“Predictors of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus with Normoalbuminuria”

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This is to certify that this dissertation entitled **"Predictors of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus with Normoalbuminuria"** is the bonafide work of **Dr S.IRSATH,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015.**

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DECLARATION

I , DR S.IRSATH , solemnly declare that this dissertation titled **"Predictors of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus with Normoalbuminuria"** is a bonafide record of work done by at the Department Of General Medicine , Government Rajaji Hospital , Madurai , under the guidance of **Dr. J.SANGUMANI ,M.D,** Professor , Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2015.**

Place: Madurai

Date:

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ABSTRACT

INTRODUCTION

Diabetes mellitus, one of the important non communicable diseases in our country and has become major health concern in recent times. Microvascular disease is a common complication in type 2 diabetes and diabetic retinopathy (DR) and nephropathy represent leading causes of visual impairment and end stage renal disease respectively in adults of both developed and developing world.

Patients with type 2 diabetes may have Diabetic Retinopathy without microalbuminuria. Various studies have shown risk factors for DR that include hypertension, longer duration of diabetes and anemia. This has been supported by several studies reporting 10-30% prevalence of DR in type 2 diabetes with normoalbuminuria. Hence, early identification and correction of these predictors are necessary to avoid sight threatening complications due to diabetic retinopathy.

AIMS AND OBJECTIVES

To estimate the prevalence of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus who have normoalbuminuria.

To study the predictors (Anemia, Duration of Type 2 Diabetes Mellitus, Hypertension) of Diabetic Retinopathy in patients with normoalbuminuria.

MATERIALS AND METHODS

STUDY POPULATION:

This study was conducted among 100 patients with Type 2 Diabetes Mellitus attending Department of General Medicine in Govt. Rajaji Hospital, Madurai.

STUDY PROTOCOL:

This study is done in 100 type 2 diabetes mellitus patients .

Patients are first performed renal function test and microalbumin in urine.

Patients with normal renal function test and normoalbuminuria are selected.

Then they undergo haemoglobin estimation, measurement of blood pressure and history of duration of type 2 diabetes mellitus are elicited.

Now the patient undergoes fundus examination and screening for diabetic retinopathy is done.

Then the prevalence of diabetic retinopathy and the predictors of diabetic retinopathy in patients with normoalbuminuria are calculated.

RESULTS:

In our study, the diabetic retinopathy estimated prevalence in patients with normoalbuminuric type 2 diabetes mellitus is around 40%. Hence in normoalbuminuric type 2 diabetes individuals, presence of other predictors like anemia (Hb < 8 gms), systemic hypertension and longer duration of diabetes can identify the individuals with diabetic retinopathy which was statistically significant in our study.

CONCLUSIONS:

In patients of type 2 DM, inspite of normoalbuminuria diabetic retinopathy is very much common. Absence of albuminuria should not be the criteria to defer for screening of diabetic retinopathy. Various predictors for the determination of DR are the estimated levels of haemoglobin, diabetes duration, and associated systemic hypertension.

. Hence, even in type 2 diabetes patients with normoalbuminuria, presence of other predictors like low haemoglobin, systemic hypertension and longer duration of diabetes can identify high risk individuals who develop diabetic retinopathy.

KEYWORDS: Type 2 Diabetes Mellitus, Normoalbuminuria, Diabetic Retinopathy, Anemia, Systemic Hypertension, Longer duration of Diabetes.

INTRODUCTION

Diabetes mellitus, one of the important non communicable diseases in our country and has become major health concern in recent times. Microvascular disease is a common complication in type 2 diabetes and diabetic retinopathy (DR) and nephropathy represent leading causes of visual impairment and end stage renal disease respectively in adults of both developed and developing world.

Patients with type 2 diabetes may have Diabetic Retinopathy without microalbuminuria. Various studies have shown risk factors for DR that include hypertension, longer duration of diabetes and anemia. This has been supported by several studies reporting 10-30% prevalence of DR in type 2 diabetes with normoalbuminuria.

Higher blood pressure was found to be independent risk factor for Diabetic Retinopathy. Anemia was found to be an another risk factor. Anemia patients were develop DR more frequently than individuals without anemia, because of retinal hypoxia due to anemia.

Anemia identification and management is important in the individuals of diabetic retinopathy. In anemic patients with (Hb<8g/dl) and diabetes mellitus, correction of anemia cause good improvement in diabetic retinopathy. Management of anemia causes better tissue oxygenation and

leads to substantial decrease in VEGF synthesis, which improves the hyper permeability and new vessel changes are inhibited.

Anemia is related to the development of DR and as a risk factor for the deterioration of DR. Hence the evaluation and treatment of anemia should be a part of the follow up visits in DM patients.

Patients with longer duration of diabetes have high risk of developing diabetic retinopathy due to chronic hyperglycaemic state. In diabetic individuals with normoalbuminuria, identifying other predictors like anemia, systemic hypertension and longer duration of diabetes may help finding the presence of diabetic retinopathy. Hence, early identification and correction of these predictors are necessary to avoid sight threatening complications due to diabetic retinopathy.

AIM OF THE STUDY

To estimate the prevalence of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus who have normoalbuminuria.

To study the predictors (Anemia, Duration of Type 2 Diabetes Mellitus, Hypertension) of Diabetic Retinopathy in patients with normoalbuminuria.

REVIEW OF LITERATURE

Diabetes, literally meaning “siphon,” to explain “liquefaction of the flesh and bones into urine”. In 1674, Thomas Willis, and professor of the natural philosophy at Oxford, discovered that the urine of individuals with diabetes was sweet by tasting. This was actually rediscovery, previously by an ancient Hindu document by Susruta in India in about 400 B.C. had described diabetic syndrome characterized by the “honeyed urine”.

. Willis could not able to pinpoint the chemical nature of the “sweet” substance, because variety of different chemical substances were equally sweet to the sense of taste. It was Matthew Dobson of Manchester, England, demonstrated, in 1776, that persons with diabetes actually excrete sugar in their urine. After boiling urine to dryness, he found that the residue, a crystalline material, had the appearance and taste of “brown sugar”.

In the majority of patients with type 2 diabetes, there was no single genetic defect found for this process. Thus, the combination effects of multigenic, heterogeneous, complex, and related causes my result in the disease..

In a very few individuals with monogenic causes of type 2 diabetes, inheritance of the two mutant genes from both parents or autosomal dominant inheritance were responsible. Despite these genetic heterogenicity, a consistent phenotype becomes manifested when the disease condition develops in an individual , characterized by the following

1. Impairement in the secretion of insulin.
2. Resistance due to insulin action.
3. Increased glucose production in the liver, due to increased gluconeogenesis and glycogenolysis.

Many factors were involved in the reduction in β-cell function, including dietary indiscretion causing progressive exhaustion of β cells, prolonged glucose toxicity, and preprogrammed genetic abnormalities in the β-cell function. Predominantly, it is the progressive β-cell deterioration which results in worsening of the hyperglycemic state in the type 2 diabetic individuals.

The majority of type 2 diabetic patients are hyperinsulinemic and were overweight at the time of diagnosis. The subsequent conversion from the state of impaired glucose-tolerant to type 2 diabetes is influenced by concomitant medical conditions, distributions of the body fat, degree of obesity, ethnicity, sedentary lifestyle, and aging. Thus, one can find that the

type 2 diabetic patient is at the end of a progressive triad of metabolic defects whose interrelationships directly affect the natural history and progression of the disease.

Illnesses related to diabetes causes large number of hospitalizations due to cardiovascular and renal diseases. At the time of initial diagnosis itself, many patients have complications due to both microvascular and macrovascular related problems.This deprives patients from primary prevention of microvascular complications. So, primary prevention is better than secondary prevention.

According to the World Health Statistics 2012, every 10 th individual is diabetic. In 2012 , 371 million had diabetes. It will increase to 552 million by 2030. Low and middle income countries people constitute about 80%.Most people are in the age of 40 to 59 years.

DIABETES: THE INDIAN SCENARIO

According to WHO (World Health Organization), there were about 32 million diabetics in 2000. According to International Diabetes Federation (IDF), estimated diabetics in 2030 will be around 121 million. There are about 62.4 million diabetics and 77 million prediabetics in India in 2011.

There are also many number of undiagnosed diabetics in India shown by various studies. Through various studies shown that around 50% of Indian diabetics have poor glycemic control. Data from CUPS (Chennai Urban Population Study) and CURES (Chennai Urban Rural Epidemiology Study) estimates the diabetic related complications.

DEFINITION

Factors opposing the action of insulin or the lack of insulin leads to the occurrence of diabetes. This results in hyperglycemia because of inadequate insulin action. When there is absolute lack of insulin, it leads to rise in the level of ketone bodies resulting in ketosis.

PATHOPHYSIOLOGY

In the early stages pancreatic beta cells over stimulated for compensating for insulin resistance. During the course of time, beta cells get exhausted due to hyperstimulation causing the blood glucose levels to rise leading to diabetes.

Normally, after meals glucose disposal occurs through tissues like brain which can utilize the glucose independently, followed by splanchnic uptake. The remaining glucose utilization occurs in insulin dependent tissues like adipose tissue and muscles.

In type 2 diabetes, the normal balance between uptake of glucose by tissues and endogenous glucose production following ingestion of glucose is disrupted.

Beta cell dysfunction plays a crucial role in type 2 diabetes. Beta cells are in constant state of changing dynamics, with regeneration from islets and corresponding apoptosis. This state of apoptosis and islet neogenesis gets altered due to numerous factors like:

1.Genetic susceptibility

2.Increasing age

3.Glucotoxicity

4.Insulin resistance

5.Reduced incretin effect

6.Lipotoxicity

7.Hexosaminases

8.Amylin

The above mentioned factors lead to failure of beta cells. Rising blood glucose values with the background of beta cell failure leads to inadequate insulin secretion. Environmental factors like obesity, gender and diet also lead to genetic susceptibility causing hyperglycaemic state.

Beta cell failure along with insulin resistance in liver and muscle is termed as “The Triumvirate” by De Fronzo. Insulin resistance leads to further decline in insulin sensitivity, poor metabolic control and hyperglycemia.

Most important causes for the development of insulin resistance are sedentary life style and obesity. Insulin resistance is due to the presence larger amount of abdominal fat in diabetics. Large number of proinflammatory cytokines are released because of adiposity which include

1.Interleukins 6 and 8

2.Monocyte Chemoattractant protein 1

3. Tumour Necrosis Factor alpha

Single Nucleotide Polymorphisms are associated with insulin resistance and beta cell dysfunction. Around 40 independent loci are associated with high risk of type 2 diabetes.

Diabetogenic Gene- Relatively specific and essential genes causing diabetes in an individual.

Diabetes related genes- Non specific and not only limited to diabetics.

Combination of both diabetogenic genes and diabetes related genes with the environmental factors leads to diabetes.

