disease. “Shoal of fish” and “elephant nose” appearances have been documented in diabetes. It has been attributed to progressive loop enlargement leading upto five times of increase as to normal.

Scientific basis of alteration of nail fold capillaries

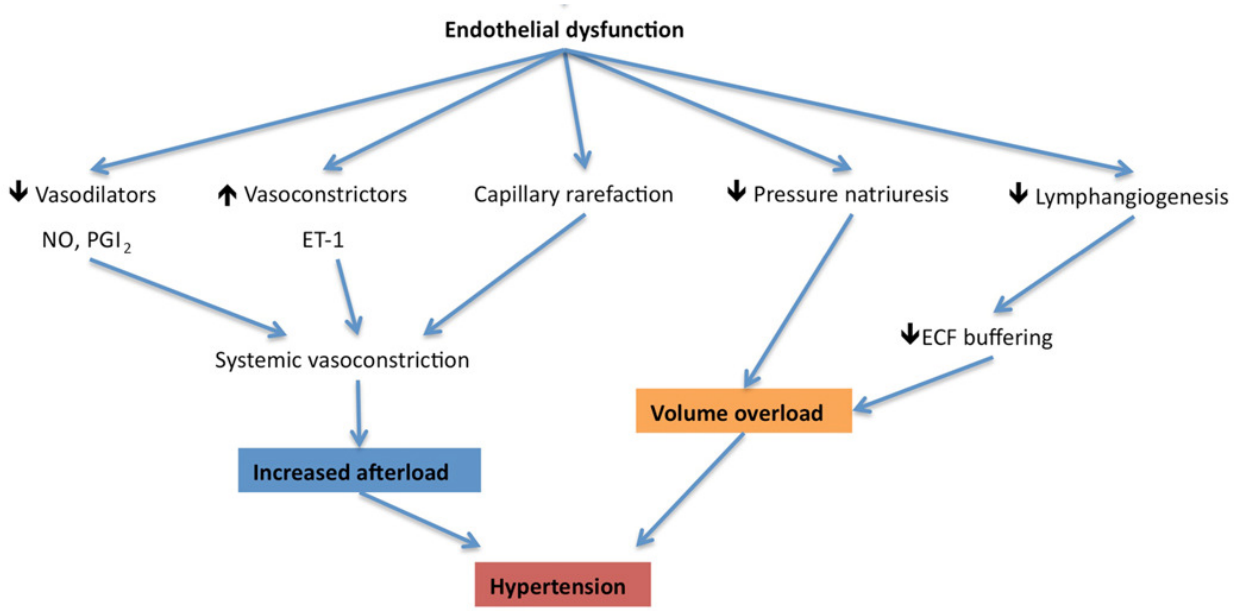
Capillary rarefaction in hypertension has been attributed to as the cause rather than the effect of hypertension because it was seen in people with risk factors of hypertension (without its development) and there was no evidence of any other organ dysfunction associated with it. Reduced capillary number as observed in people with elevated blood pressure may be due to maintenance of increased

peripheral vascular resistance.[76] As a result there is reduction in vessels that contribute to tissue exchange and naturally there is reduced recruitment of capillaries manifested as capillary rarefaction. VEGF polymorphisms probably accounts for some of the genetic predisposition in such patients.

It has also been proposed that the reduced capillary density in hypertensives is due to abnormal angiogenesis especially in young who have higher diastolic blood pressure. Anatomical reduction of capillaries[77] leads to reduced capillary surface area for diffusion of oxygen and nutrients resulting in increased distance between target cells and vessels. As a result of this ischemia, there is enhanced platelet activation and inflammatory changes.[78] These interactions cause ADP release by erythrocyte, small-vessel occlusion and erythrocyte sludging which activates platelets and leucocytes and maintains a vicious circle of interactions. Increased blood viscosity resulting in higher venous resistance in such patients leads to micro vascular flow abnormalities and inversion phenomenon further terminating in increased peripheral arterial resistance.[79]

It was already proposed that people with hypertension are born with low birth weight. Cohorts were followed up for several decades and numerous reports supporting this hypothesis stemmed up. Hence, people with low birth weight, as a result of compensatory catch-up overgrowth, tend to be obese but the

capillaries and vessels do not compensate that fast leading on to relative microcirculatory deficiency state.



This alternative explanation for capillary rarefaction was put forward in late 1980's by Barker et al.[80] Low birth weight not only predisposes such a risk but there has also been theories stating reduced number of nephrons in both kidneys at birth. As a result of this, people are at risk of chronic kidney disease at an early age when compared to normal. After appropriate statistical adjustments, the estimate was a 0.6 mmHg lower blood pressure per one kg higher birth weight. The conclusion was, "Claims of a strong inverse association between birth weight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular results, and inappropriate adjustment for current weight and for confounding factors. These findings suggest that birth weight is of

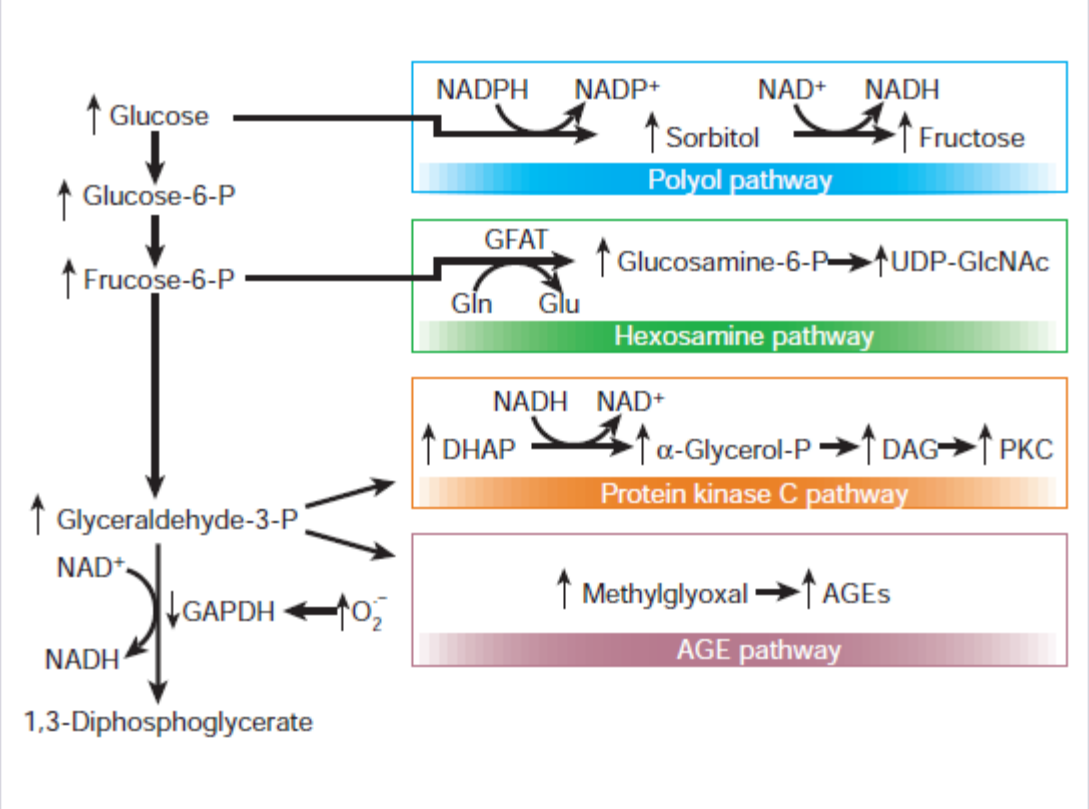
little relevance to blood pressure levels in later life."[81] Support for this conclusion comes from a large cohort study in which higher newborn and maternal weight were stronger predictors of adult blood pressure than low birth weight.[82]

Insulin causes vasodilatation in dermal vessels in normal individuals and before onset of insulin resistance in diabetics, through endothelium dependent and independent pathways. As a result of this there is recruitment of capillaries and direct alteration in vasomotion resulting in increased capillary blood flow.[83] The nerve axon reflex, which requires intact autonomic nervous system, accounts for 36% of the total acetylcholine induced vasodilatation in healthy individuals.

Diabetic microangiopathy results in the normal venoarteriolar reflex loss that normally causes reduction in arterial blood inflow, enhanced precapillary constriction, reduction of excessive capillary pressure development.[84] The loss of auto regulation and ensuing elevation in blood flow raises the shear stress on the blood vessels, which may be a stimulus for the production of vasoactive substances, vascular leakage and inflammation.

Micro vascular vasoreactivity is reduced due to endothelial dysfunction (ED). While both type 1 and 2 diabetics have a reduced endothelium-dependent response to acetylcholine, only type 2 patients have reduced endothelium-independent sodium nitroprusside response. ED is linked to impaired recruitment of capillaries during transient occlusion of arteries.[85] While fasting hyperglycemia

is associated with ED, insulin resistance is not. In diabetics, there is proportional reduction in capillary diffusion of nutrients but increased arteriovenous shunting. [86] sE- selectin (soluble form of E-selectin) is a marker of endothelial activation and angiogenesis. Similarly, IL-18 is a proinflammatory cytokine involved in angiogenesis, β cell destruction and arteriosclerosis. Both sE-selectin and IL-18 were found to be increased in type 1 diabetics compared to controls and such diabetics had significant nail fold capillary changes.[87]



Potential mechanism by which hyperglycaemia-induced mitochondrial superoxide overproduction activates four pathways of hyperglycaemic damage.[88]

Excess glucose shunts glycolytic intermediates into the hexosamine pathway, producing uridine diphosphate-N-acetyl glucosamine, the one which modifies transcription factors essential for normal cell function. Increased metabolites through the hexosamine pathway results in cellular damage and enhanced oxidative stress.[88]

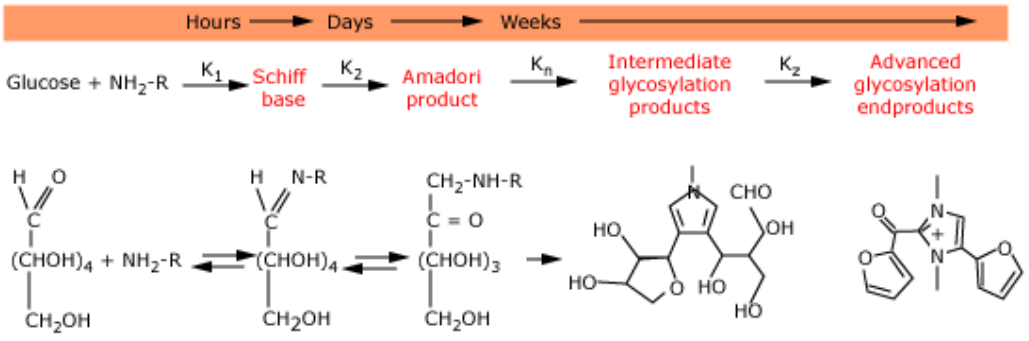
Glucose that enters the normal cells is metabolized partially through the enzyme aldose reductase to sorbitol, which is more common in chronic hyperglycemia. Sorbitol accumulation inside the cells results in reduced supply of NADPH, elevation of the absolute cellular osmolality, a reduction in intracellular myoinositol levels, altered Na/K-ATPase activity, impaired phosphatidylinositol metabolism, increased prostaglandin production, and alterations in the activity of protein kinase C isoforms, all of which result in abnormal cellular metabolism and enhances oxidative stress to the cells.[89]

Hyperglycemia-induced protein kinase-C (PKC) activation appears to contribute to endothelial dysfunction by increasing expression of vascular endothelium growth factor (VEGF), thromboxane and endothelin, and decreasing the levels of nitric oxide and prostacyclin resulting in increased vasoconstriction and permeability. Extracellular matrix synthesis, fibrosis, dysregulation of cytokines and monocyte activation and impaired insulin-stimulated glucose transport in muscle may all result from PKC activation.[90,91]

In chronic hyperglycemia, a part of the excess glucose combines reversibly and nonenzymatically with available free amino acids and tissue proteins forming early glycosylation products. These products form advanced glycosylation end products (AGEs) via an Amadori rearrangement which remains irreversible.

Serum AGE concentrations are elevated in diabetics and as a result it gets accumulated in tissues where it cross links the collagen in the interstitium, whereby it initiates micro vascular complications. Also to note is the fact that the interaction of AGEs with their receptor generates reactive oxygen species and subsequently vascular inflammation.[92]

Formation of advanced glycosylation end products



Adapted from Bucala, R, Vlassara, H, , Drug Development Research 1994; 32:77.

Growth factors promote the growth of new blood vessels from adjacent vessels in an abortive attempt to revascularize the diseased tissue. Studies in

experimental models have shown that neovascularization is due to the interaction between VEGF and insulin like growth factor-1 (IGF-1).

Nerve axon reflex contributes to only to 20% of endothelial vasodilatation in diabetics with neuropathy and peripheral disease, 8% in diabetic neuropathic patients and 5% in diabetics with charcot joint. This contributes to loss of venoarterial reflex and to impaired vasoreactivity with metabolic demands.[83]

Before capillary dilation develops, abnormal fluorescein diffusion in nail fold capillaries has been found. This reiterates that there was a preexisting vascular dysfunction prior to structural changes.[83]

Unifying both topics – nail fold capillaries and systemic diseases

Now that non communicable diseases have reached epidemic proportion and there is urgent need to prevent serious morbidity due to the long term complications, there must be an easy and reliable screening tool that could cover a wide range of population. As endothelial dysfunction and micro vascular dysregulation are the cornerstone of both diseases, the microvascular complications could become predictable if we identify the pattern of involvement, if present, in various organs depending on the duration of disease. Ophthalmoscopic evaluation of fundus in diabetes and hypertension is standardized. Capillaries are easily accessible in nail fold with just a hand held

dermoscopy and hence neither there is technical nor is there a practical difficulty in evaluating nail fold for capillary abnormalities. With highly suggestible correlation of specific morphologies in capillaries and systemic diseases such as hypertension and diabetes, there is still only a pending string to connect capillary abnormalities with other end organ failure.

Hypothesis generation

The main clarification and hence comparison was attempted between specific nail fold capillary changes in hypertension and diabetes and fundus findings in both of these diseases. In order to accomplish this comparison, cooperation between ophthalmology and dermatology department were sought. Since both were micro vascular diseases and micro vascular complications accounted for major morbidity of the disease, capillaries at nail bed, eyes, kidneys were examined. Blinded patients were examined in both departments and results were collected and compared.

Benefits of positive study

The ultimate purpose of this study was to find an innovative, easily available, hassle free, uncomplicated technique to identify, prognosticate and stage the end organ dysfunction in both diabetes and hypertension. In case of positive correlation in this study, several conclusions could be deduced.

Firstly, just a short examination at the nail bed could identify the magnitude of retinal disease, renal disease and other systemic microcirculation. Secondly, certain specific patterns could account for specific risks in both end organs. For example, hypothetically loop formation at nail bed could correlate with arterial dilatation or so. Thirdly, there is a direct assessment of the state of systemic micro vessels and hence actual amplitude of the disease and the duration could be determined.

MATERIALS AND METHODS

Study design and participants

This was a single centre cross sectional study with patients admitted in the Government Royapettah hospital medical wards. 100 people (54 males and 46 females) were recruited, after their consent from the medical department to participate in the study. The study lasted from April 2012 to August 2012.

All individuals aged between 20 and 50 years and those diagnosed already or newly with diabetes or hypertension but not both were included in the study. People with connective tissue disorders, systemic diseases causing retinopathy, smoking history, pregnancy, history of retinal photocoagulation, history of nail biting, prolonged contact with water/detergent during work, sepsis, organ dysfunction (liver, kidney, heart) and encephalopathy were excluded from the trial and others were enrolled as participants. Formal oral and written consent were obtained from them. The study was approved by ethical committee board before starting.

Procedures and outcome measures

As and when a participant was identified, he/she was randomly assigned to call upon either a registered ophthalmologist or a registered dermatologist for

fundus or nail fold examination respectively. Then they would visit the complementary investigator. All participants were examined by a single ophthalmologist with Heine® mini ophthalmoscope after complete mydriasis. Similarly a single dermatologist investigated nail fold with Heine® mini dermatoscope in the non dominant hand. The results were collected on weekly basis by primary investigator and in this way the study was blinded. Urine protein creatinine ratio (PCR) was measured for as many people as possible.

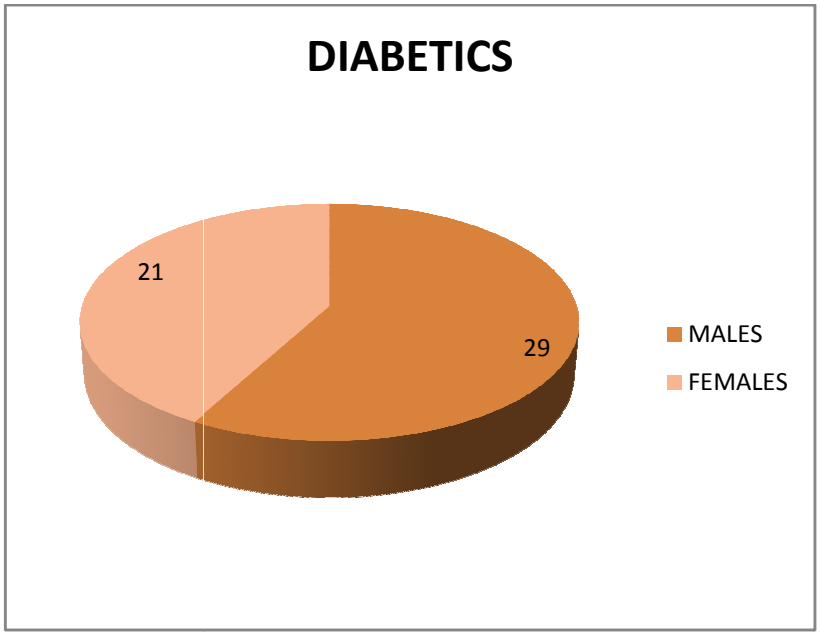
The outcomes were measured in ophthalmology in the form of presence or absence of retinopathy and grading them. Diabetic retinopathy was graded into non proliferative (mild, moderate, severe, very severe) or proliferative (early, high risk, severe). Hypertensive retinopathy was graded into four grades. Nail fold capillaries were reported as normal or abnormal (in these variables - architecture, density, loop diameter, neovascularisation and exudates). Urine PCR was measured by biochemists with spot test. Apart from this, baseline characteristics for comparison such as age, duration of the disease, drugs currently on were also collected and compiled.

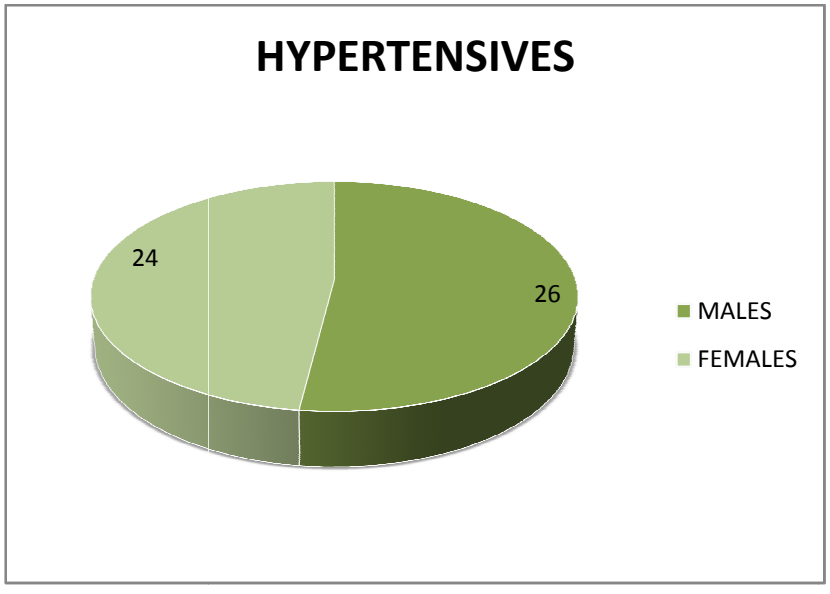
Statistical analysis

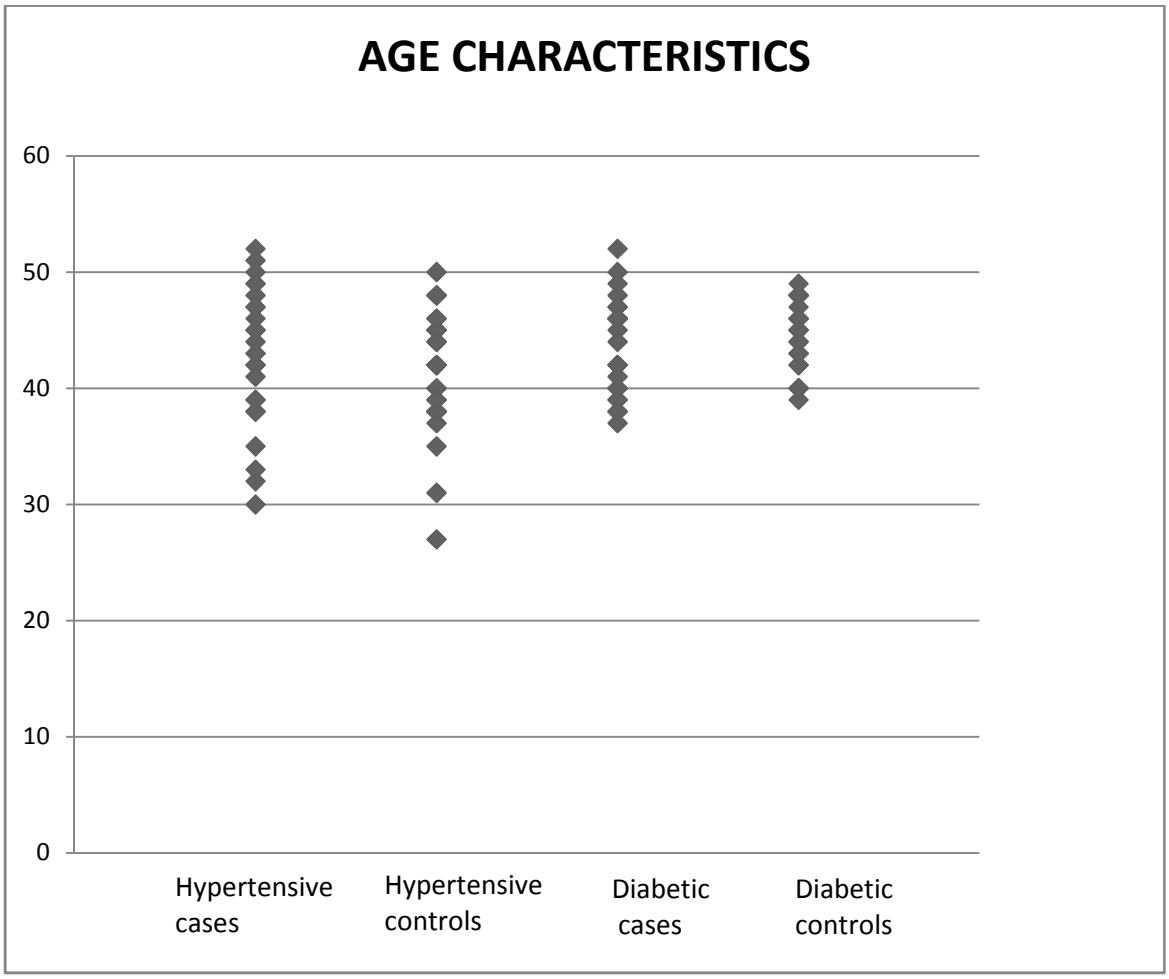
After acquiring the complete set of data and preparing the master chart, statistician working in another facility was approached. The data was analysed

with Statistics Products Services Solutions (SPSS)® software for windows with age, sex, duration of disease, degree of retinopathy, urine PCR and nail fold changes as variables. A chi squared test was used to analyze the probability of differences in frequency distributions between the groups and $p<0.05$ was taken to be statistically significant in all calculations. Graphs were prepared using Graphpad prism 5.0®