DIAGNOSTIC CRITERIA

Random blood sugar more than 200 mg/dl(>11.1 mmol/L) with symptoms of diabetes

Or

Fasting blood glucose level more than 126 mg/dl(>7 mmol/L)

Or

HbA1C > 6.5%

Or

After oral glucose tolerance test , 2 hour blood glucose more than 200 mg/dl(>11.1 mmol/L)

RISK FACTORS

1. Obesity (BMI > 25)

2.History of cardiovascular disease

3.Polycystic ovary syndrome or acanthosis nigricans

4.Previous Gestational Diabetes Mellitus history or delivery of baby weight more than 4 kg

5.Systemic Hypertension > 140/90 mmHg

6.HDL cholesterol < 35 mg/dl

7.Triglycerides > 250 mg/dl

8.Previous History of Impaired fasting glucose, Impaired glucose tolerance, or HbA1C of 5.5 to 6.5 %

9.Sedentary lifestyle

10.Diabetes mellitus history in family members

11.Race/Ethnicity – African American, Native American, Asian American, Pacific Islander

12.Physical inactivity

PATHOGENESIS

Hyperglycemic state causes extensive tissue damage at the tissue level. Abnormal glucose tolerance causes damage to signalling and critical pathways at the cellular level. Various ways through these pathways activated are :

A. Hyperglycemic state leading to direct toxicity.

B. Hyperglycemic state causing release of metabolic derivatives and their by-products.

C. Continuous effects on special signaling pathways at the cellular level .

Complications of Type 2 Diabetes mellitus at the cellular level by various pathways are:

1. Aldose reductase overactivity.

2. Electron transport chain in the mitochondria causing overproduction of superoxide anions which leads to activation of hexosamine pathway .

3. Formation of Advanced Glycation End Products .

4.Reactive oxygen intermediates causing increased oxidative stress.

5. Isoforms of protein kinase C gets activated.

6. Polyol pathway activation .

AMERICAN DIABETES ASSOCIATION CLASSIFICATION OF DIABETES MELLITUS

The American Diabetes Association divides diabetes into five different classes. They are :

1. Gestational diabetes.

2. Malnutrition-associated diabetes

3. Diabetes associated due to other factors like drugs, chemicals.

4. . Type 2 diabetes.

5. Type 1 diabetes.

CHRONIC COMPLICATIONS OF DM

The chronic complications of DM affecting many of the organ systems and are responsible for the majority of morbidity and mortality due to the disease. Chronic complications of DM are of two types :

1. Complications due to Vascular problems.

2. Complications due to nonvascular Problems.

The vascular complications of DM are further subdivided into macrovascular complications and microvascular complications.

1.Microvascular complications

A. Diabetic Neuropathy

B. Diabetic Retinopathy

C. Diabetic Nephropathy

2.Macrovascular complications

A. Cerebrovascular disease

B. Coronary Heart Disease (CHD)

C. Peripheral Arterial Disease (PAD) .

Nonvascular complications which not as common as vascular complications include problems such as

A. Skin changes

B. Gastroparesis

C. Infections

Hearing loss may occur in the long term. Impaired mental status in the older age group is not very well studied.

Longer the duration of diabetes leads to the high chances for developing chronic complications due to persistent hyperglycemia. They usually will become manifest in the second and third decades of hyperglycemia. Most individuals with type 2 DM have complications at the time of diagnosis due to symptom less period of hyperglycemia.

Longer the duration of chronic hyperglycemia, more chances of developing . microvascular complications due to type 1 and type 2 DM. Most studies proved that whenever there is very good control of blood glucose, complications such as neuropathy, retinopathy and nephropathy can be prevented. Other not completely studied factors may also influence the development of complications.

Some individuals even after long-standing DM, will never develop retinopathy or nephropathy. This shows that there are still some influences due to genetic predisposition which is responsible to develop such complications.

Unlike microvascular complications, the chances of developing macrovascular complications due to chronic hyperglycemia is not very much conclusive. But mortality and morbidity due to coronary heart events are high in diabetic individuals than in non diabetics.

HbA1C and postprandial plasma glucose values very well correlate with such events. Other influences such as hypertension and dyslipidemia also play crucial roles in macrovascular complications.

Chronic complications of diabetes include

1. Macrovascular complications

2. Microvascular complications

3. Other complications

MICROVASCULAR COMPLICATIONS

1. Neuropathy

2.Eye diseases

Retinopathy

Macular edema

3.Nephropathy

MACROVASCULAR COMPLICATIONS

1. Cerebrovascular Disease

2.Peripheral Arterial Disease

3.Coronary Heart Disease

OTHER COMPLICATIONS

1.Hearing loss

2.Periodontal disease

3.Glaucoma

4. Cataracts

5.Infections

6. Dermatological diseases

7.Genitourinary

Uropathy

Sexual dysfunction

8. Gastrointestinal

Diarrhea

Gastroparesis

Around 35 to 45 % of all diabetics are affected by microvascular complications.

DCCT (Diabetes Control and Complications Trial) and UKPDS (United Kingdom Prospective Diabetes Study) have shown that progression of complications related to diabetes is prevented through good glycemic control.

ETIOPATHOGENESIS

POLYOL-SORBITOL MECHANISM

Aldose reductase is an enzyme that leads to accumulation of sorbitol at the cellular level in various diabetic conditions. Various protective organic osmolytes levels are decreased in diabetics due to high intracellular sorbitol levels, they can lead to promotion of developing macro and micro vascular complications.

This mechanism was used in developing the drugs which inhibit aldose reductase, which causes reduction in intracellular sorbitol levels by restoring protective osmolytes levels. Signal transduction mediated in cellular functions are affected due to high sorbitol levels which then leads to reduction of protective osmolytes such as taurine and myoinositol.

MYOINOSITOL PATHWAY

Plasma and tissues in mammals contain cyclic hexitol known as Myoinositol. It is the most important content in cell membranes and phospholipids. Peripheral nerves contain high concentration of myoinositol. Glucose 6 phosphate synthesis and phosphoinositol hydrolysis causes maintenance of tissue myoinositol levels maintenance.

High intracellular glucose levels leads to myoinositol depletion in tissues, which leads to Na+K+ATPase inhibition. Myoinositol uptake is decreased in presence of low Na+K+ATPase.

Nerve fibre regeneration gets impaired in presence of low myoinositol and correlates well with the clinical neuropathy responsible for impaired and neurological damage seen in patients with diabetes.

Metabolism of prostaglandins and synthesis of nitric oxide gets impaired in presence of deficiency in myoinositol. This leads to defective nitric oxide production and alteration in cyclo oxygenase pathways leading to peripheral nerve defects causing complications.

Treatment with analogs of prostaglandin E 1 causes improvement in myoinositol levels, thereby leading to some kind of improvement in microvascular complications.

PERICYTES LOSS

Pericytes gets destroyed due to accumulation of sorbitol. Loss of pericytes leads to altered blood flow in retina, leading to tissue hypoxia and capillary permeability gets increased. These changes lead to diminished synthesis of vasodilatory molecule nitric oxide. Low levels of nitric oxide leads to sympathetic tone augmentation, excess release of acetyl choline and increase in angiotensin 2 production.

Protective intracellular osmolytes gets depleted because of low blood flow due to diminished nitric oxide leading to complications of microvasculature.

NITRIC OXIDE PATHWAY

Maintanence of sodium–potassium adenosine triphosphatase activity is mediated by nitric oxide, which is important for transmission of impulses and metabolism of nerves. Many metabolic defects occur due to disruption in pathway of nitric oxide.

Aldose reductase inhibitors have benefit of preventing most of the microvascular problems from the disease and preserve nerve conduction velocity. Most patients gets their symptom relieved and microvascular complications progression gets halted due to use of aldose inhibitors.

Many pathways are involved in the pathogenesis of complications, aldose inhibitors alone provide only some benefit.

ADVANCED GLYCATION END PRODUCTS (AGE)

AGE are formed due to lipoproteins or proteins glycation by sugar moieties. High blood glucose within the tissue causes production of AGE both in the intracellular and extracellular tissues.

Various modes of formation of AGE are:

1. Glucose derived deoxy fructose lysine adducts decomposition causes formation of Amadori products
2. Phosphate compounds fragmentation
3. Glucose oxidation intracellularly

Glycosylated hemoglobin used to measure average blood sugar in 60 days is an good example of AGE. Increased permeability of the basement membrane in the glomeruli of renal interstitium is due to advanced glycosylation. Microalbuminuria and macroalbuminuria result due to increase in capillary permeability.

Procoagulant and molecules of pro inflammation gets expressed due to AGE binding to its receptors. This leads the patient to high risk of infections and wound healing impairment. Formation of AGE enhances with increase in age and also in conditions like diabetes.

In recent times many AGE inhibitors are identified. They act through various mechanisms that include :

1.Inhibition of periodontal inflammation

2.Inhibition of albuminuria

3.Increased nerve terminal conduction velocities

4.Increase in arterial elasticity

REACTIVE OXYGEN SPECIES (ROS)

Various enzymatic and non enzymatic mechanisms due to oxidative stress from increased blood sugar causes formation of free radicals. Imbalance between Reactive oxygen species and endogenous cellular defense causes oxidative stress.

Presence of oxidative stress causes within endothelium inhibition of barrier function leading to adhesion of leukocytes and reduction in levels of nitric oxide.

These free radicals leads to activation of various signalling pathways which leads to oxidation of proteins, lipids, intracellular mitochondrial DNA causing tissue damage. Low nitric oxide due to free radicals causes adhesion of inflammatory cells to the endothelium. This results in impairment of endothelial barrier function leading to endothelial dysfunction and occurrence of microvascular complications.

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PROTEIN KINASES C (PKC)

The Protein Kinase C (PKC) are group of phospholipid-dependent protein kinases. These kinases mediate various cellular responses to growth factors, hormones and the neurotransmitters. They make an important part in vasodilatory substances release mechanisms and also in activation of endothelium.

PKC levels rise to massive levels due to persistent hyperglycaemic state. Since PKC is an substance of pro inflammation, it causes increased permeability of endothelium due to release of Vascular Endothelial Growth Factor (VEGF).

PKC also leads to increase in the production of Plasminogen Activator Inhibitor 1 (PAI 1) which leads to complications in the heart due to activation of Nicotinamide Adenine DiNucleotide Phosphate (NADPH)-dependent oxidases.

Based on the patient's genetic background, the prevention of impairment in angiogenesis in diabetic retinopathy due to the use of PKC inhibitors varies.

Signal transduction are mediated through PKC-activated NF-κB (a nuclear transcription factor) which leads to proinflammatory effects.

Various other growth factors which get transcripted by protein kinase family include the following:

1. Vascular Endothelial Growth Factor (VEGF) , which causes increase in neovascularisation and permeability due to endothelium increases.

2. A potent vasoconstrictor, Endothelin 1.

3.Promotion of expansion of matrix due to Transforming growth factor (TGF)

4. Vascular wall growth induction by the Platelet-derived growth factor-β (PDGF)

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HEXOSAMINE PATHWAY

Excess blood glucose present in the intracellular environment due to hyperglycaemic state causes this glucose to enter the hexosamine pathway. This leads to synthesis of many proteoglycans due to diversion of fructose phosphate from glycolytic pathway.

Activation of hexosamine pathway leads to intracellular increase of hydrogen peroxide. This increased hydrogen peroxide causes dysfunction of beta cells due to insulin release impairment since hexosamine pathway is actively sensitised by beta cells present in the pancreas.

Hexosamine pathway activation also leads to high stress on beta cells in the pancreas which causes dysfunction of the beta cells as well as impairment of resistance to insulin.There are many studies regarding inhibitors of hexosamine pathways. The best results came from N- Acetyl Cysteine which is a potent anti oxidant. It causes decrease in the various changes occurred due to pathway of hexosamine.

OTHER MECHANISMS

1.Electron transport chain in mitochondria causes over production of superoxide anions. This leads to all major manifestations in the diabetes. Progression of retinopathy even with good glycemic control is due to the production of these superoxide anions.

2. Peroxisome proliferator-activated receptor (PPAR) activation inhibition due to mutations in the DNA of mitochondrium due to hyperglycemia. This leads to defective electron transport chain leading to production of superoxides causing damage to tissues.