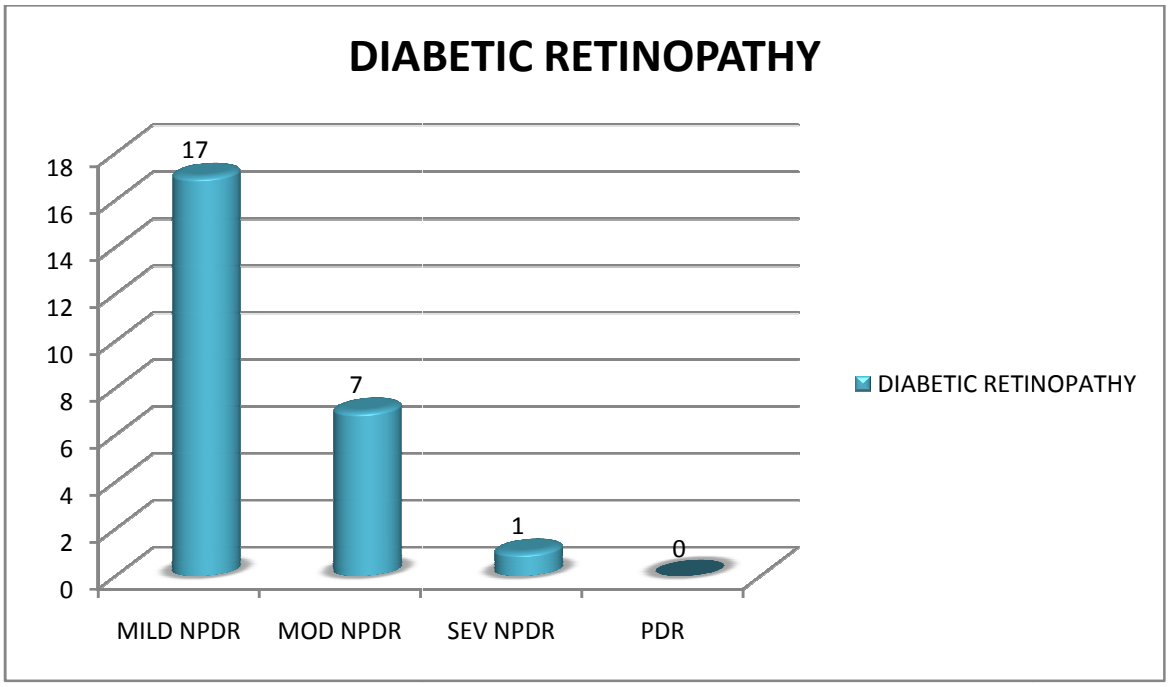
RESULTS

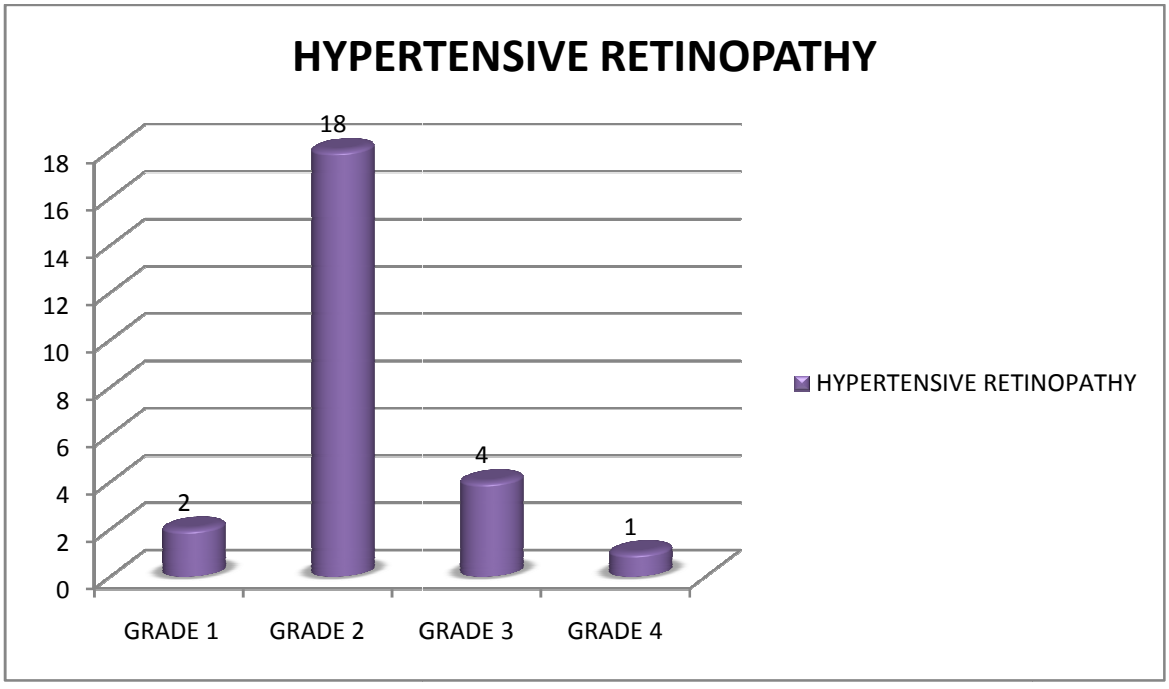

DIABETICS
21
29
MALES
FEMALES

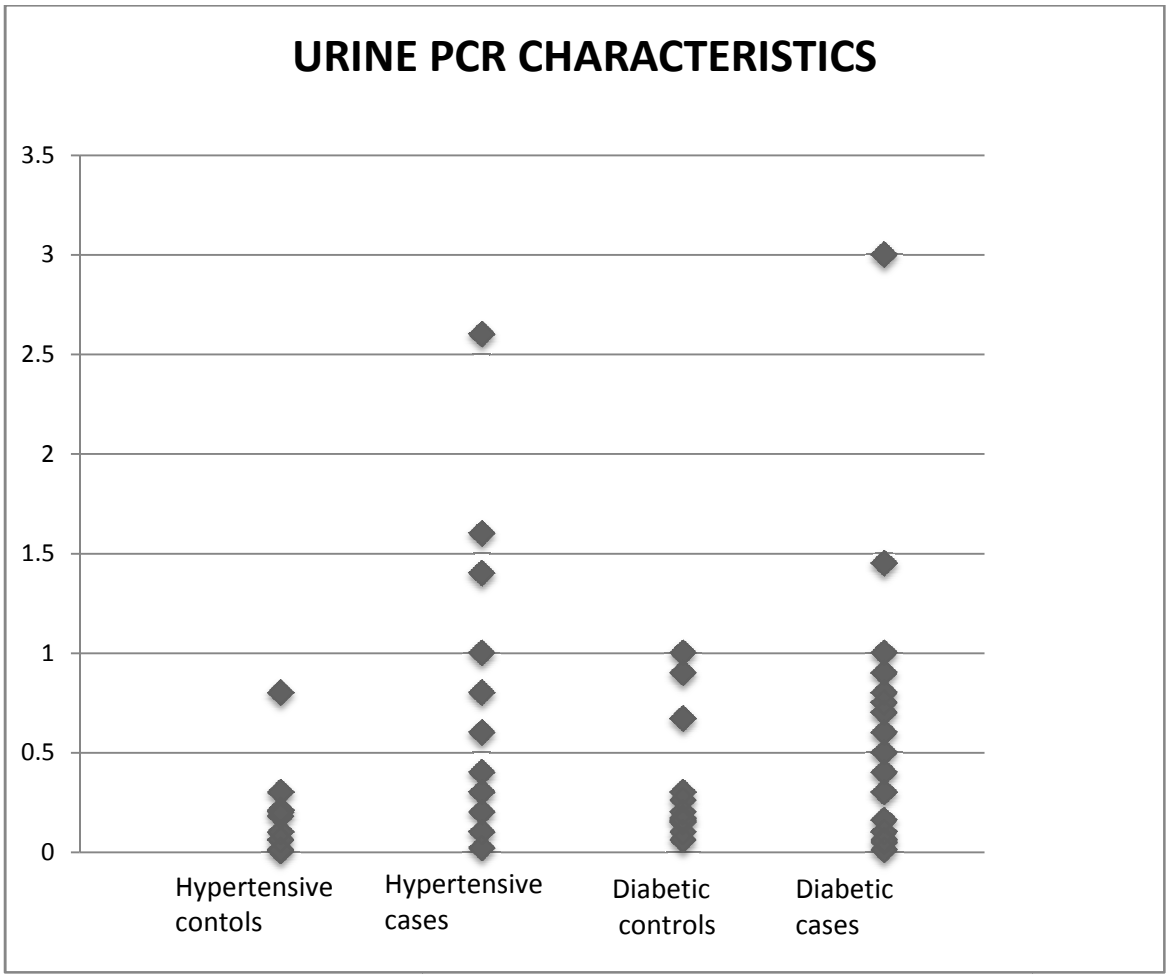

HYPERTENSIVES
24
26
MALES
FEMALES



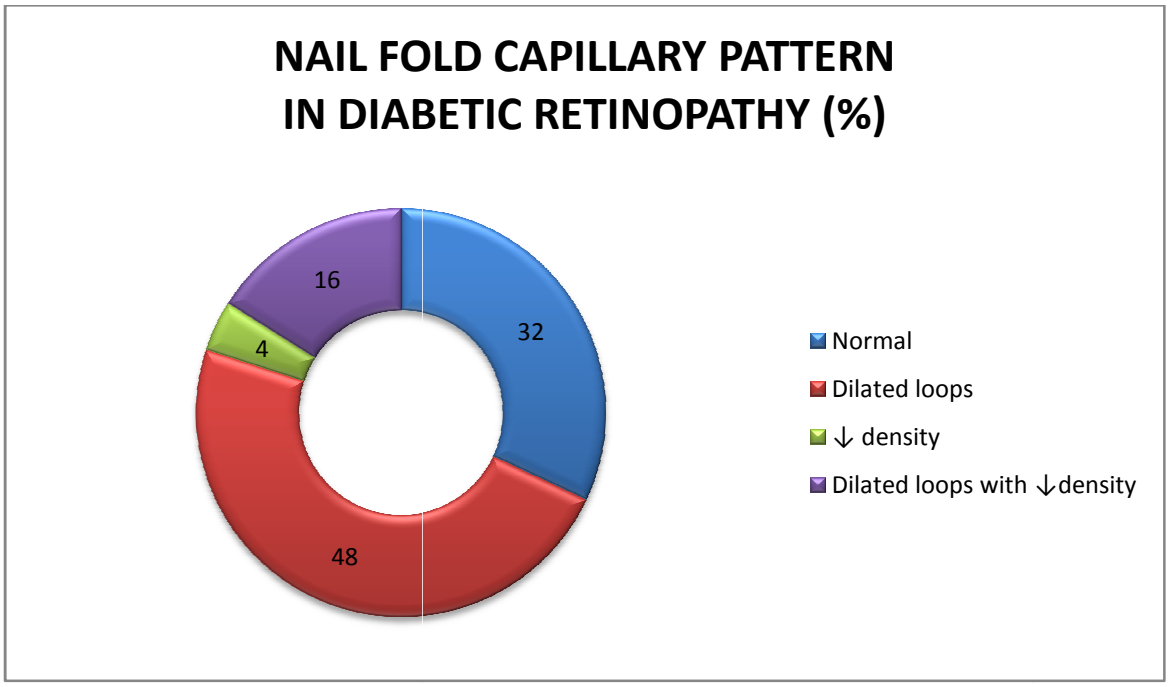
In this study, both males and females were represented almost equally and hence removing the confounding factor of sex if it had been present. Age clustering was around mid 40's in both the sex for both diabetes and hypertension. When tests of significance were performed for both age and sex influencing the outcome of the study, there were *no statistical significance* of either.

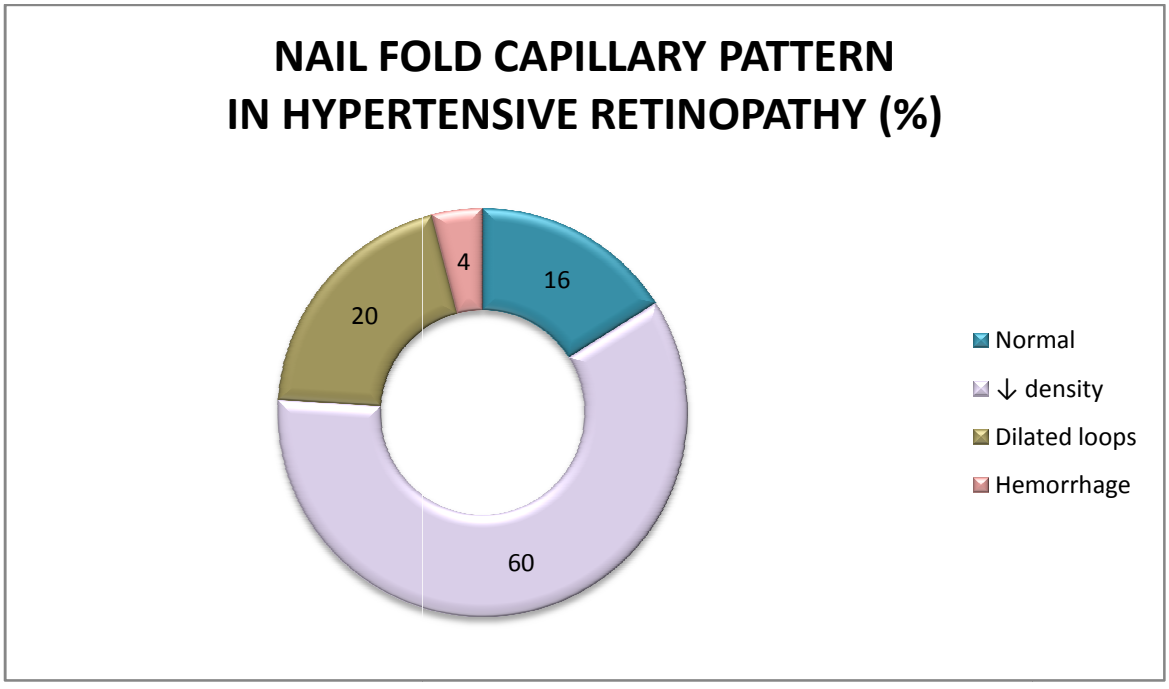

DIABETIC RETINOPATHY
18
16
14
12
10
8
6
4
2
0
17
7
1
0
MILD NPDR
MOD NPDR
SEV NPDR
PDR
DIABETIC RETINOPATHY

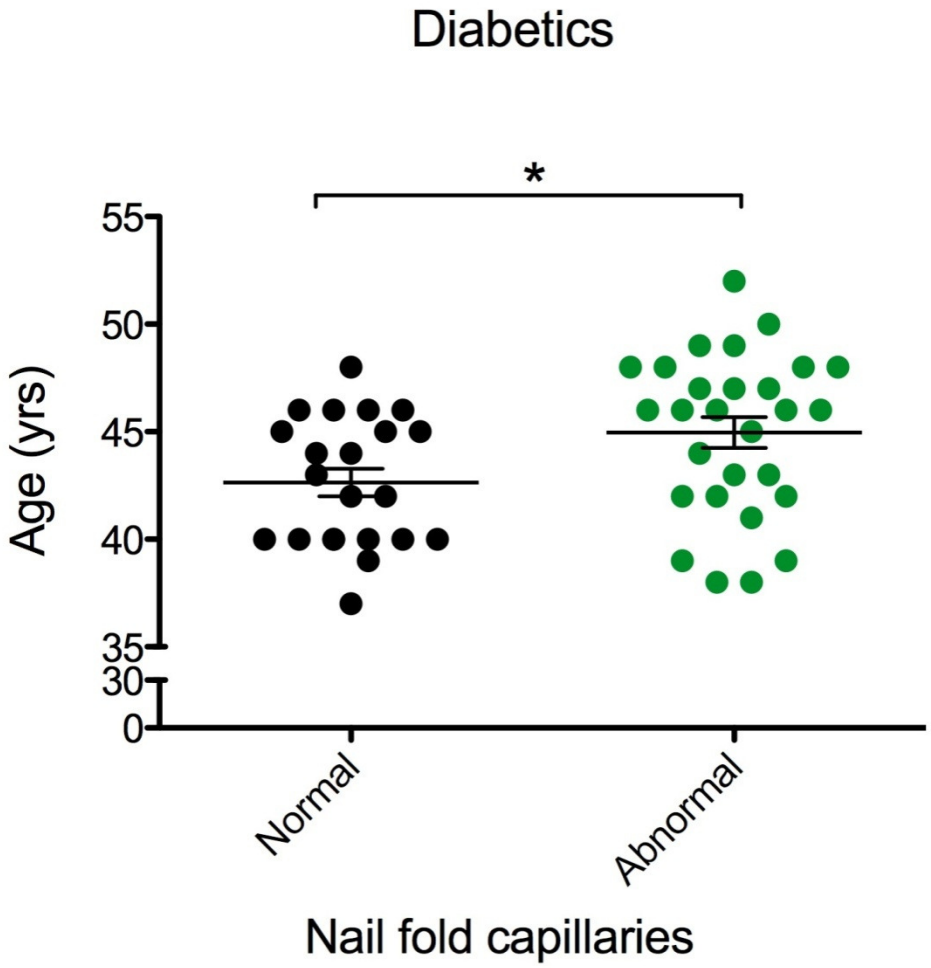

HYPERTENSIVE RETINOPATHY
18
16
14
12
10
8
6
4
2
0
2
18
4
1
GRADE 1
GRADE 2
GRADE 3
GRADE 4
HYPERTENSIVE RETINOPATHY



A6s noted from this observation, urine PCR – a spot method of quantitative protein excretion per day, shows a wide range across different groups. Hence, whether this sole factor could indicate the presence of nephropathy is of question. Combination of cystatin and creatinine would have better correlated with the degree of renal injury.


NAIL FOLD CAPILLARY PATTERN
IN DIABETIC RETINOPATHY (%)
16
32
4
48
Normal
Dilated loops
↓ density
Dilated loops with ↓density

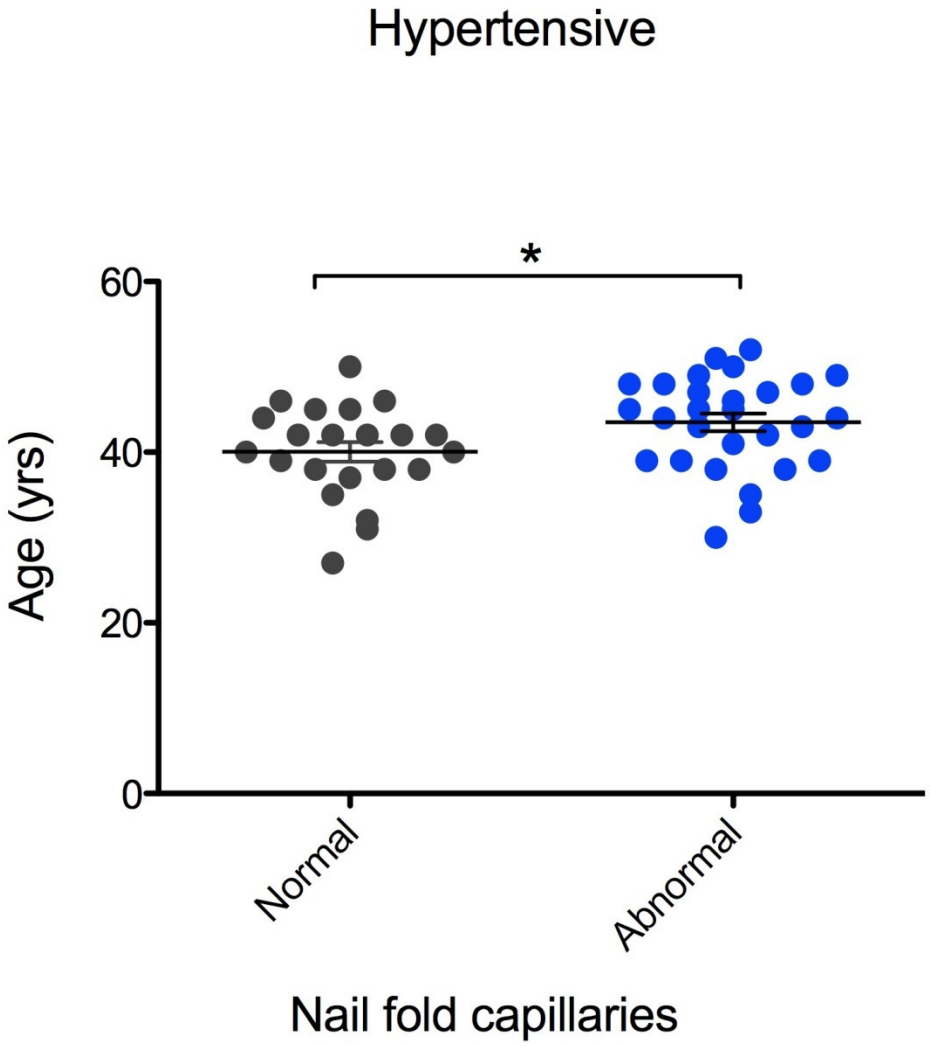

NAIL FOLD CAPILLARY PATTERN
IN HYPERTENSIVE RETINOPATHY (%)
4
16
20
60
Normal
↓ density
Dilated loops
Hemorrhage



COMPARISON OF AGE AND NAIL FOLD CHANGES IN DIABETICS

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	79.825[a]	56	.020
Likelihood Ratio	69.360	56	.108
N of Valid Cases	50		

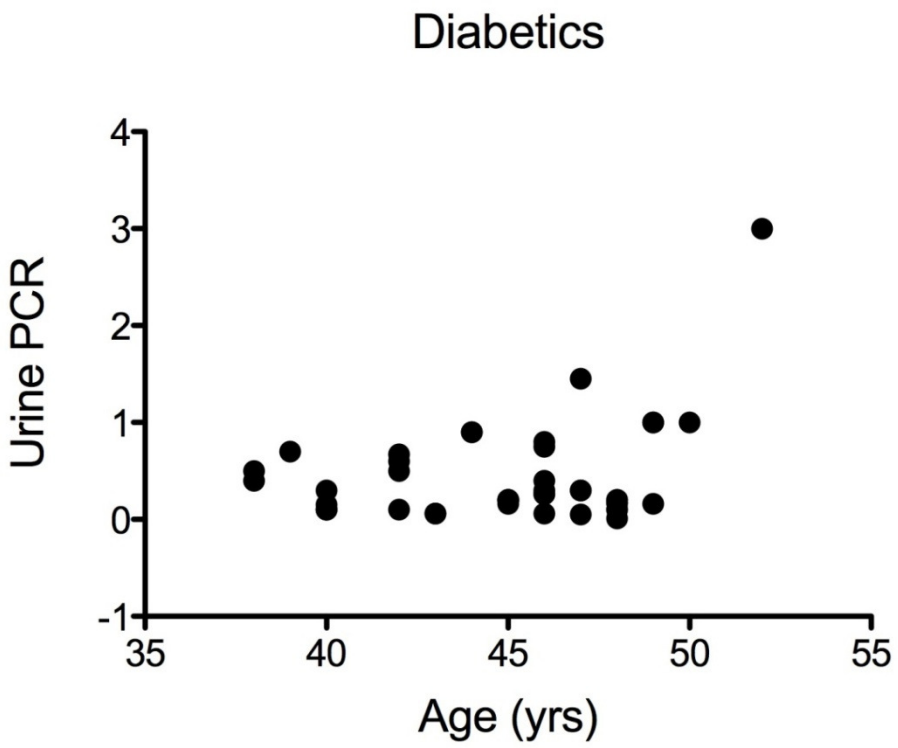
a. 75 cells (100.0%) have expected count less than 5. The minimum expected count is .02.



COMPARISON OF AGE AND NAIL FOLD CHANGES IN HYPERTENSIVES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	83.55[a]	56	0.01
Likelihood Ratio	70.33	56	0.11
N of Valid Cases	50		

a. 75 cells (100.0%) have expected count less than 5. The minimum expected count is .01.



COMPARISON OF AGE AND URINE PCR VALUE IN DIABETICS

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	272.944[a]	240	.071
Likelihood Ratio	130.928	240	1.000
Linear-by-Linear Association	3.753	1	.053
N of Valid Cases	34		

a. 273 cells (100.0%) have expected count less than 5. The minimum expected count is .03.

Hence, **age** related changes in the **nail fold** both in diabetics and hypertensives were *significant statistically*. Urine PCR value was not related to age.

COMPARISON OF SEX AND NAIL FOLD CHANGES IN DIABETICS

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.952[a]	4	0.745
Likelihood Ratio	2.317	4	0.678
N of Valid Cases	50		

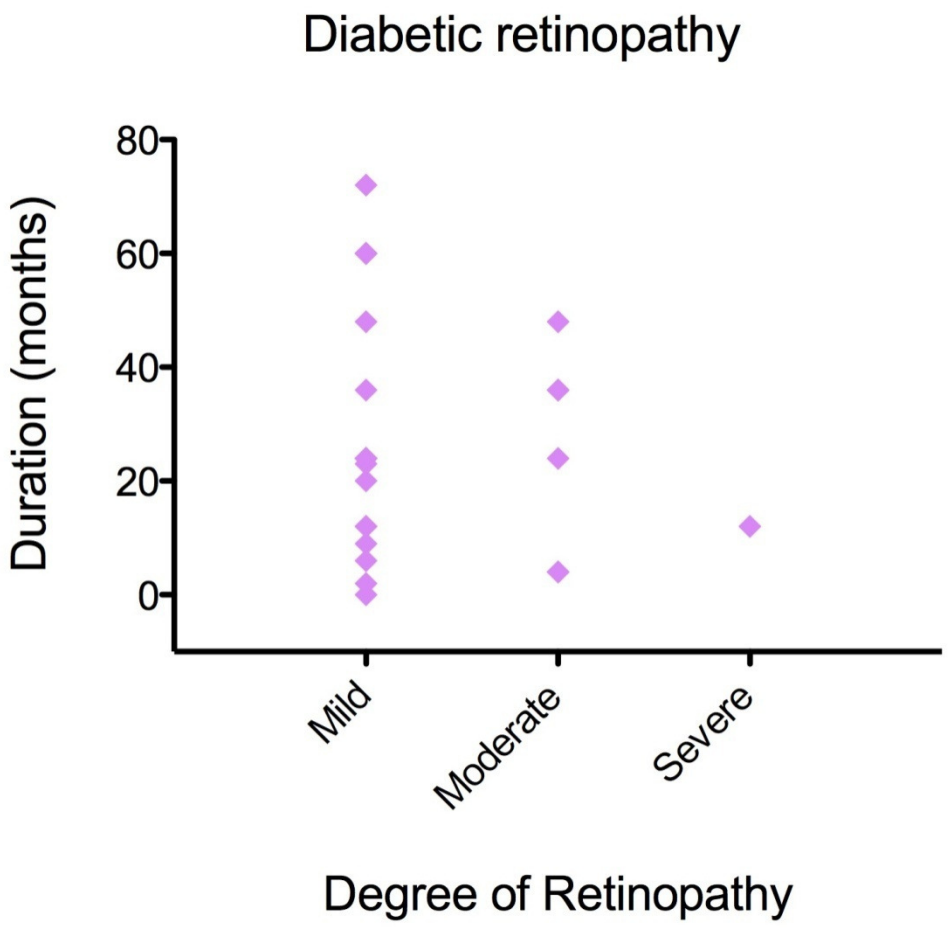
a. 4 cells (40.0%) have expected count less than 5. The minimum expected count is .42.