3. NF-κB pathway aberrant regulation leading to arteriosclerosis and damage to tissues. This pathway causes dysregulation of various receptors like VEGF expression which leads to various derangements in the metabolism.

These other mechanisms causes tissue damage by different pathways leading to various complications seen in the patients with type 2 diabetes mellitus.

GLUCOSAMINE

Glucosamine leads to increased effect on Plasminogen Activator Inhibitor 1 (PAI 1). This effect leads to protein kinases c activation. Hence use of glucosamine in the diabetic individuals should be weighed against this potential risk.

OTHER KINASE PATHWAYS

The net reslts of various other kinases pathways activation include:

1.Enhancement of insulin resistance,

2.Related tissue damaging

3.Worsening hyperglycemia

These changes end in a continuum of increased insulin resistance due to deteriorating hyperglycemia. This causes activation of various cell damaging mechanisms.Few studies have proven that α-lipoic acid an antioxidant causes retardation in the progression of these destructive molecular pathways. This antioxidant also found to cause reduction in fructosamine levels in some patients with diabetes mellitus.

DIABETIC RETINOPATHY

21% of patients were found to have diabetic retinopathy even at the time of diagnosis of diabetes. Diabetes is one of the leading cause of blindness in individuals between the ages of 20 and 74 years. After 15 years of duration of diabetes, around 90% of patients were found to have retinopathy and.

Retinopathy is causing upto 12,000 to 24,000 cases of blindness every year. Permanent retinal injury with ongoing visual loss may have already occurred when the patient approaches the doctor with complaints of blurred vision. Therefore initial screening by the the primary care physician is critical.

Every part in human eye is susceptible to the detrimental effect of diabetes. Comparing to non diabetics, diabetic people have 25 times more chance of developing blindness. In India , DR ranks sixth common cause of blindness.

The relative risk is more in the age group of 30 to 60 years. It is unusual under children of 10 years of age. DR is usually present at the time of onset of symptoms in type 2 diabetes mellitus, whereas type 1 diabetes mellitus patients are free of DR during first 5 years of diagnosis.

The incidence of loss of vision increases with increasing age, severity of retinopathy, diabetes duration ,presence of proteinuria and high glycosylated haemoglobin levels.

Blindness in a patient with retinopathy usually results from any one of the following causes:

1.Non resolving vitreous hemorrhage

2.Traction retinal detachment

3.Diabetic macular edema.

However, the 5-year risk of severe visual loss can be greatly reduced to less than 2% if a person with diabetic retinopathy approaching or just when reaching high-risk proliferative retinopathy, as defined below, undergoes the procedure -Scatter (Panretinal) laser photocoagulation surgery. Intensive glycemic control causing delay in onset and slowing progression of retinopathy were clearly proven by DCCT and UKPDS trials.

Furthermore, people with CSME, Clinically Significant diabetic Macular Edema can decrease their risk of visual loss from 50% to approximately 12% or less, if they undergo appropriate focal laser surgery.

Because diabetic retinopathy is most often asymptomatic in its most treatable stages, early detection and treatment of diabetic

retinopathy through regularly scheduled ocular examination is critical.

Sudden loss of vision in a patient with retinopathy is usually the result of any of the following:

1. CNS stroke

2. Onset of bilateral macular edema, which is associated with cardiac or renal failure or severe anemia.

3. Retinal vascular occlusion

4. Lens changes caused by fluctuating alterations in blood sugar

5Vitreous hemorrhage

RISK FACTORS FOR DIABETIC RETINOPATHY

1. DURATION OF DIABETES MELLITUS

The most important determining factor of retinopathy is duration. Around 50% of patients develop DR after 10 years of onset, 70% after 20 years of onset and 90% after 30 years of onset of the diabetes.

2. GENDER

Incidence is more in female population than in male population (4:3).

3. METABOLIC CONTROL

Poor metabolic control correlates with the development and progression of DR.

4. HEREDITY

DR is transmitted as an Autosomal recessive trait without sex linkage. This effect is more on the proliferative type of retinopathy (PDR).

5. PREGNANCY

Moderate acceleration in the changes of diabetic retinopathy occurs in pregnancy.

6. HYPERTENSION

When patients have associated hypertension, it causes acceleration of the changes of diabetic retinopathy.

7. OTHER RISK FACTORS

1. Alcohol
2. Hyperlipidemia
3. Smoking
4. Anemia
5. Obesity

PATHOGENESIS OF DIABETIC RETINOPATHY

Diabetic retinopathy predominantly affects the veins, venules and venous end of capillaries. Basic pathophysiologic processes in the development of diabetic retinopathy include:

(a) Pericytes loss associated with retinal capillaries

(b)Basement membrane thickening

(c) Changes in the blood flow in retina

(d)Outpouching of capillary walls forming microaneurysms

(e) Closure of retinal capillaries and arterioles resulting in retinal nonperfusion

(f) Increased vascular permeability of retinal capillaries due to breakdown in the Blood/Retinal barrier.

(g) Proliferation of vessels in retina and iris

(h) Development of the fibrovascular tissue

(i) Fibrous proliferation and contraction of vitreous causes vitreous hemorrhage and retinal detachment due to traction.

HEMORRHAGES AND/OR MICROANEURYSMS

The various diabetic retinal lesions and along with their severity, both alone and in aggregate, are the exact predictors of the diabetic retinopathy progression and ensuing visual loss. Various lesions in diabetic retinopathy is because of various pathologic processes and interactions during the diabetes course and development of diabetic eye disease.

The retinal pericytes, which are intimately associated within the basement membrane of the endothelial cells in retina, are normally present in a one-to-one ratio with the endothelial cells. This is a ratio higher than found anywhere else in the body. This finding and other cell-culture data have strongly suggested that the retinal pericytes were critical supporting cells for the retinal capillaries.

The loss of this retinal pericytes is thought, therefore, to be a factor contributing for the development of endothelial cell dysfunction and weakness within the retinal capillary wall, possibly

contributing to the formation of the microaneurysms, which, along with venous dilatation, producing early clinicals.

Micro-aneurysms, which occur due to retinal capillaries saccular outpouchings are the early clinical signs of patients with diabetic retinopathy. Intraretinal haemorrhages are common due to IRMA, IntraRetinal Microvascular Abnormalities.

These hemorrhages reflect the retinal level of the hemorrhage and retinal architecture due to the ruptured microaneurysms and leaking capillaries.

Since the structure of the nerve-fibre layer runs exactly parallel to the retinal surface, it gives it a flame-shaped appearance. The more characteristic lesions of diabetic retinopathy are the pinpoint or dot shaped haemorrhages which occur in the deeper retinal layers. Here the arrangement of cells is perpendicular to the surface of the retina and gives itsclassical appearance.

The term “dot/blot hemorrhages” were used to describe these small intraretinal hemorrhages which were characteristic of diabetic retinopathy. Because it is very difficult, if not impossible, to distinguish these small dot/blot hemorrhages from that of microaneurysms, and because critical evaluation of these two lesions has determined that there is little additional clinically significant information is obtained by differentiating two lesions, they are

classically evaluated together and referred as “hemorrhages and microaneurysms.”

VENOUS CALIBER ABNORMALITIES

Venous caliber abnormalities are now found to be the early indicators of possible diabetic retinopathy. It is an indicator of severe state of hypoxia in retina. They can be loop formation, beading, venous dilatation. These venous changes occur usually where there are areas of loss of perfusion nearby to the veins. Treatment by scatter (panretinal) photocoagulation may cause these kind abnormal veins to become more normal in appearance over time.

INTRARETINAL MICROVASCULAR ABNORMALITIES

Through areas of nonperfusion, there is proliferation of endothelial cell that act as “shunts”. These pre existing vessels that some consider new vessel growth occur within the retina and are called Intraretinal microvascular abnormalities (IRMAs).

IRMAs are seen in severe stages of Non Proliferative Diabetic Retinopathy (NPDR). It is a sign that neovascularization is about to appear on retinal surface or on the optic disc within a short time. They are seen adjacent to cotton-wool spots. They are nothing but micro infarcts in the nerve- fibre layer of the retina.

RETINAL NEOVASCULARIZATION

Proliferative Diabetic Retinopathy (PDR) is marked by the abnormal development of new vessels in the retina.. Neovascularization occur either at or near the optic disc [neovascularization of the disc (NVD)] or any other area on the retinal surface [neovascularization elsewhere (NVE)]. Fibrous tissue are found along with the new vessels which appear opaque. Later they become adherent to the nearby vitreous. There is variable rate of growth of these new vessels.

High-risk PDR patients are treated with scatter laser photocoagulation. High-risk PDR is diagnosed by any of the following lesions:

(a) If fresh vitreous or pre retinal hemorrhage is present, size of NVE greater than or equal to one half of the disc area; or

(b) Size of NVD approximately one fourth to one third of the disc area or more in size; or

(c) Size of NVD less than one fourth the disc area with fresh preretinal or vitreous hemorrhage;

Because identification of these high-risk characteristics is critical for determining the delivery of sight-saving care, the presence or absence of the preretinal or vitreous hemorrhage, the location of new vessels, the presence or absence of new vessels and the severity of the new vessels must be noted carefully.

LEVELS OF DIABETIC RETINOPATHY:

Scatter (panretinal) laser photocoagulation surgery should be considered in an individual with high-risk stage of Proliferative diabetic retinopathy eye. The high-risk stage is suspected when there are signs of severe or very severe NPDR or new vessels which are not satisfying the definition of high-risk PDR (Proliferative Diabetic Retinopathy), especially if it coexists with stage of very severe NPDR.

When changes in two eyes are unequal, changes in the eye with more severe involvement is taken for classification.

The following is the clinical classification of diabetic retinopathy :

LEVELS OF RETINOPATHY

NON PROLIFERATIVE DIABETIC RETINOPATHY	
A.	Mild NPDR
	Presence of at least one significant microaneurysm
	Not meeting criteria for B, C, D, E, or F
B.	Moderate NPDR
	Presence of IRMA or H/Ma is greater than standard photograph 2A or SE, VB.
	Not meeting the criteria for C, D, E, or F
C.	Severe NPDR
	In at least one quadrant IRMA is greater than standard photograph 8A

	VB in two or more quadrants or H/Ma greater than standard photograph 2A in all four quadrants
D.	Very severe NPDR
	Any two or more of C
	Not meeting criteria for E or F
PROLIFERATIVE DIABETIC RETINOPATHY (PDR)	
At least one of the following, Composition of PDR	
	Fibrous tissue proliferation
	NVD or NVE
	Preretinal or vitreous hemorrhage
E.	Early PDR
	Presence of New vessels

	Not meeting criteria for F
F.	High-risk PDR
	NVE ≥ ½ disc area and preretinal or vitreous hemorrhage or
	NVD ≥¼–1/3 disc area or
	NVD and vitreous or preretinal hemorrhage
CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA	
	HE located ≤500 μm from the centre of the macula with adjacent retinal thickening or
	A zone of retinal thickening, of size one disc area or larger, with any portion located ≤1 disc diameter from the centre of the macula or
	Retinal thickening located ≤500 μm from the centre of the macula

NONPROLIFERATIVE DIABETIC RETINOPATHY

NPDR also known as BACKGROUND RETINOPATHY is broadly divided into NPDR and PDR. Macular edema of diabetes can occur with either NPDR or PDR. Accurate diagnosis of the "diabetic retinopathy level" is crucial. The ongoing risk of progression to PDR and high-risk PDR varies according to it and is closely correlated with the specific level of NPDR in a patient.