COMPARISON OF SEX AND NAIL FOLD CHANGES IN HYPERTENSIVES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.727[a]	5	0.242
Likelihood Ratio	9.049	5	0.107
N of Valid Cases	50		

a. 8 cells (66.7%) have expected count less than 5. The minimum expected count is .50.

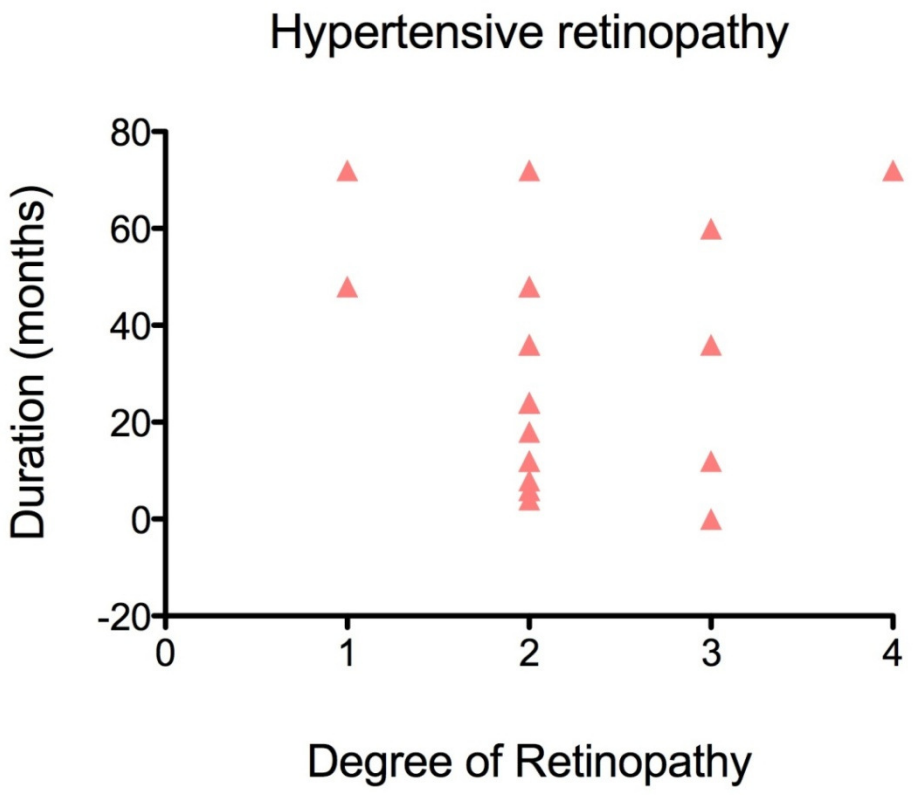
Both in diabetics and hypertensives, there were *no significance* between **sex** and degree of **nail fold changes**.



CORRELATION BETWEEN DURATION AND DEGREE OF RETINOPATHY IN DIABETICS

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	68.613[a]	72	0.591
Likelihood Ratio	48.458	72	0.985
N of Valid Cases	50		

a. 89 cells (97.8%) have expected count less than 5. The minimum expected count is .02.

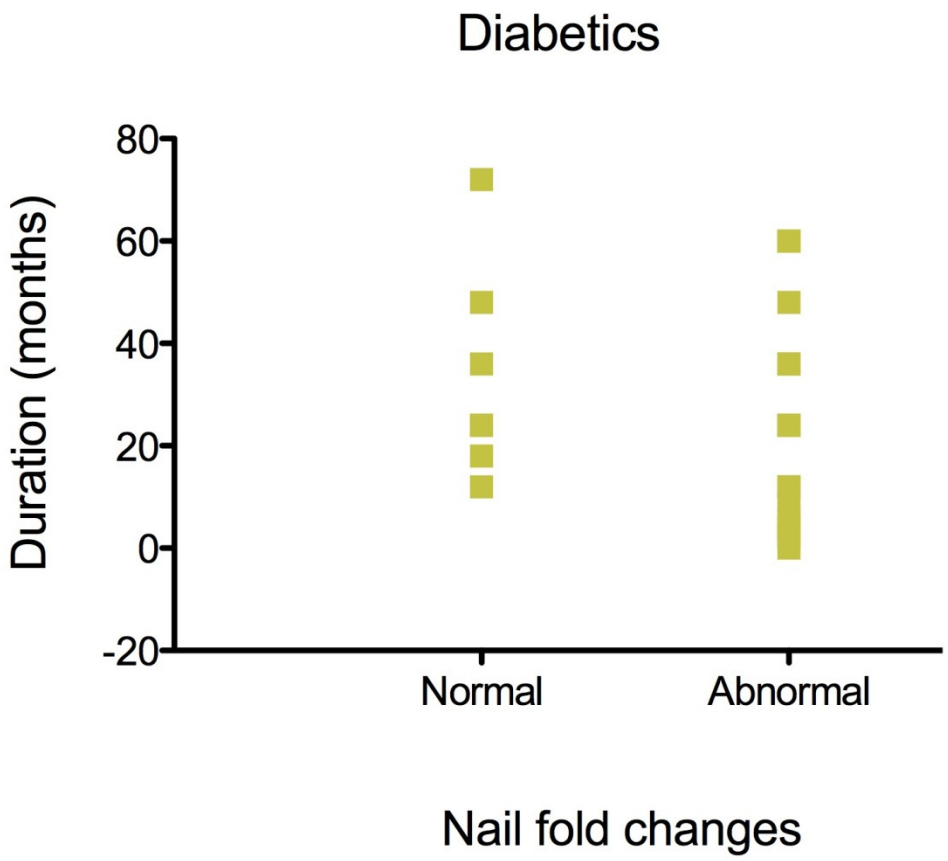


CORRELATION BETWEEN DURATION AND DEGREE OF RETINOPATHY IN HYPERTENSIVES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	44.389[a]	44	0.455
Likelihood Ratio	33.332	44	0.879
Linear-by-Linear Association	.417	1	0.518
N of Valid Cases	50		

a. 59 cells (98.3%) have expected count less than 5. The minimum expected count is .02.

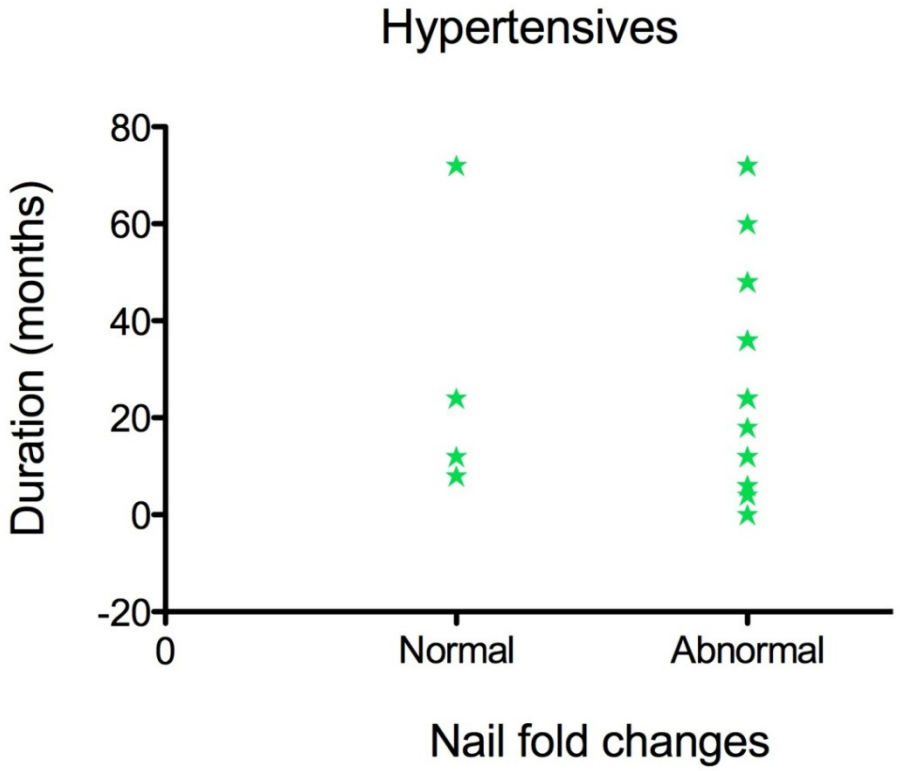
There were *no significant correlation* between **duration** of the disease and the **degree of retinopathy** in both diabetics and hypertensives.



CORRELATION BETWEEN DURATION OF DIABETES AND NAIL FOLD CHANGES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	71.756[a]	48	0.015
Likelihood Ratio	52.691	48	0.298
N of Valid Cases	50		

a. 64 cells (98.5%) have expected count less than 5. The minimum expected count is .02.

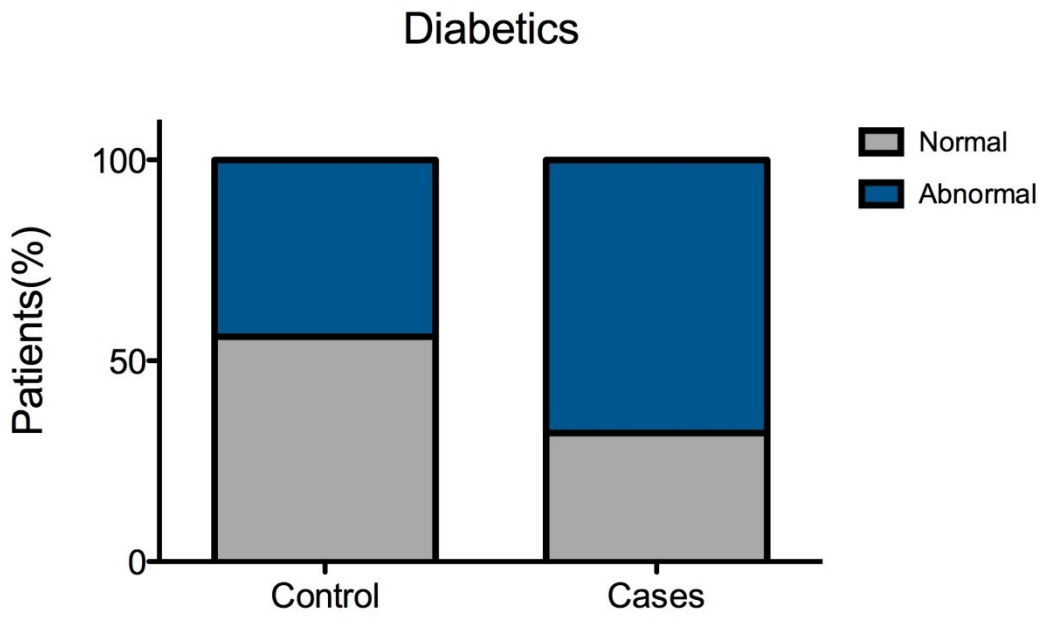


CORRELATION BETWEEN DURATION OF HYPERTENSION AND NAIL FOLD CHANGES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	62.100[a]	55	0.238
Likelihood Ratio	42.390	55	0.893
N of Valid Cases	50		

a. 70 cells (97.2%) have expected count less than 5. The minimum expected count is .02.

It was noted that, there was *no significance* between **nail fold changes** and **duration of hypertension** but **duration** was *statistically significant* in **diabetes.**

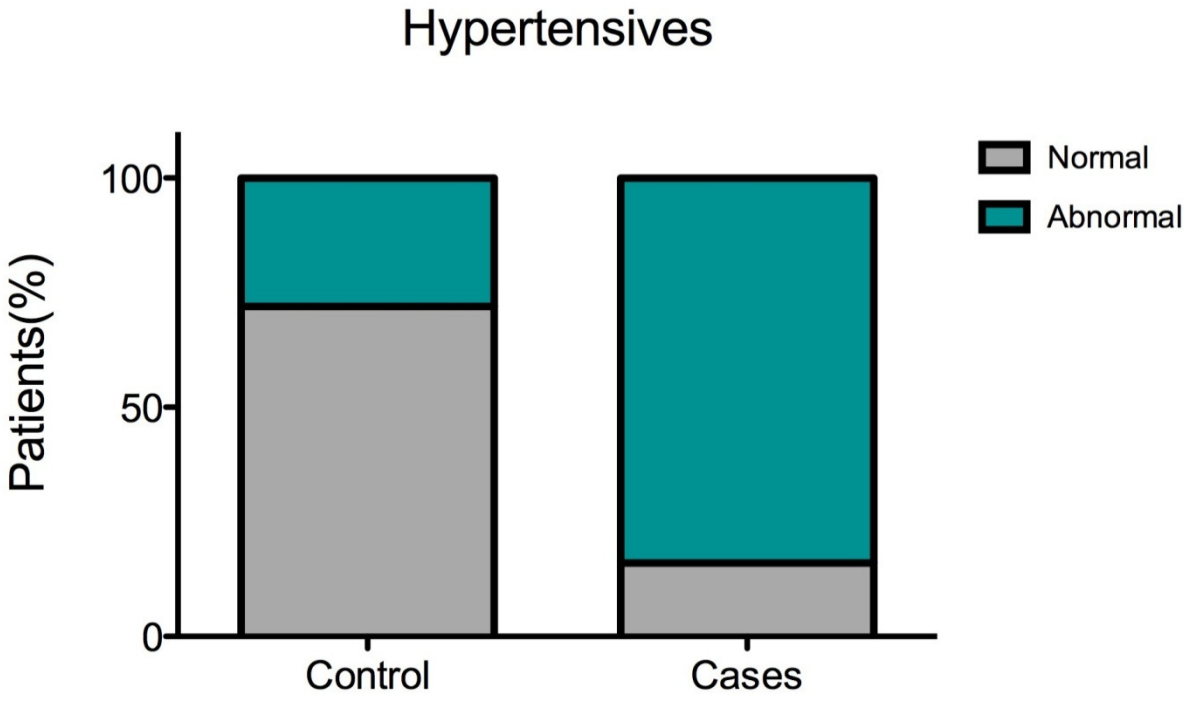


CORRELATION BETWEEN DIABETIC RETINOPATHY AND NAIL FOLD CHANGES

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	48.117[a]	24	0.002
Likelihood Ratio	54.352	24	0.000
N of Valid Cases	50		

a. 31 cells (88.6%) have expected count less than 5. The minimum expected count is .02.

Nail fold changes were *very significantly* associated with **diabetic retinopathy** grades as was hypothesized.

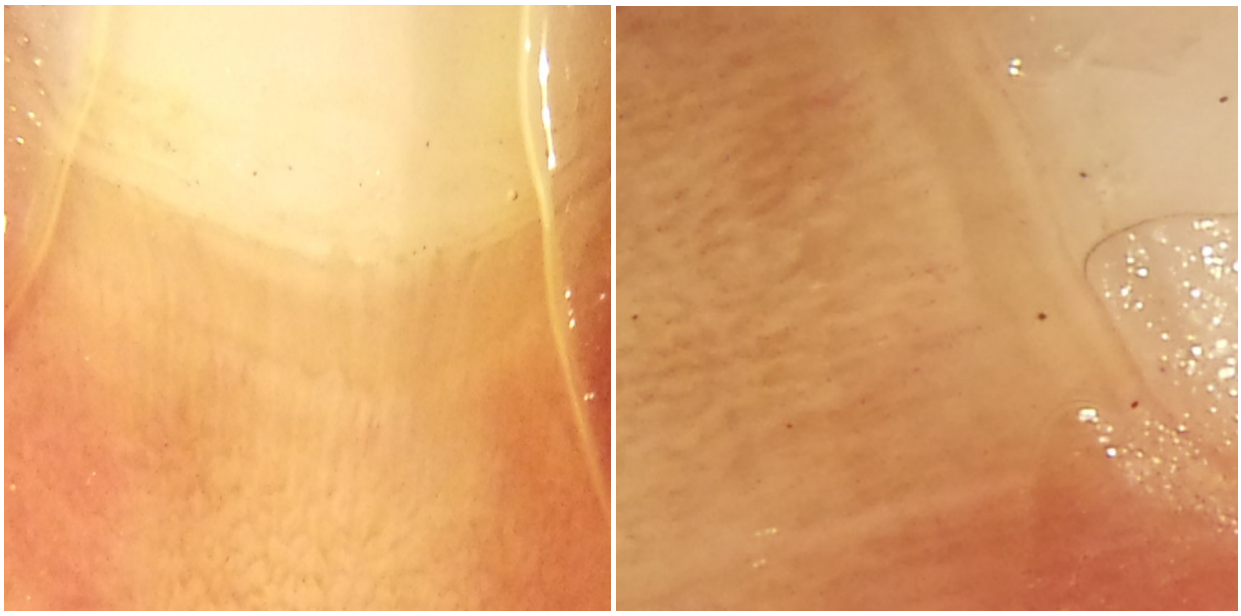


CORRELATION BETWEEN HYPERTENSIVE RETINOPATHY AND NAIL FOLD CHANGES

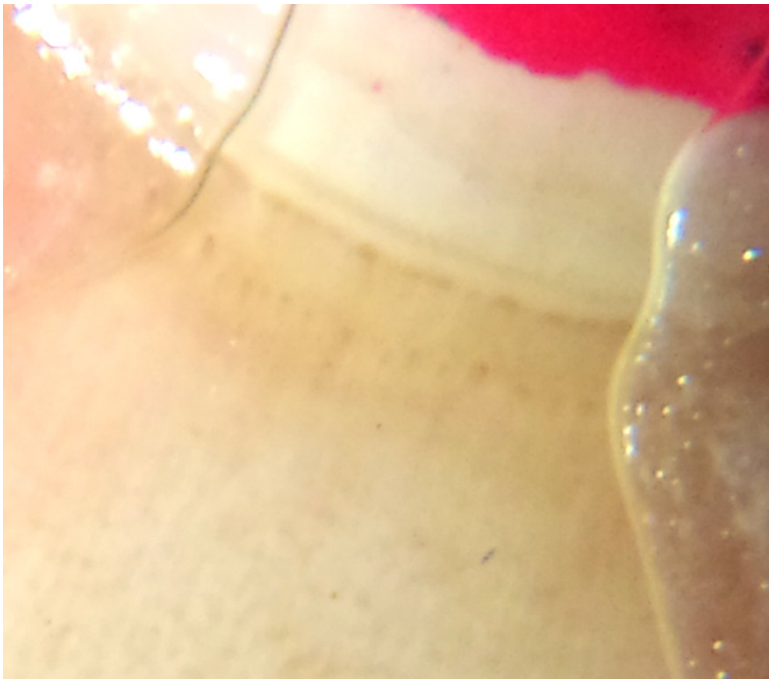
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	53.720[a]	20	0.001
Likelihood Ratio	30.862	20	0.057
N of Valid Cases	50		

a. 26 cells (86.7%) have expected count less than 5. The minimum expected count is .02.

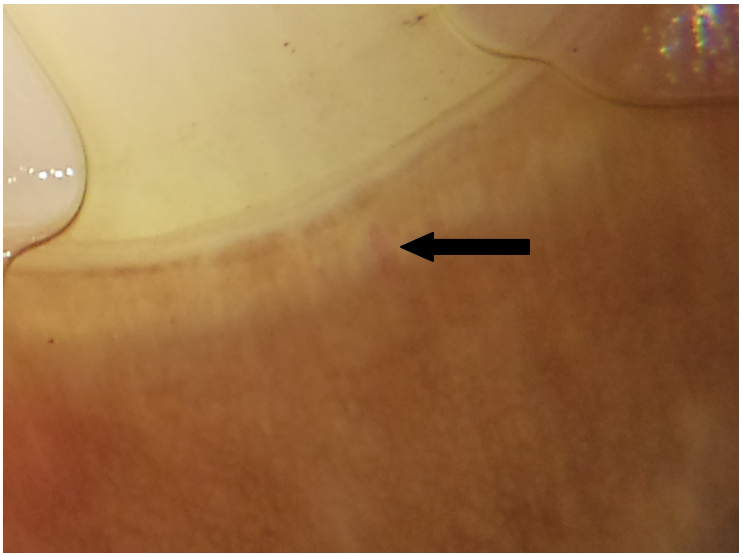
Similarly, there were *positive correlation* between various **hypertensive retinopathy** grades and **nail fold changes** too.



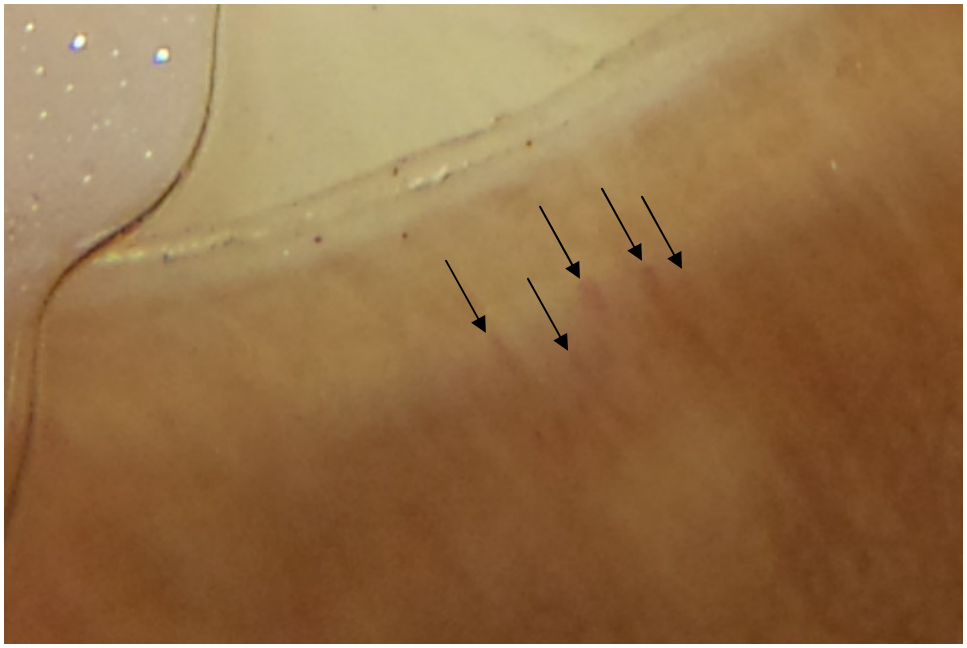
Reduced capillary density



Dilated terminal loops of all hairpin capillaries



Dilated single loop



Multiple dilated loops

DISCUSSION

There were approximately equal numbers of participants from either sex in order to reduce the confounding effects if present. There were no major differences in nail fold changes, proteinuria, duration of disease of diabetes or hypertension and degree of retinopathy of either disease between either of sexes. It is in line with general expectations and until now there is no literature regarding sexual variability in the above described factors.

It is to be noted that the average duration of the examination of the nail fold by the trained dermatologist took about 2 minutes in total for all four fingers in the non dominant hand. Again, here we emphasize the simplicity of the procedure in trained hands. This also excludes the discomfort of mydriasis performed routinely for fundus examination.

In this study, the most observed grade of retinopathy in diabetics was mild non proliferative (68% of all patients). It probably is due to the fact that more advanced types have morbidity due to vision loss and hence seek treatment earlier. Hence, patients do not remain asymptomatic. However, this pattern is different from generally observed prevalence of retinopathy, where moderate NPDR is most common.[93] In contrast, the most commonly observed degree of retinopathy in hypertensives was grade 2 (72% of all patients) which was in accordance with

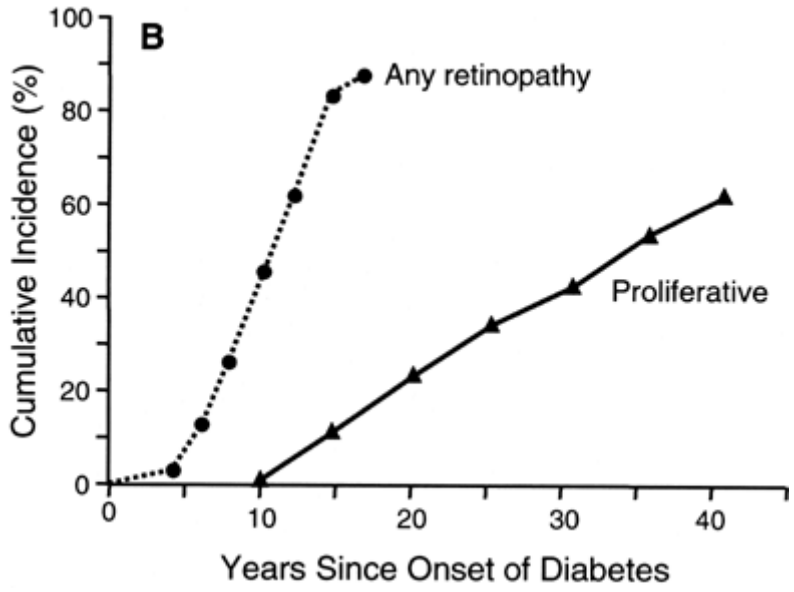
general prevalence studies. There is no significant vision loss from hypertensive retinopathy when compared to diabetic retinopathy except for malignant hypertension, which occurs very rarely in population. As a result, patients remain asymptomatic for longer duration. But as emphasized earlier, importance of hypertensive retinopathy lays in the fact that diet and/or pharmacotherapy has to be further intensified to reduce the target of BP.