Microaneurysms were the early evidence for DR in around 25% of the patients. They are visualised as "red dots" in the posterior fundus.

Hemorrhages- Flame shaped when appear in superficial nerve fibre layer; Blot shaped when appear in deeper layers.

Soft exudates- Also known as cotton wool spots. They represent infarcts in nerve fibre layer. They are sign of capillary non perfusion.

Hard exudates- white or yellow in colour. More common in elderly, increase in frequency with increasing duration of diabetes. They consist of lipoproteins.

Mild NPDR is marked by at least one retinal microaneurysm, but hemorrhages and microaneurysms are less in frequency than those in ETDRS standard photograph 2A in all four retinal quadrants. No other retinal lesions or abnormalities associated with diabetes were present.

Patients with mild NPDR on diagnosis have 5 percent risk of progressing to PDR within 1 year and a 15 percent risk of progressing to high-risk PDR within 5 years.

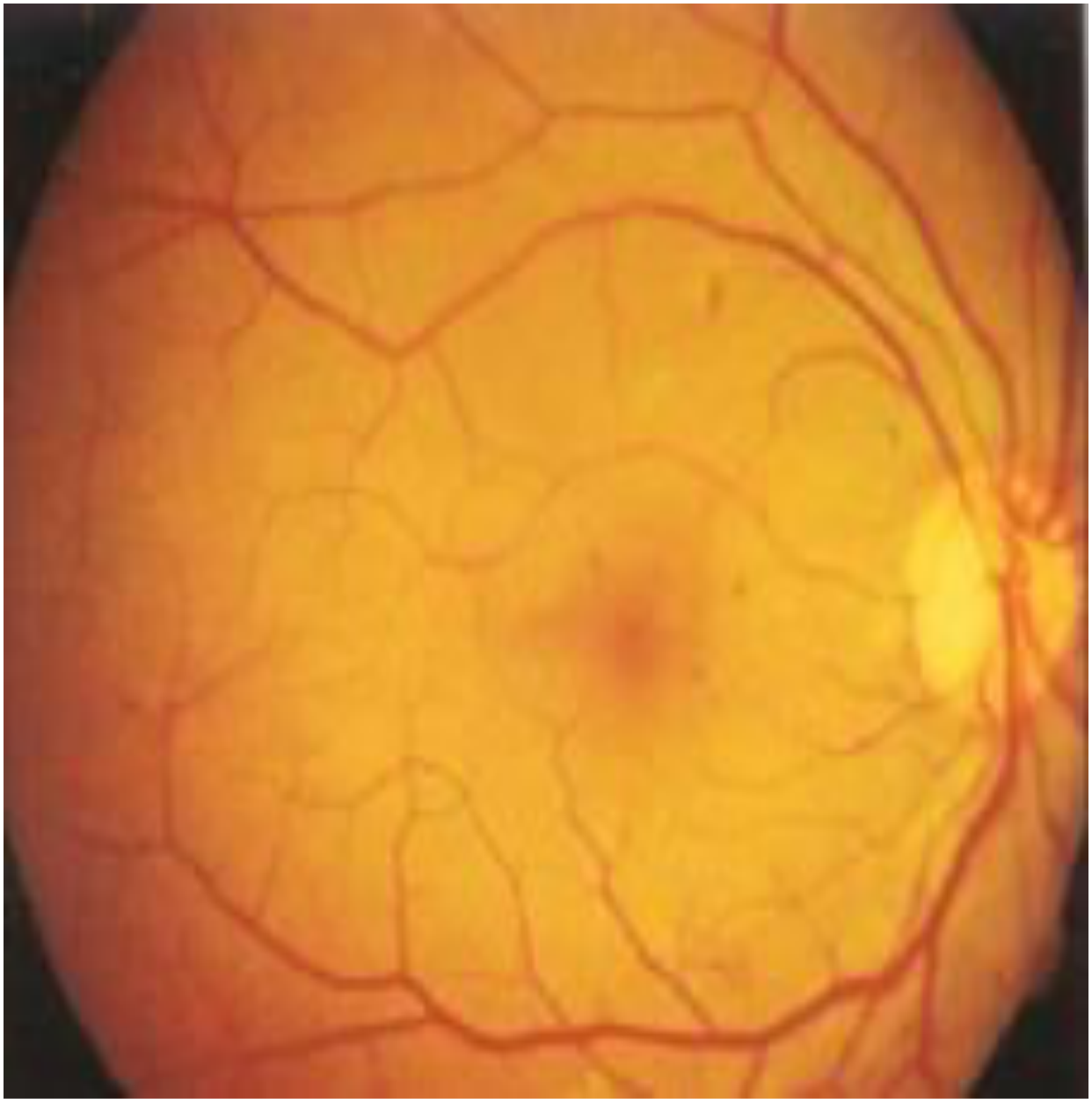

Figure 1 shows Mild Non Proliferative Diabetic Retinopathy

Moderate NPDR is diagnosed by microaneurysms and/or hemorrhages greater than those seen in ETDRS photograph 2A in at least one quadrant but in less than in four retinal quadrants, with or without evidence of venous beading and IRMA to a mild degree. The risk PDR to progress within 1 year is 12% to 27% and the amount of risk to progress to high-risk PDR is is 33% for 5 years .

Panretinal laser surgery is not preferred for patients with mild or moderate NPDR. They can be followed up at 6- to 12-month intervals. The presence of macular edema, even with mild or moderate degree of NPDR, requires follow-up in a shorter period of time.

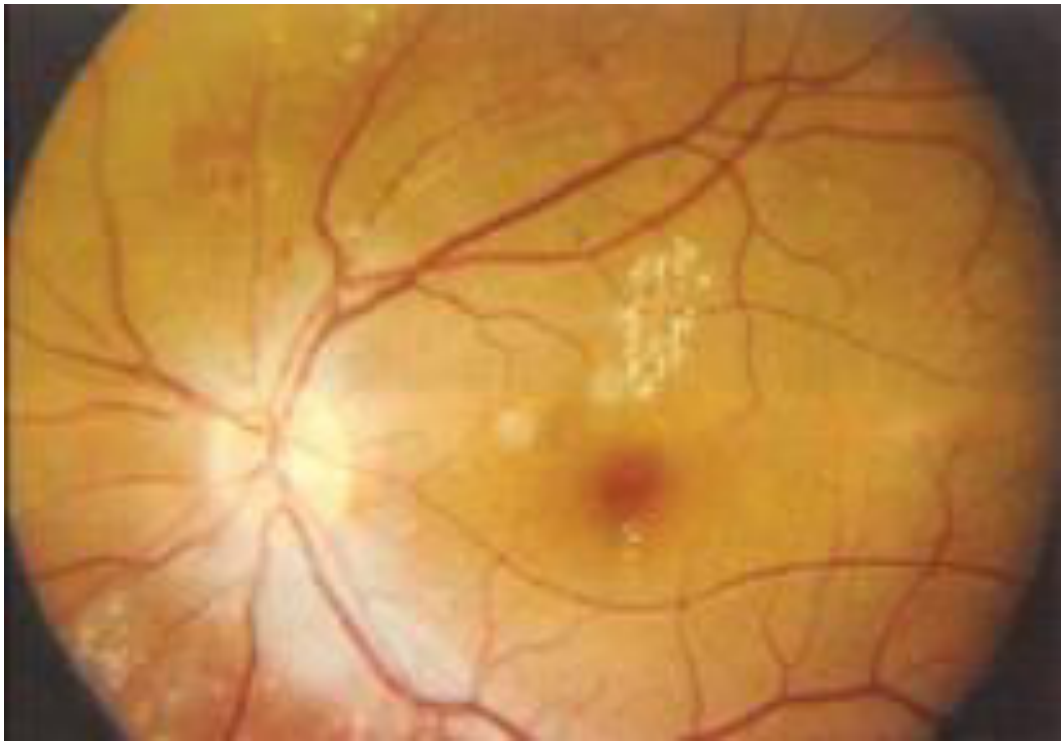

Figure 2 : Moderate Non Proliferative Diabetic Retinopathy

Severe NPDR is based on the severity of H/Ma, IRMA, and/or venous beading and was determined by any one of the following lesions :

(a) In at least one quadrant,IRMA greater than in ETDRS standard photo 8A or

(b) In four quadrants, H/Ma greater than in ETDRS standard photo 2A or

(c) Two or more quadrants has venous beading

In 1 year, patients with severe NPDR have 52% risk of developing PDR. In 5 years there is 60% risk of developing high-risk PDR. These patients require follow-up in 2- to 4-month intervals. The clinical effectiveness of the laser photocoagulation for the CSME along with PDR may be greatly reduced compared with treatment of CSME alone.

Treatment of clinically significant macular edema in patients with severe or very severe stage of NPDR is strongly indicated because of a high risk of developing PDR and requiring scatter (panretinal) laser surgery in a relatively short span of time.

In addition, scatter (panretinal) laser surgery can worsen macular edema is the another reason for optimizing the macular edema status of these patients who were likely to require scatter (panretinal) laser photocoagulation in the near term.

4-2-1 Rule : Presence any one of the following indicates severe diabetic retinopathy:

Microaneurysms	- 4 quadrants
Venous beading	- 2 quadrants
IRMA	- 1 quadrant

Patients with ***very severe NPDR*** have lesions of that of severe NPDR but there is no frank neovascularization. Within 1 year, these patients have 70-75% risk of PDR. Patients with severe or very severe NPDR are the ideal candidates for scatter (panretinal) laser surgery, particularly those with type 2 diabetes, and the presence of macular edema, if present, often requires treatment. Frequent reevaluation at 2- to 3-month intervals is very important for these kind of eyes.

Figure 3 shows Severe Non Proliferative Diabetic Retinopathy

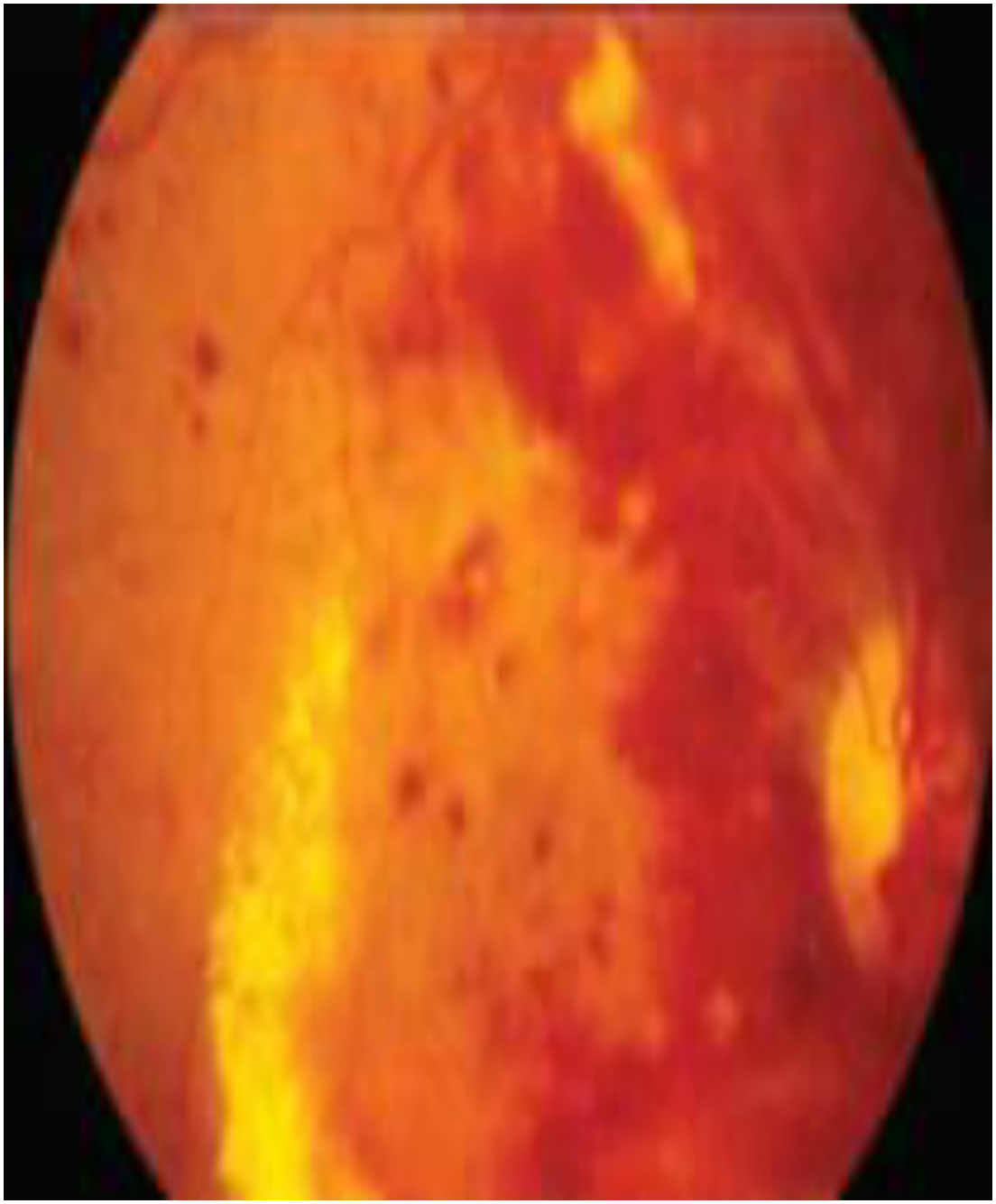

Figure 4 : Very Severe Non Proliferative Diabetic Retinopathy

PROLIFERATIVE DIABETIC RETINOPATHY

Diabetic retinopathy, characterised by neovascularisation on the optic disc (NVD) or elsewhere in the retina (NVE) or by the fibrous tissue proliferation is designated as PDR. Early PDR need not fulfil the definition for high-risk PDR . Eyes with early changes of PDR (less than high risk) have a 75 percent risk of development of high-risk PDR in a course of period of five years.

These eyes may require the scatter (panretinal) laser surgery. Macular edema, even if not significant clinically, may benefit from the focal treatment before scatter is initiated, as discussed previously (nonproliferative diabetic retinopathy).

In patients with early PDR changes (less than high-risk PDR), early scatter (panretinal) laser surgery must be considered if any of the associated findings are present

(a) any new vessels accompanied with severe or very severe NPDR,

(b) elevated new vessels,

(c) or NVD.

In patients with severe NPDR changes, if macular edema is present, focal treatment of macular edema is done even if the macular edema is not clinicallyimportant, as an initial preparation for the use of scatter laser photocoagulation in future.

In severe or very severe NPDR or early PDR, the type of diabetes is very important. It has been demonstrated by the ETDRS that in type 2 diabetes patints risk of severe visual loss is more. Hence vitrectomy surgery can be avoided to almost 50% if scatter (panretinal) laser surgery is initiated before the onset of high-risk PDR.

In contrast, type 1 diabetes patients showed not much advantage in the risk of loss of vision or for vitrectomy even if laser surgery is delayed until the development of PDR with high-risk characteristics.

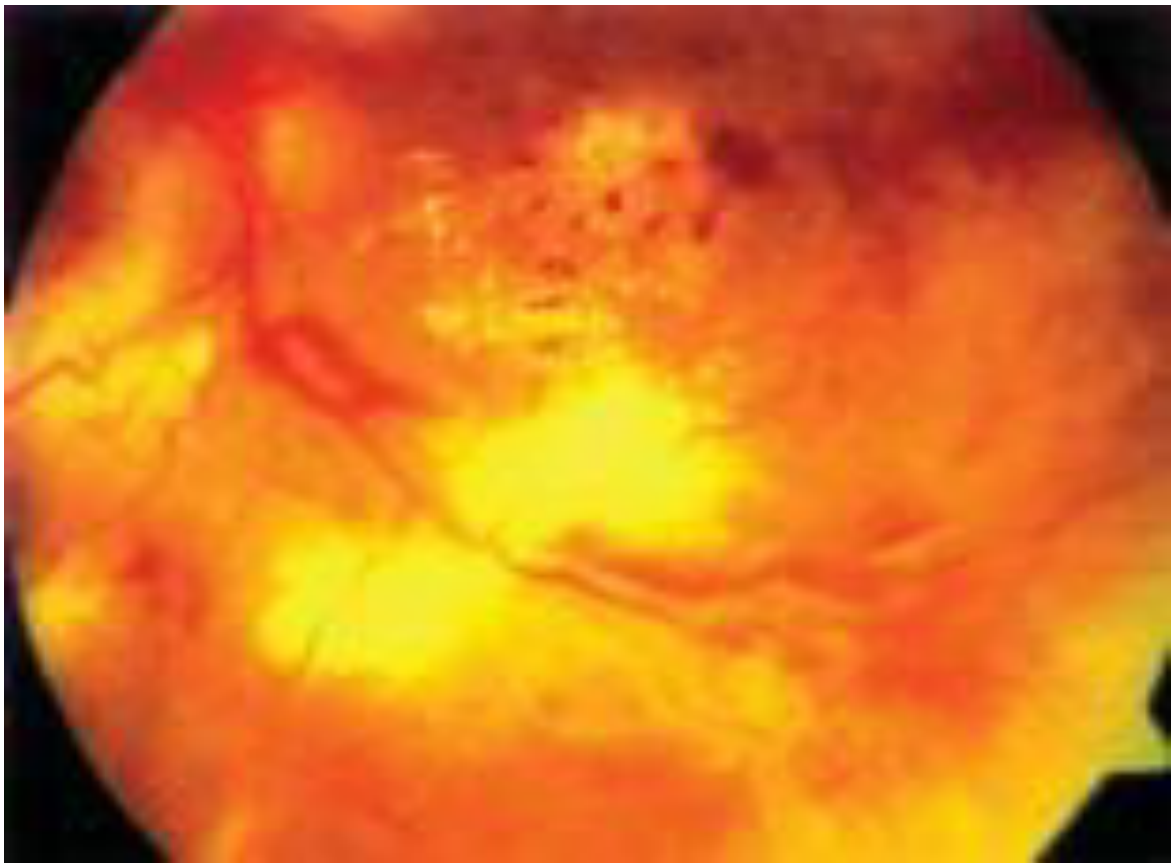

Figure 5 : Proliferative Diabetic Retinopathy

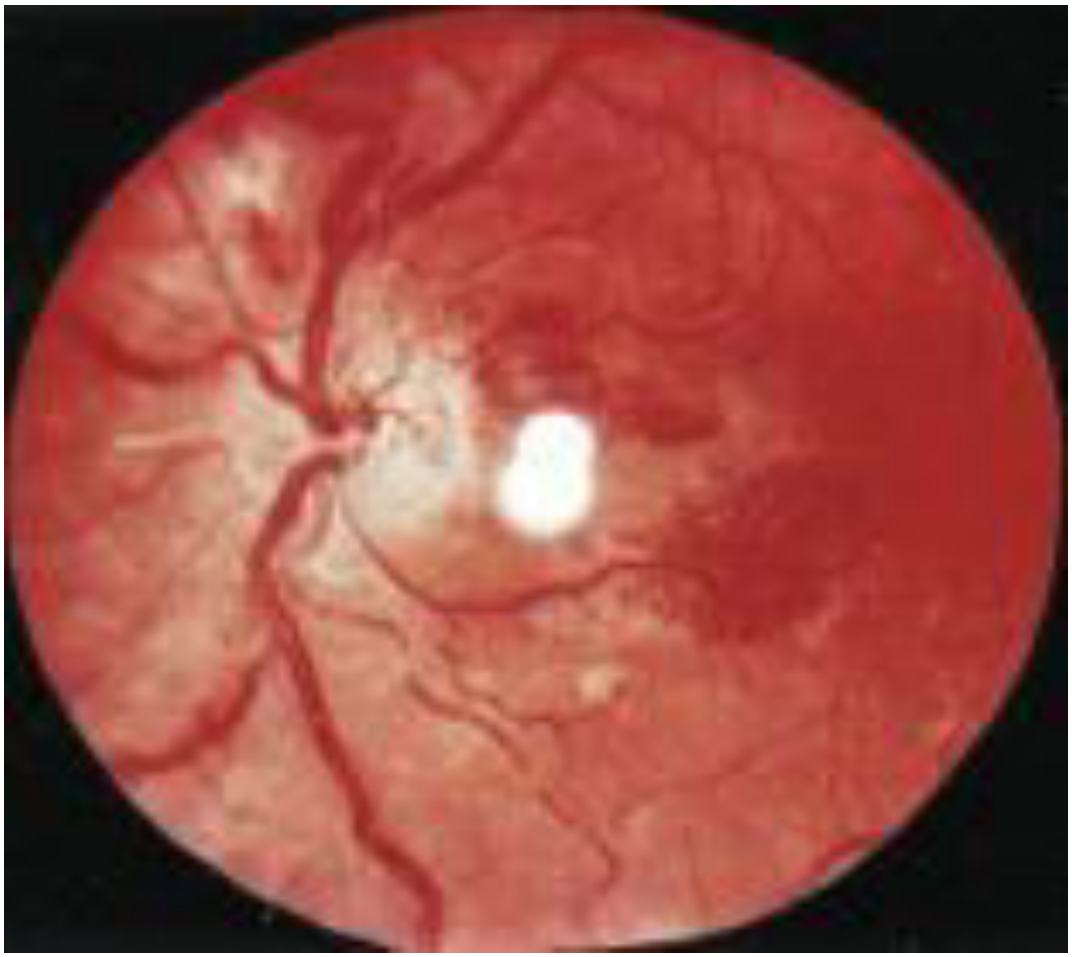

Figure 6 : Clinically Significant Macular Edema

DIABETIC MACULAR EDEMA

Diabetic macular edema can be associated with any stage of retinopathy .

Alterations in the macular structure observed in diabetes include :

(a) Fibrous-tissue proliferation causes dragging of retinal tissue, surface wrinkling, detachment of the macula producing traction in the macula

(b) Parafoveal capillaries nonperfusion with or without intraretinal fluid

(c) Full-thickness or lamellar hole formation in retina

(d) Preretinal or intraretinal hemorrhages in the macula

(e) Intraretinal fluid collection in the macula with or without lipid exudates with or without the cystoid changes and intraretinal fluid collection in the macula

(f) Multiple combinations of the above.

Macular edema is defined as retinal thickening within two disc diameters in the centre of the macula. This definition is not based on the presence of the fluorescein leakage. Hard exudates with adjacent retinal thickening threatening or involving the centre of the macula is clinically important.

CSME elaborated by the ETDRS has any one of the following lesions as mentioned:

(a) Retinal thickening of at least one disc area in size, part of it is within one disc diameter within the centre of the macula.