Age was an important factor determining the morphology of nail fold capillaries. As was detailed earlier, there is generalized capillary rarefaction and dilation of loops with age. In young patients with a risk of getting hypertension at later age, capillary rarefaction has an important role of earlier identification and risk stratification so that therapeutic intervention could be undertaken earlier. Whereas hypertension per se causes morphological changes in the capillaries, age related arteriosclerosis also complements the changes in elderly hypertensives and should be remembered. The correlation of age and diabetic capillary changes ($p = 0.02$), as noted in this study could be attributed to generalized attrition of vasculature with age in addition to specific micro vascular disturbances due to endothelial dysfunction. Apart from this there were no age related proteinuria or other physiological changes noted in this study. Moreover, age had no correlation with degree of either diabetic or hypertensive retinopathy. This is easily understandable because of the fact that retinopathic changes are proportional to the

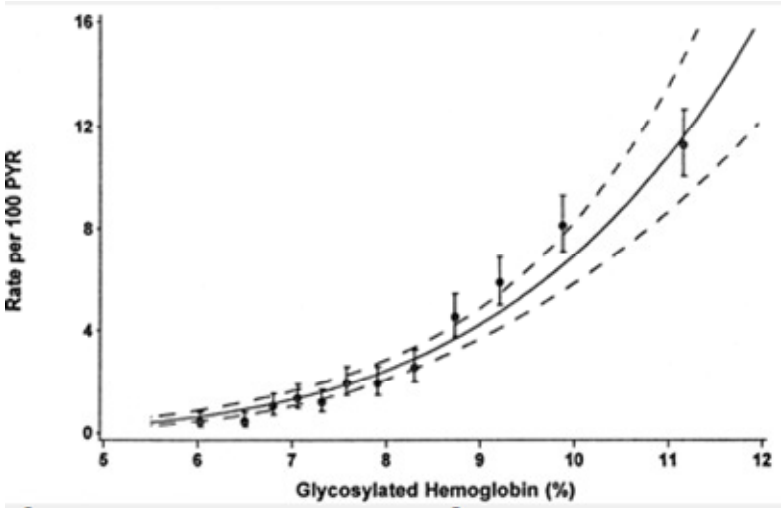
actual pathologic duration of the disease. A 20 year old type 1 diabetic would have a severe retinopathy when compared to a 45 year old type 2 diabetic of recent onset of disease because of the presence of pathology for about a decade in the former while it is of short duration in the latter.

In our study, the microalbuminuria in both diabetic and hypertensive individuals showed no correlation with either duration of the disease or degree of retinopathy. Moreover most of the patients had normal range of proteinuria. Hence, the reliability of spot PCR alone as an index of proteinuria and of renal dysfunction is of question. Though there are gradation systems for diabetic nephropathy, there is no rule that the disease progresses through the increasing grades. Hence, microalbuminuria need not necessarily precede overt nephropathy in all cases. Comprehensive renal assessment is necessary for early detection.

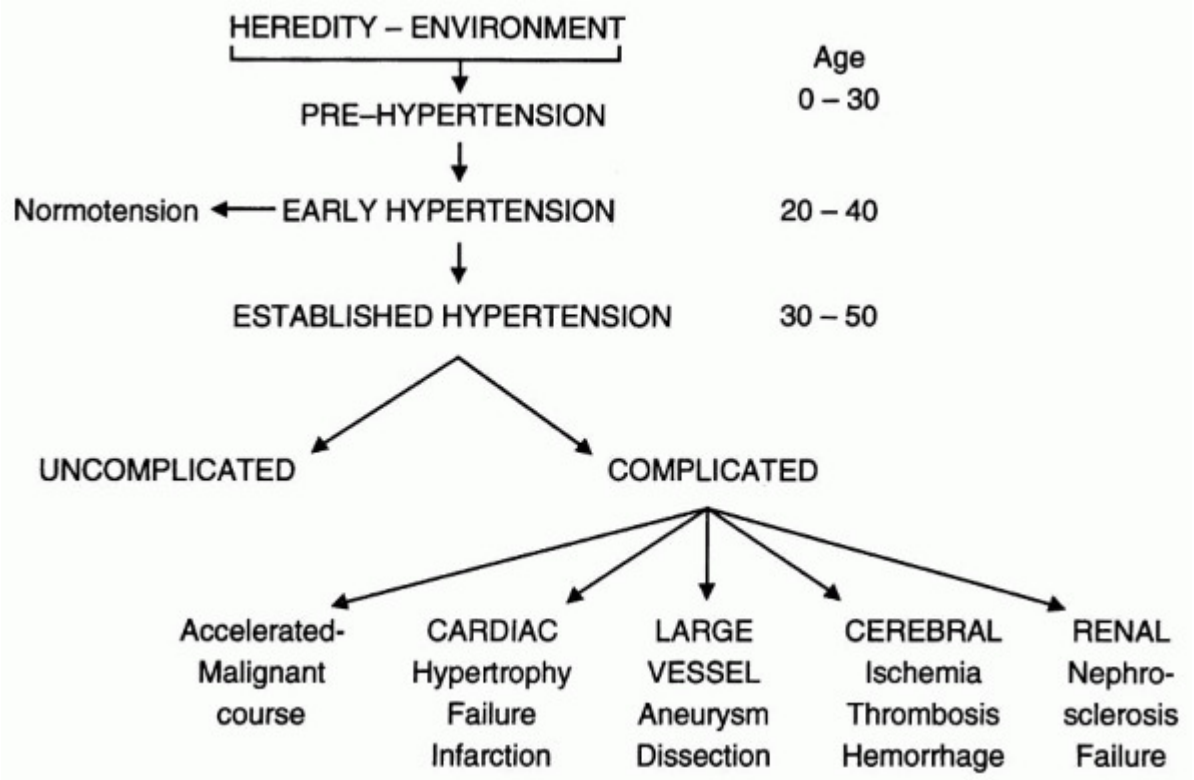
From the discussion above and in the pathogenesis section, we have known that duration of disease in both hypertension and diabetes is the most important determinant of the severity of retinopathy. Also, the degree of glycemic control is an important determinant in diabetics. In this aspect, metabolic memory has to be invoked. Even a short duration of strict glycemic control would carry over its benefits lifelong. The time of diagnosis of type 2 diabetes varies in population and hence the heterogeneity in the patient reported duration of disease.



Cumulative risk of background and proliferative retinopathy, according to the duration of type 1 diabetes.[5]



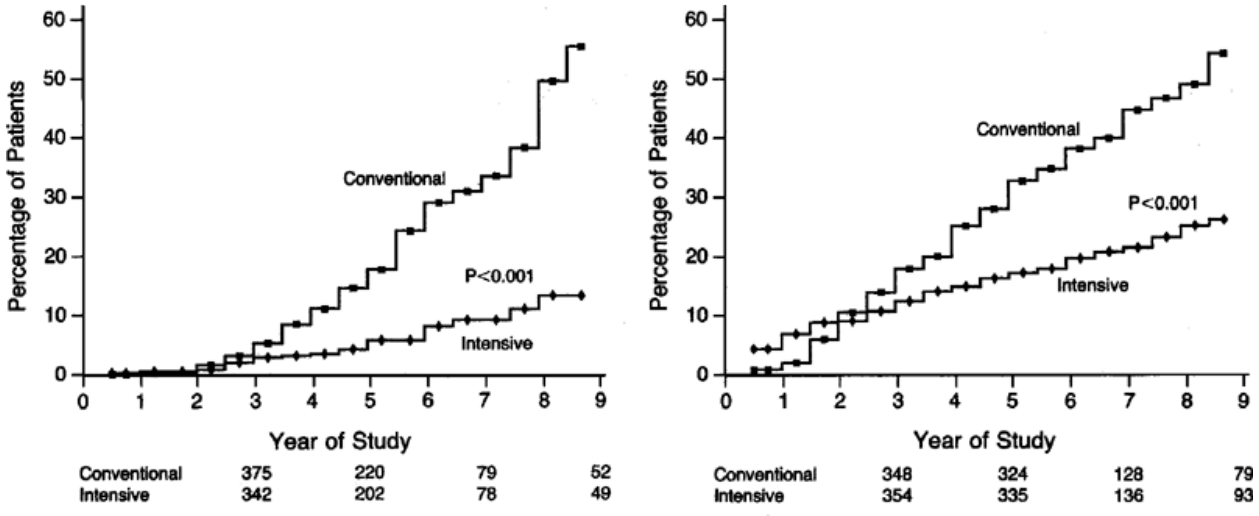
Association of mean percentage of glycosylated hemoglobin A_{1c} and sustained retinopathy[94]



Natural history of untreated essential hypertension [95]

But in essential hypertension, the natural course of disease is supposedly constant. It is the time of its diagnosis in the natural history of the disease (whether due to end organ complications or asymptomatic detection) that determines the morbidity as appropriate early intervention would definitely delay the morbidity. For example, a 35 year old detected to have hypertension on routine screening has less morbidity than a 46 year old who presents with stroke and has been subsequently found to have hypertension.

In a prospective study group, influence of metabolic memory on the capillary function has to be tested in future. It has long been thought that the changes taking place in the capillaries are due to irreversible structural modification of proteins. After strict glycemic control partial reversibility of capillary function, if present, would definitely be a boost for clinicians and researchers for it would help us identify and stratify patients whose microvasculature could refunction normally.



*Effects of intensive therapy on development (**A**) and progression (**B**) of retinopathy in the Diabetes Control and Complications Trial.*[96]

Duration of both the diseases (time from the diagnosis of either diabetes or hypertension till now and *not the actual pathologic duration* of disease) were not related to the age because there is a very long period of subclinical disease in both as a result of which patients remain asymptomatic for long duration. Hence, duration of diabetes or hypertension had not correlated with

degree of retinopathy (p = 0.59 in diabetics and p = 0.45 in hypertensives) because firstly, the nature of both of the diseases are dormant for prolonged period of time; secondly, retinopathy unless severe does not produce symptoms; thirdly, routine evaluation of fundus though advocated during initial evaluation has not been carried out in majority of settings. While the duration of diabetes correlated with nail fold capillary changes (p=0.015), it had not correlated in hypertension (p = 0.22). Whether there were some other confounding factors involved in diabetes has to be resolved because logically there shouldn't have been correlation between the two.

The primary objective of this study was to test the hypothesis whether the micro vascular dysfunction, central to pathogenesis of both diabetes and hypertension in a single vascular bed could influence other vascular beds as, it is a generalized process. As a result, retinopathy prediction by simple capillary changes in nail bed was intended in this study. The results obtained from this blinded study confirmed the hypothesis that, patients with retinopathy had significant nail fold changes complimented by age related changes. The result was highly significant (p=0.002 in diabetic retinopathy and p=0.028 in hypertensive retinopathy). Probably due to the above discussed reasons in the section of age related changes in nail fold capillaries and the changes being compounded by

arteriosclerosis, hypertensive patients had comparatively less significant correlation.

The most common pattern recognized in hypertensive retinopathic patient's fundus was reduced capillary density (60% of retinopathic patients). Since it also occurs with advancing age there has to be further studies clarifying the role of age and to identify some other method of distinguishing the age related attrition of vessels with the primary angiogenic abnormality in hypertensives. Conversely, if there could be a way to differentiate arteriosclerotic type of reduced capillary density, it could be of very great utility. There was one patient with nail fold hemorrhage – the importance of which has to be analyzed. There was no specific retinopathic change (especially dot and blot or flame shaped hemorrhage in the fundus) in that patient. Dilated loops were also encountered in hypertensive individuals which again invokes explanation. Again the fundus of such patients showed no specific alteration in vascular pattern.

Dilated loops of capillaries (48% with isolated and 16% with associated reduced capillary density) were the most common abnormality noted in diabetic retinopathy patients. This was consistent with other studies too. Single loop dilatation was also encountered in several patients. Structural dysfunction of cytoskeleton along with impaired auto regulation results in increased flow through

capillaries which causes capillary loop dilatation. There has been no study correlating each pattern of nail fold capillaries with respective retinopathic patterns which, if present could help us know the pathophysiology of the disease. For example, possibly loop dilation could correlate with fundal arteriolar dilatation. In contrast to other studies, neovasularization was not noted in our study. Though proliferative retinopathy was not encountered in this study group, it could have clarified the importance of dilatation of capillary loops had it been present. The absence of florid cases of proliferative retinopathy could be due to morbidity produced by the condition rather than reduced prevalence in the population.

Limitations

The following were found to be the limitations of this study-

- The sample size was small and further studies with larger number of people representing different ethnic groups have to be done to verify the results.
- Majority of participants were in age group of 40-50 years and wide range of ages should have been tested.
- Fundus examination was not done by gold standard seven-field stereoscopic fundus photography. But there are several studies to show that an experienced ophthalmologist could give comparable results on a mydriatic eye even with hand held ophthalmoscope.[8]

- ❖ Urine microalbuminuria is not the sensitive measure of decline of renal function in diabetics. A combination of urine PCR, serum creatinine and serum cystatin could have been a more sensitive measure.
- ❖ There were no ways to counter check the findings of investigators in both departments. Probably by increasing the number of investigators and blinding them and by using videocapillaroscope the validity of the results could have been increased.

Implications for future

- In hypertensive patients with magnetic resonance evidence of cerebral gliosis, there were significant findings in the nail fold.[97] The cause of MR findings whether as to a result of recurrent long-standing ischemia and replacement gliosis or subclinical stroke has to be examined. Hence probably it could serve the purpose of supplementing chronic infarct's etiology.
- There was a significant degree of nail fold alterations in patients with high resistive index by renal doppler ultrasonography.[98] Hence, just by examining the nail fold, the presence of atherosclerotic renal vasculature or

renovascular hypertension could be ruled in. Further studies are required to clarify the utility of dermoscope in clinical diagnosis of renal artery stenosis.