(b) Thickening of retina in or within 500 µm from the centre of the macula

(c) Adjacent retinal thickening with hard exudates at or within the 500 µm from the centre of the macula

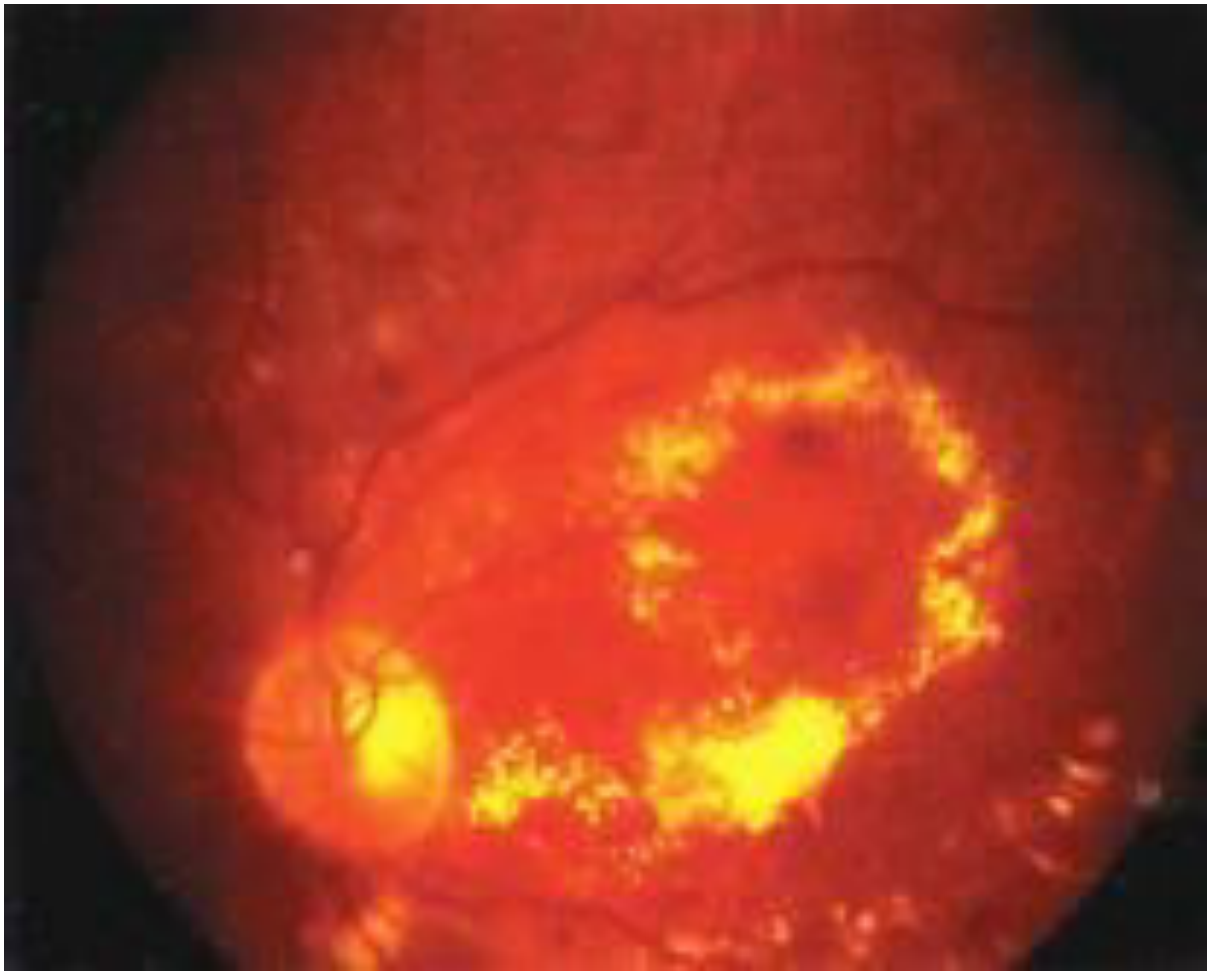

Figure 7 : Clinically Significant Macular Edema

ROLE OF CLINICAL FLUORESCEIN ANGIOGRAPHY IN MANAGEMENT OF RETINOPATHY:

In the presence of CSME it is valuable to detect potentially treatable lesions by doing Fluorescein angiography to the macula. However, its not used to identifying lesion like NVE or feeder vessels as it is usually unnecessary because the lesions are clinically evident and scatter (panretinal) laser surgery is the treatment method of choice for of diabetic retinopathy as it approaches or reaches the stage of high-risk.

Certain risk factors for the progression of NPDR to full blown PDR have been identified in angiography. Analysis of the data for the untreated (deferred) eyes in the ETDRS indicates that the following lesions were independently related to outcome:

(a) leakage of the fluorescein,

(b) capillary loss on the fluorescein angiography,

(c) capillary dilatation on the fluorescein angiography, and

(d) the following color fundus photographic risk factors: IRMA, venous beading, and H/Ma.

Hard and soft exudates have an inverse relationship to the progression of diabetic retinopathy. It is widely accepted that capillary loss as documented in the fluorescein angiography is a risk factor for progression from NPDR to PDR .

However, capillary dilatation on the fluorescein angiography, fluorescein leakage capillary loss on the fluorescein angiography, and the ETDRS color fundus photographic retinopathy are all very closely correlated.

Color fundus photography used in grading of retinopathy levels of the eyes also give prognostic results . Therefore, it is not of significant clinical importance to warrant routine use of fluorescein angiography to predict disease progression.

Follow-up retinal examinations, however, are very important. The appropriate interval can be determined by the skillful grading of seven standard-field stereo color fundus photographs and/or retinal evaluation by the experienced examiner.

The stage of diabetic retinopathy derived from the color fundus photography or retinal ophthalmic evaluation is very closely correlated with the rate of diabetic retinopathy progression, the accurate determination of retinopathy level becomes paramount clinical importance and it determines the appropriate retinal reevaluation interval.

Fluorescein angiography cannot “identify all cases destined to progress”. Periodic follow-up of all patients with diabetic retinopathy continues to be of fundamental clinical importance because scatter (panretinal) laser photocoagulation should be doneas diabetic retinopathy nears the high-risk stage .

LASER PHOTOCOAGULATION

Timing of Photocoagulation

In the ETDRS, the risk from moderate visual loss due to macular edema without any treatment with focal laser was around 30 percent. Focal laser surgery for CSME reduces this risk to 15% or less , a reduction in risk of approximately around 50%, and focal treatment also increases the chance of improvement in the visual acuity of one line or more.

On the other hand, scatter (panretinal) laser surgery was not as effective in managing diabetic macular edema and in few cases may have had a deleterious effect on the progression of macular edema.

Eyes with CSME and retinopathy approaching to high-risk PDR are best treated initially with focal photocoagulation for the macular edema for about 6 to 8 weeks before initiating scatter (panretinal) laser surgery. Eyes with mild to moderate NPDR and CSME respond well to prompt focal photocoagulation, with scatter treatment delayed.

Delaying scatter photocoagulation during focal treatment is being completed is unlikely to worsen the risk of visual loss, provided the retinopathy is not progressing very rapidly and regular follow-up can well be pursued. Late scatter photocoagulation while the focal treatment is completed in eyes with high-risk PDR usually is not advised, and the macular edema will usually be treated in the first treatment session of scatter photocoagulation.

Focal treatment was not attended by the adverse effects on central visual field or color vision in comparison with the eyes assigned to deferral of focal treatment in the ETDRS. Any harmful effects due to early photocoagulation as reflected by constriction of the peripheral visual fields seem to be due mostly to the scatter photocoagulation.

Because the principal benefit of the treatment is the prevention from further decrease in the visual acuity, focal laser surgery should be considered in all eyes with the level of CSME, especially if the macula is threatened, even with normal vision.

However, it should be noted that macular edema that is not particularly extensive may spontaneously resolve in as many as 30% of patients. Thus, in cases where visual acuity is excellent, the fovea is not particularly threatened due to edema, hard exudates, or subretinal fibrosis, the likelihood for requirement of scatter (panretinal) photocoagulation in the near future is very

low, and the patient demonstrates excellent compliance with the follow-up evaluations, the edema may, at the discretion of the patient and the treating physician, should be monitored carefully without the immediate focal photocoagulation.

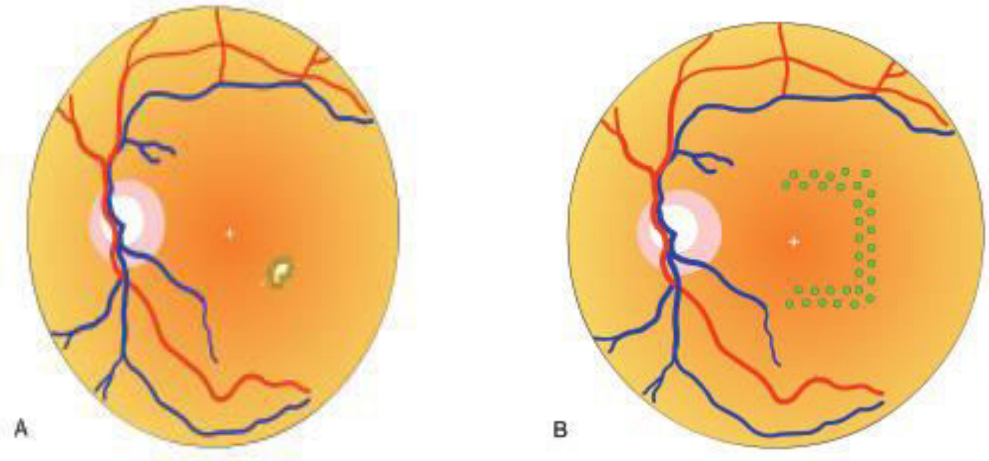

Figure 8 : Focal Photocoagulation

However, should the visual acuity show the signs of deterioration, the macular edema show signs of progression, or the retinopathy level advance to a stage where panretinal scatter laser photocoagulation is most likely in the near future, prompt focal laser surgery for the macular edema is usually indicated.

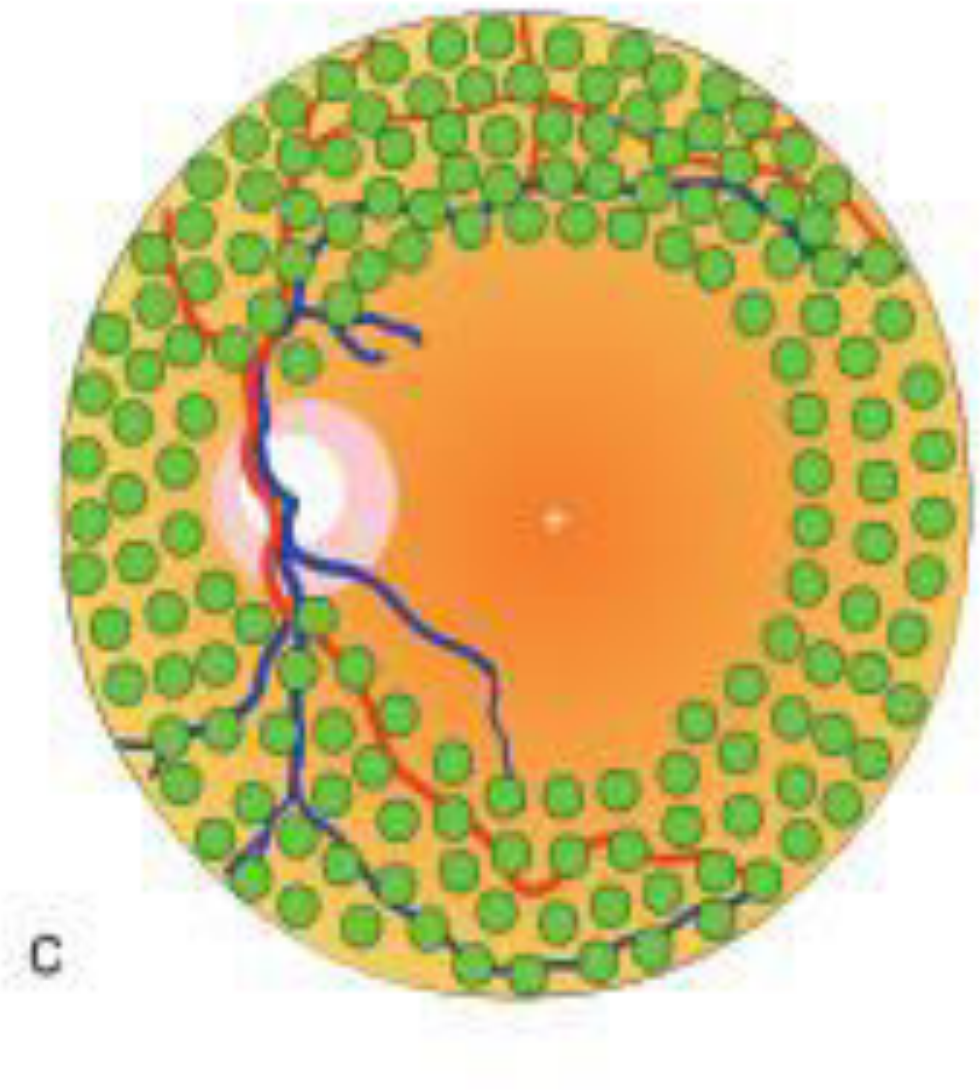

Figure 9 : Pan retinal Photocoagulation

The DRS showed in 1976 that pan retinal scatter photocoagulation was very effective in reducing the risk of severe visual loss due to high-risk PDR. The DRS did not provide a clear guidance between the treatment or deferral of the treatment unless there was high-risk PDR.

So one question of concern of the ETDRS is whether to go for earlier laser photocoagulation, before the progress to high-risk PDR, justified the side effects and risks of the laser surgery.

Side Effects and Complication of Scatter Laser Photocoagulation

Side effects
Changes in color vision
Internal ophthalmoplegia
Constriction of peripheral field
Night blindness (Nyctalopia)
Complications
Tractional retinal detachment due to progression of retinopathy
Rhegmatogenous retinal detachment and secondary retinal hole
Burn in fovea

Macular edema
Traction of fovea
Lens and corneal burns
Retrobulbar anesthesia injection which is rarely used now causes retrobulbar hemorrhage
Acute angle–closure glaucoma
Choroidal or serous detachment

In the ETDRS, during early treatment, compared with deferral of photocoagulation therapy until signs of PDR appears, was associated with a insignificant lowering in the incidence of impairment of vision; however, the 5-year rates were similar for both the early-treated group and the group which is assigned to “deferral” of treatment (2.6% and 3.7%, respectively).

If careful follow-up is done, scatter laser surgery is not usually recommended for mild or moderate NPDR. For severe or very severe NPDR and early PDR, scatter photocoagulation should definitely be done and usually

should not be delayed if the eye has reached to the high-risk proliferative stage". When the high-risk stage is reached the benefits and the risks of early photocoagulation may be roughly balanced and weighed.

Initiating scatter photocoagulation early in at least one of the eye seems particularly appropriate when both of the patient's eyes are approaching to the high-risk stage, as optimal timing of photocoagulation may be very difficult if both eyes require photocoagulation simultaneously. Also, prompt scatter photocoagulation of the retina should be considered when new vessel formation takes place in the angle of anterior chamber irrespective of high-risk PDR.

It has been demonstrated in the ETDRS that patients diabetes have decreased risk from severe loss of vision or vitrectomy by around 50% if scatter (panretinal) laser surgery is initiated early. In contrast, patients with type 1 diabetes showed not much difference, even though visual loss or the laser surgery was delayed until later stage.

Treatment Program

The treatment program for diabetic retinopathy consists of

(a)Initial scatter laser photocoagulation procedure

(b) careful follow-up regularly at 3- to 4-month intervals following the treatment

(c) re-treatment of recurrent treatable or persistent lesions

(d) Use of focal laser photocoagulation for the macular edema prior to scatter (panretinal) photocoagulation method to reduce the risk of progression of macular edema that is secondary to scatter photocoagulation.

As high-risk PDR stage is reached, the major threat for severe visual loss is traction retinal detachment. A lesser threat is persistent loss of vision, but a more common complication, is vitreous hemorrhage. The primary goal of scatter laser surgery is that the prevention of traction retinal detachment, particularly that involving the macula.

Various strategies are involved in the treatment follow-up. The ocular lesions which are to be considered for follow-up photocoagulation include new neovascularization which is flat or elevated neovascularization and new, persistent, or recurrent CSME.

The treatment methods include additional scatter laser treatment, local laser treatment to NVE, focal laser theraphy for CSME, *pars plana* vitrectomy for recurrent hemorrhages with fibrovascular proliferation leading to traction and when appropriate, continued observation. Furthermore scatter treatment may be placed in between previously placed laser scars as long as these kind of scars do not become confluent and the extent of the scatter treatment is not such as to totally destroy the retinal function.

Although laser surgery often considered to be painless, some patients may experience discomfort in association with the treatment procedure. There usually is some discomfort or pain for all patients when the peripheral retina is treated.

In summary, the risk of severe visual loss from PDR is reduced by scatter laser treatment. Both early scatter treatment prior to the development of high-risk PDR and deferral of the treatment until later reduces significantly the risk of visual loss. The mean rates of visual loss are same for each group after the treatment.

Consequently, it is concluded that the laser treatment need not be used for mild and moderate NPDR. For severe NPDR and early PDR stages, scatter treatment is ideally appropriate when close follow-up of these patients is unlikely, the disease process is progressing very rapidly, or in type 2 diabetes patients.

FUTURE HORIZONS

Molecular /Cellular Advances

In the past several decades, remarkable advances in the understanding of the basic mechanisms underlying the diabetes and diabetic retinopathy have been achieved.

These new insights into the processes which underly the fundamental molecular and cellular changes ultimately leading to sight-threatening complications of diabetic retinopathy are permitting to the development of new interventional approaches. These newer therapeutic modalities hold great promise for the further reduction or elimination of the complications of diabetic eye disease.

Advances have been made in understanding many of the areas, including the changes which underlying in the sorbitol pathway, the development of the oxidative stress, protein kinase C activation and the formation of the advanced glycosylation end-products. Each of these various pathways has been associated with variety of the complications of diabetes, and they are often intimately related to each other.

An area of substantial study has been in the increased flux through the sorbitol pathway in those cells exposed to a hyperglycemic environment. Consequently, aldose reductase inhibitors have been extensively evaluated for their potential use in ameliorating the diabetic retinopathy. A multicenter clinical trial, tested whether the daily dose of sorbinil could reduce the complications of diabetes mellitus.

Over a 3-year period, the drug had found to have no effects on the type 1 diabetes of moderate duration . However, the group which were taking sorbinil did show a slight lowering in the microaneurysms number. Unfortunately, there were complications in nearly 5-7% of the initial participants taking the drug.

These adverse reactions in the skin included are toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome. Because of the lack of efficacy in humans and the associated major side effects, no aldose reductase inhibitors were currently being used on a routine clinical basis for diabetic retinopathy treatment.

A variety of studies has also looked at the antioxidants as a potential ameliorator of the oxidative stress present under the diabetic conditions. Preliminary data on the antioxidants such as vitamin E have been promising with regard to prevention or reversal of early changes in retinal

circulation and in correcting the abnormal retinal blood flow present in patients with history of short-duration of diabetes and minimal diabetic retinopathy .

When proteins were exposed to high levels of the glucose for extended period of time, AGEs may be formed. Recent studies have suggested that the formation of these AGEs can cause a variety of changes in the cellular processes and may contribute to diabetic ocular complications. Inhibitors of AGEs are being in evaluation for clinical usefulness.

Newer modalities of treatment include PKC inhibitors. Activation of this protein kinase C enzyme can result in wide-ranging effects underlying endothelial dysfunction in eyes and other organs. In addition, protein kinase C is the key mediator of signaling processes induced by other growth factors involved in the retinal neovascularization, diabetic macular edema, and perhaps also in the earlier stages of diabetic retinopathy as well.

A particular isoform (the β isoform) of protein kinase C appears specifically to mediate many of the complications arising in the eyes. Consequently, inhibitors of the protein kinase C β have been evaluated in detail, with documented ability to normalize the retinal blood flow, suppression of retinal permeability, prevention of retinal neovascularization,

and normalization of retinal blood flow in patients with no or mild nonproliferative retinopathy.

These agents are currently in the clinical trials to determine whether they can prevent or cause slowing of the progression of diabetic retinopathy and/or diabetic macular edema. Results from these studies are expected in the forthcoming few years.

Another promising area in the investigations is the evaluation of the various growth factors which mediate the later-stage complications of diabetic retinopathy. Numerous angiogenic agents, such as vascular endothelial growth factor, which have been identified as the key modulators of the retinal neovascular response and the increase in the retinal vascular permeability.

Several inhibitors of these agents have been developed with very promising results observed over time and in the next few years may add significantly to the therapeutic armamentarium.

In addition, preliminary results from some small uncontrolled studies suggest that intravitreal administration of the steroids may have a significant effect in reduction of the diabetic macular edema and may actually cause improvement in vision in a subset of these patients. Currently, a number of these agents were in clinical trials.

PREGNANCY AND DR

Women with diabetes mellitus who are above to get pregnant should undergo a detailed eye examination before they conceive. In each trimester of their pregnancy diabetic pregnant women should ideally have eyes examination very early or often more frequently, as indicated by the levels of retinopathy, and usually 6 weeks after delivery.

Pregnant women can have worsening of retinopathy, as well as they may also have coexistent systemic hypertension, they should be monitored carefully throughout the course of pregnancy.

In women with PDR, in some cases cesarean delivery may be considered rather than vaginal delivery to reduce the risk of vitreous hemorrhage. A team work is needed between various faculties of medical team for caring of pregnant diabetic individual .

Various treatment modalities available such as laser photocoagulation should be discussed in detail with the patients even with the milder forms of retinopathy for diminising the visual loss. Furthermore, patients with the visual impairment of any degree, legal blindness, or total blindness should be informed about the availability of visual, vocational, and psychosocial rehabilitation programs.

During early stages of DR, symptoms are not much prominent in the individuals. Vision may be very good at the time of initial diagnosis of diabetic retinopathy, even when significant ocular disease is present.

Educational program at regular intervals and medical and ocular follow-up should be instituted at the very early stages itself.

As the retinal disease progresses, visual acuity may become compromised by the macular edema, episodes due to hemorrhage in the vitreous, macular non perfusion, or traction retinal detachment. Significant difficulties in the work or in the home environment can be caused due to such kind of loss of vision. This loss very often puts extreme psychologic stress on patients with the diabetes and their families. The healthcare provider should identify some stress factors , and appropriate support for the patients should be offered in the early stage of the disease itself.

In many cases, the patient will experience a significant drop in the visual acuity for a period of time. Although in many cases excellent vision can be ultimately obtained and retained over many decades, the period during which the diabetes patient experiences this kind of visual decline can lead to great uncertainty and anxiety.