- Improvement of the peripheral microcirculation indices when measured before and after treatment may be associated with reversal of vascular dysfunction in hypertensive patients on treatment.[99] This signifies that certain amount of vasospasm in hypertensive individuals is reversible- whether it is related to the duration of hypertension also requires verification.
- Dermoscopy could help differentiate hypertensive nephrosclerosis from CKD resulting on to hypertension as, in the former there would be capillary rarefaction in the nail fold. At the time of presentation in such patients, frank recognition could help decide the further line of management.
- Due to already existent data regarding the risk of development of hypertension in the cohort of children whose parents are hypertensive and the role of dermoscope in stratifying the high risk group, nail fold capillaroscope could help in early lifestyle and pharmacological intervention in that group.
- Dermoscopy could supplement creatinine, urine micro albumin in predicting the onset of nephropathy. Further clarifications regarding this correlation

could also establish it as a way to diagnose and/or prognosticate chronic kidney disease (CKD) in diabetics and hypertensives.

- As there is direct information regarding micro vessels and its auto regulation through dermoscopic examination, the nail fold findings could help in risk stratification of diabetics for development of peripheral neuropathy and trophic ulcers. In high risk individuals along with neurologic examination, intervention like MCR footwear, frequent foot care visits would prevent morbidity.
- Autonomic dysfunction could also be identified as there is a defect in auto regulation of dermal capillaries due to impaired axon reflex test. It could hence take a place in autonomic nervous system testing in diabetics.
- Since the coronary heart disease in diabetics is mostly silent, we could use nail fold capillaries as a index of micro vessel occlusion in coronary bed that could result in silent ischemia/infarct. However, it has to be evaluated with echocardiography and angiographic studies for routine use.
- Capillary rarefaction in diabetes especially in toes can predict the risk for diabetic foot syndrome if validated. Because rarefaction in such cases is not due to coexistent hypertension, vasospasm and failed recruitment of the dermal vessels is the probable etiology.

- Though reversibility of capillary function has been documented to a certain extent in hypertensives, its existence in diabetics is to be tested. If that is the case then, the reversal of insulin resistance would result in reestablishing the auto regulation of micro vessels. This would mean that some of the pathology in diabetes is reversible.
- Nail fold abnormalities in diabetic individuals pose a higher risk for reduced joint mobility. Diabetic sclerodactyly has been positively correlated with the extent of nail fold capillary change.

CONCLUSION

The importance and ease of examining the nail fold capillaries and their reliability in predicting the retinopathy was thus evident from this study. Hence, in diabetics and hypertensives, presence of nail fold capillary abnormality suggests the presence of microvascular abnormalities elsewhere (especially the retina). A simple ophthalmoscope (with power of +10 and oil immersion) could serve the purpose of dermoscope at the bed side. This could well be the beginning of new dimension of use of ophthalmoscope in medicine.

Disclosure

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ANNEXURES

DATA COLLECTION FORM

NAME		AGE/SEX	
INPATIENT NUMBER			
DIABETIC DETAILS			
DURATION		INSULIN THERAPY	
RETINOPATHY GRADE		URINE PCR	
DERMATOSCOPY FINDINGS	a) Architecture b) Loop diameter c) Density d) Angiogenesis e) Extravasate f) Others		
HYPERTENSIVE DETAILS			
DURATION		DRUGS	
RETINOPATHY GRADE		URINE PCR	
DERMATOSCOPY FINDINGS	a) Architecture b) Loop diameter c) Density d) Angiogenesis e) Extravasate f) Others		

சுய ஒப்புதல் படிவம்

பங்கு பெறுபவரின் பெயர்:

முகவரி:

திட்டத்தின் தலைப்பு: நீரிழிவு மற்றும் இரத்த அழுத்தத்தால் விழித்திரை பாதிப்பும், விரல் நுனி இரத்த தந்துகிகளின் தொடர்பும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன். நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரத்தினாலோ, எந்த சட்டசிக்கலுக்கும் உட்படாமல், நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலுமாய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மருக்கமடேன். இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்: _____

தேதி: _____

PARTICIPANT CONSENT FORM

Participant's name: Address:

Title of the project: Correlation of diabetic and hypertensive retinopathy with nail fold capillary changes.

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant: _____

Date: _____

ETHICAL COMMITTEE CLEARANCE FORM

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,CHENNAI-10
Ref.No.1463/MEI(Ethics)/2012 Dt: 03.04.2012
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College , Chennai reviewed and discussed the application for approval entitled "Correlation of Diabetic and Hypertension induced nail fold capillary and retinal changes"- For Dissertation Purpose submitted by Dr.S.M.Karthik, MD(GM), PG STUDENT, KILPAUK MEDICAL COLLEGE, CHENNAI-600010.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
14 DEC 2012
Kilpauk, Chennai-10.

14/12/12

CHAIRMAN,
Ethical Committee
Govt. Kilpauk Medical College,
Chennai

MASTER SHEET- HYPERTENSIVES

S.NO	NAME	AGE	SEX	IP NO	DURATION	RETINOPATHY	NFC CHANGES	URINE PCR
1.	Radhakrishnan	44	M	981765	6 yrs	N	↓ density	0.21
2.	Hari	45	M	OP	2 yrs	N	N	-
3.	Suresh	27	M	OP	4 yrs	N	N	-
4.	Satish	35	M	OP	2 yrs	N	N	-
5.	Sugumar	42	M	OP	3 yrs	N	N	-
6.	Vadivelan	38	M	OP	2 yrs	N	N	-
7.	Chakravarthy	45	M	998721	1 yr	N	↓ density	0.18
8.	Ramgopal	42	M	999543	6 mon	N	↓ density	0.8
9.	Srinivasan	46	M	999872	3 mon	N	↓ density	0.01
10.	Kadirvel	40	M	OP	1 yr	N	N	-
11.	Janakiraman	39	M	100128	3yrs	N	↓ density	0.06
12.	Taufiq ali	48	M	104561	5 yrs	N	↓ density	0.1
13.	Mir Mustafa	50	M	OP	4 yrs	N	N	-
14.	Waha khan	45	M	OP	2 yrs	N	N	-
15.	Meena	48	F	986490	3 yrs	N	↓ density	0.2
16.	Shanty	42	F	OP	6 mon	N	N	-
17.	Selvarani	46	F	OP	6 mon	N	N	-
18.	Mary	31	F	998100	1 yr	N	N	0.004
19.	Sulochana	38	F	OP	2 yrs	N	N	-
20.	Suganthi	40	F	OP	1 yr	N	N	-
21.	Kalyani	42	F	OP	2 yrs	N	N	-
22.	Faisad bee	44	F	100119	1 yr	N	N	0.06
23.	Samshad	38	F	OP	1 yr	N	N	-
24.	Ramani	39	F	104681	6 mon	N	N	0.1
25.	Ravanamma	37	F	105494	2 mon	N	N	0.3
26.	Pushparaj	52	M	997311	3 yrs	2	↓ density, H'ge	1
27.	Munusamy	51	M	101726	6 yrs	2	↓ density	0.8
28.	Selvam	30	M	OP	3 yrs	2	↓ density	-
29.	Rajamani	45	M	OP	2 yrs	2	↓ density	-
30.	Subramani	44	M	OP	6 mon	2	↓ density	-
31.	Babu	46	M	OP	6 yrs	1	N	-
32.	Ramaraj	47	M	OP	4 yrs	1	↓ density	-
33.	Kumar	32	M	OP	1 yr	2	N	-
34.	Munusamy	39	M	109391	4 yrs	2	↓ density	0.2
35.	Kanagasabai	42	M	109279	2 yrs	2	N	0.2
36.	Pushparaj	43	M	109151	2 yrs	2	↓ density	0.3
37.	Karpagam	50	F	997480	5 yrs	3	↓ density	1.4
38.	Parveen begum	45	F	997695	1 yr	3	Dil loop	0.6
39.	Mariya begum	48	F	989798	New	3	↓ density	1.6
40.	Sustana	38	F	979927	6 yrs	4	↓ density	2.6
41.	Yasoda	38	F	OP	2 yrs	2	Dil loop	-
42.	Malini	42	F	OP	8 mon	2	N	-
43.	Anjalai	49	F	OP	4 mon	2	Dil loops	-
44.	Saraswathi	35	F	OP	1.5 yrs	2	Dil loops	-
45.	Selvi	33	F	OP	2 yrs	2	Dil loops	-
46.	Rajeshwari	47	F	100287	3 yrs	3	↓ density	0.02
47.	Gnanamani	41	F	101022	3 yrs	2	↓ density	0.3
48.	Vasantha	43	F	103102	6 mon	2	↓ density	0.1
49.	Janath nisha	39	F	105023	1 yr	2	↓ density	-
50.	Parimala	49	F	108712	4 yrs	2	↓ density	0.4

DIABETICS

S.NO	NAME	AGE	SEX	IP NO	DURATION	RETINOPATHY	NFC CHANGES	URINE PCR
1.	Mayavel	45	M	989754	5 yrs	N	↓ density	0.2
2.	Senguttuvan	40	M	987465	1 yr	N	N	0.1
3.	Kadiravan	45	M	993765	1 yr	N	N	0.2
4.	Marthandam	46	M	OP	5 yrs	N	↓ density	-
5.	Srinivasan	43	M	999127	2 yr	N	↓ density	0.06
6.	Balaji	48	M	101123	2 yr	N	↓ density	0.1
7.	Ragavendran	44	M	OP	1 yr	N	N	-
8.	Ravindran	46	M	OP	2 yrs	N	N	-
9.	Ashok kumar	42	M	OP	6 mon	N	N	-
10.	Sabari	39	M	OP	9 mon	N	N	-
11.	Mustaqahmed	48	M	OP	4 yrs	N	↓ density	-
12.	Rafiq	43	M	OP	6 mon	N	↓ density	-
13.	Kodhandam	40	M	OP	2 yrs	N	N	-
14.	Anantaraman	44	M	108223	3 yrs	N	N	0.9
15.	Gnanavel	49	M	OP	7 yrs	N	↓ density	1
16.	Krishnaveni	42	F	992792	1 yr	N	N	0.67
17.	Logavathy	48	F	997792	2 yr	N	↓ density	0.2
18.	Saraswathy	40	F	101761	1 yr	N	N	0.1
19.	Kalyani	40	F	996796	1 yr	N	N	0.15
20.	Suganya	46	F	101171	1 yr	N	↓ density	0.26
21.	Fathima bee	47	F	101711	2 yr	N	↓ density	0.3
22.	Arshad	45	F	OP	3 yrs	N	N	0.16
23.	Ameena	48	F	102987	7 yrs	N	↓ density	0.17
24.	Thilagammal	46	F	OP	2 yrs	N	N	-
25.	Parvathy	43	F	OP	3 yrs	N	N	-
26.	Ravi	47	M	997042	New	Mild NPDR	Dil loops,↓ Dens	1.45
27.	Manimaran	38	M	997692	5 yrs	Mild NPDR	Dil loops	0.4
28.	Mariyaselvam	52	M	999176	5 yrs	Mild NPDR	Dil loops	3
29.	Gurusamy	50	M	102404	3 yrs	Mild/mod NPDR	↓ density	1
30.	Latchumanadas	46	M	104271	4 yrs	Mild NPDR	N	0.4
31.	Sachidanandam	42	M	106178	9 mon	Mild NPDR	Dil loops,↓ dens	0.5
32.	Rangasamy	46	M	107261	4 mon	Mod NPDR	Dil loops	0.75
33.	Arunachalam	40	M	OP	6 yrs	Mild NPDR	N	-
34.	Ramamurthy	42	M	109697	4 mon	Mod NPDR	Dil loops	0.6
35.	Arunkumar	39	M	109971	1 yr	Mil/mod NPDR	Dil loops	0.7
36.	Samuel basha	45	M	OP	3 yrs	Mild NPDR	N	-
37.	Taufiq aaziz	41	M	OP	2 yrs	Mild NPDR	Dil loops	-
38.	Shanmugam	39	M	OP	2yrs	Mod NPDR	Dil loops	-
39.	Venugopal	37	M	OP	2 yrs	Mild NPDR	N	-
40.	Malliga	48	F	995784	1.5 yrs	Mild NPDR	N	0.01
41.	Paravamma	47	F	995790	3 yrs	Mod NPDR	Dil loops, ↓ dens	0.05
42.	Veerammal	49	F	996560	1 yr	Mod/sev NPDR	Dil loops	0.16
43.	Manimegalai	46	F	919761	5 yrs	Mild NPDR	Dil loops	0.8
44.	Emilia	44	F	104075	6 mon	Mild NPDR/N	Dil loops	0.9
45.	Jothi	38	F	108176	2 mon	Mild NPDR	Dil loops	0.5
46.	Arunmozhi	46	F	109191	2 yrs	Mild NPDR	N	0.3
47.	Kavitha	42	F	109799	4 yrs	Mod NPDR	↓ dens, dil loops	0.1
48.	Charulatha	40	F	109780	2 yrs	Mild NPDR	N	0.3
49.	Faizunisha	46	F	109919	2 yrs	Mild NPDR	Dil loops	0.06
50.	Parimala	40	F	OP	1 yr	Mild NPDR	N	-