It is of critical importance that the level of ocular disease should be monitored carefully and appropriate observation, laser treatment, vitreoretinal surgery, or other interventional procedures to be applied promptly whenever indicated. If these approaches are strictly followed, most patients

can very well retain excellent vision over many decades of stable ocular status once the diabetic retinopathy has become quiescent. New therapies on the horizon promise even more better outcomes.

Thus, it is obvious that a very close interaction between the diabetes patient and a diverse healthcare team is essential. The healthcare team will commonly require services from both the ophthalmologist and internist, as well as from the diabetologist, nursing practitioner, diabetes educator, dietician, psychosocial worker, and very many other specialties, depending on the particular situation.

With such access, carefully monitored and well planned routine ophthalmic follow-up, optimization of the glycemic and systemic medical control, and timely initiation of laser photocoagulation, the risk of blindness in persons with the diabetes mellitus can essentially be eliminated.

Fetal loss is more in presence of diabetic retinopathy and the rate increases with increasing severity of the retinopathy. The explanation is that the retinopathy is often associated with angiopathy elsewhere and poor placental blood perfusion because of microangiopathy may be the cause of high fetal loss. While the mere presence of diabetic retinopathy in a pregnant women is

not an indication for termination of pregnancy, it may become necessary if the retinopathy shows progression.

Though there is a extreme view that diabetic women with retinopathy should be advised not to conceive, there are no enough evidence to support this concept. Malignant retinopathy certainly worsens rapidly during pregnancy, but the exact reason behind this is not known. In a proportion of patients after delivery, diabetic retinopathy shows regression.

HYPERTENSION AND DIABETIC RETINOPATHY

Patients with higher blood pressure were more likely to develop diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) also found the higher relative risk for incidence of retinopathy with higher systolic blood pressure in an individual.

Hypertension causes hyperperfusion and auto regulation impairment which causes changes in hemodynamics and leads to the development of DR. In addition, formation of diabetic retinopathy due to hypertension is by increased expression of vascular endothelial growth factor in the endothelial cells of retina and ocular fluids, leading to new vessels formation.

Presence of both systolic as well as diastolic hypertension can lead to the progression of DR.

In the UKPDS trial, it was proven that there occurs major reduction in complications due to micro vasculature by very good control of systemic hypertension.

Presence of hypertension leads to the formation of DR by several mechanisms.These include the following:

1.Proliferation of small and new vessels due to increased expression of vascular endothelial growth factor.

2.Damage and destruction of endothelium of retina.

3.Impairment of autoregulation of vasculature in retina.

With the occurrence of microalbuminuria, blood pressure begins to rise. Once macroalbuminuria sets in, 60 to 70 % of the patients will develop hypertension. In the stage of renal failure most of the patients will have systemic hypertension. There are very well proven evidences that hypertension causing acceleration of microangiopathic complications particularly the retinopathic complications.

In a large randomised studies, average mean systolic blood pressure was found to be 10 to 12 mm higher in diabetic subjects when compare to the general population. Prevalence of systemic hypertension in type 2 diabetes mellitus is twice as that of non diabetic population. Subjects with hypertension have more hyperglycemia than those with normal BP and hypertensive patients are more susceptible to develop DM. Hence in a patient with DM and HT achieving normotension is as important as achieving euglycemia.

ANEMIA AND DIABETIC RETINOPATHY

Anemia is suggested as another long term complication of DM and defined as hemoglobin level less than 13 g/dl in men and 12g/dl in women. The prevalence of anemia in diabetes mellitus individual is reported as around 14-48% . In diabetes mellitus patients, anemia is associated independently with the development of diabetic retinopathy, chronic kidney disease and cardiovascular illnesses like heart failure.

In type 2 diabetes, anemia is the second cause leading to diabetic retinopathy next to hypperglycemia. Recent studies found that patients with low haemoglobin are in high risk to develop retinopathy changes. Anemia is also frequently seen in renal disease individuals.

It was found that in individuals with low haemoglobin, there are high chances for retinopathy and significant loss of vsion. Patients were also at high risk for developing macular edema due to anemia. Treatment of anemia causes resolution of macular edema in few individuals.

The causes of anemia in an diabetes individual with mellitus are multifactorial. They are :

1. Decreased synthesis of erythropoietin.

2.Chronic hyperglycemia is involved in the pathogenesis of anemia by means of creating abnormalities in RBCs, oxidative stress, autonomic neuropathy and renal sympathetic denervation. These conditions put the renal interstitium in a

hypoxic state and consequently, the production of erythropoietin by peri tubular fibroblasts is impaired .

3.The other possible causes of anemia include functional erythropoietin deficiency, diabetic nephropathy, chronic inflammation, high levels of ultimate glycosylated products, iron deficiency, anti- DM drugs and low testosterone levels as suggested by others .

Regarding the effect of anemia on diabetic retinopathy , it seems that the anemia-induced hypoxia leads to the increased release of vasoproliferative factors (X factor) and bring about the progression of to severe form of retinopathy .

Preceeding studies reported that the flexibility of RBCs in DM patients is much less compared to normal individuals and this may be the reason for deterioration of complications of DM .

DR due to anemia develops in an individual with duration of diabetes more than five years. From the above mentioned observations, it is better to evaluate of anemia at an early stage and should be considered in all individuals with DR.

Anemia identification and and its treatment is important in the management of DR. In few patients who had both anemia (Hb-8g/dl) and DM, Friedman and associates found that treatment of anemia was correlated with very good resolution of macular hard exudates.

The increase in haemoglobin concentration causes diminished production of VEGF and improves oxygenation to tissues leading to improvement in hyperpermeability and diminishes the trigger needed for new vessel formation.

MATERIALS AND METHODS

STUDY POPULATION:

This study was conducted among 100 patients with Type 2 Diabetes Mellitus attending Department of General Medicine in Govt. Rajaji Hospital, Madurai.

Inclusion criteria:

- Type 2 DM patients with:
    - Fasting plasma glucose level≥126 mg/dl

      or
    - 2-hour post prandial glucose level >200 mg/dl
- Patients treated with dietary modification alone or in combination with Oral hypoglycemic agents or insulin were also categorized as type 2 DM
- Patients with Normoalbuminuria, which is defined as a urinary albumin excretion rate (UAER) <20 μg/min or <30 mg/g in 2 out of 3 tests taken within 2–3 months consecutively.
- Normal Renal function Test

Exclusion criteria:

- ✓ Age <18 years or >80 years
- ✓ Dyslipidemias
- ✓ Hepatic failure

- ✓ Renal failure
- ✓ Smokers
- ✓ Thyroid dysfunction
- ✓ Acute systemic infection
- ✓ Exercise
- ✓ On treatment for anemia
- ✓ Pregnancy
- ✓ Malignancies
- ✓ Refractive errors

ANTICIPATED OUTCOME

Diabetic patients with retinopathy have lower level of hemoglobin and higher frequency of anemia. It is suggested that the level of hemoglobin should be evaluated periodically in diabetic patients. In type 2 diabetes mellitus Patients even with normoalbuminuria, presence of other risk factors such as anemia, high blood pressure, longer duration of diabetes have high incidence of Diabetic Retinopathy.

DATA COLLECTION:

- Detailed history
- Detailed clinical examination.
- Ophthalmoscopic examination of fundus
- Hemoglobin examination
- Measurement of Blood Pressure

Laboratory investigations:

- Hemoglobin estimation
- Fundus Examination
- Urine albumin
- Renal function test
- Liver function test
- Lipid profile
- RBC, PCV
- Peripheral Smear

STUDY PROTOCOL

This study is done in 100 type 2 diabetes mellitus patients .

Patients are first performed renal function test and microalbumin in urine.

Patients with normal renal function test and normoalbuminuria are selected.

Then they undergo haemoglobin estimation, measurement of blood pressure and history of duration of type 2 diabetes mellitus are elicited.

Now the patient undergoes fundus examination and screening for diabetic retinopathy is done.

Then the prevalence of diabetic retinopathy and the predictors of diabetic retinopathy in patients with normoalbuminuria are calculated.

DESIGN OF STUDY

Prospective cross sectional study

PERIOD OF STUDY:

JUNE 2014 to AUGUST 2014

CONSENT:

Individual written and informed consent.

ANALYSIS:

SIMPLE STATISTICAL ANALYSIS

CONFLICT OF INTEREST:

NIL

FINANCIAL SUPPORT:

NIL

RESULTS AND ANALYSIS

Table 1: Age distribution in the study population (n= 100)

Age group	Frequency	Percent
18-35 years	13	13
35-50 years	34	34
50-65 years	33	33
65-85 years	20	20
Total	100	100

Comments: About 67% of the study subjects were in the age group of 35-65 years while the 20% were in the age group 65-85 years.

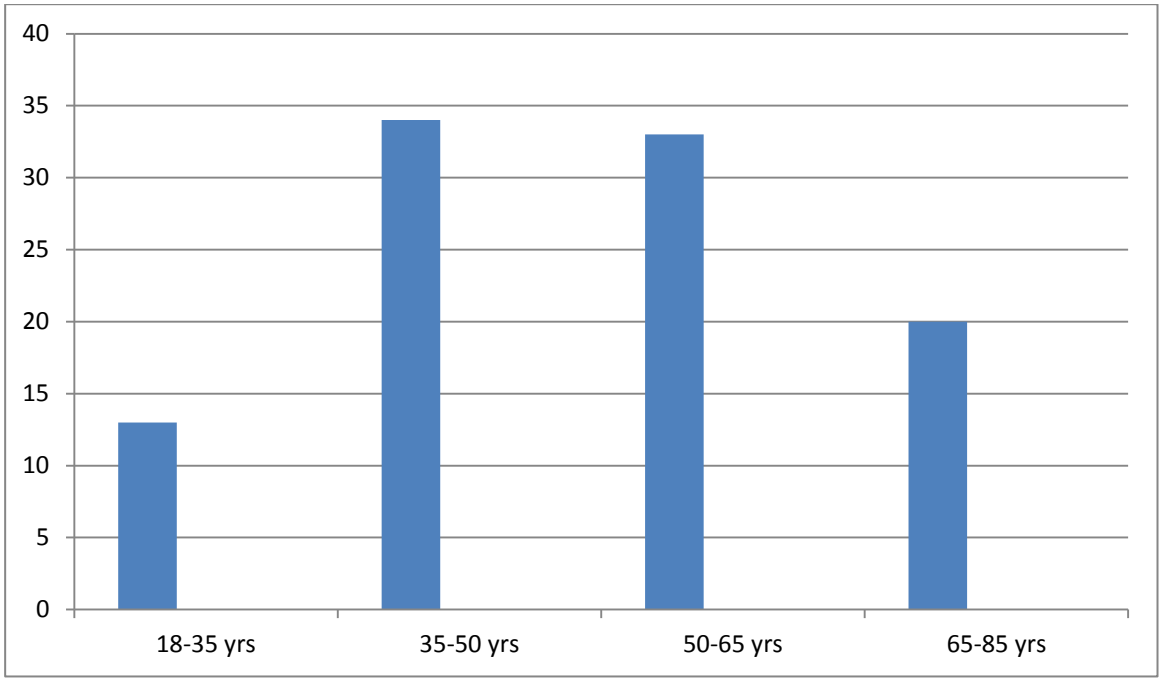

Figure 10 : Age distribution in the study population

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Table 2 : Distribution of gender in the study population (n=100)

Gender	Frequency	Percent
Female	48	48
Male	52	52
Total	100	100

Comments: Majority of the study subjects were males (52%) while the remaining 48% were females.

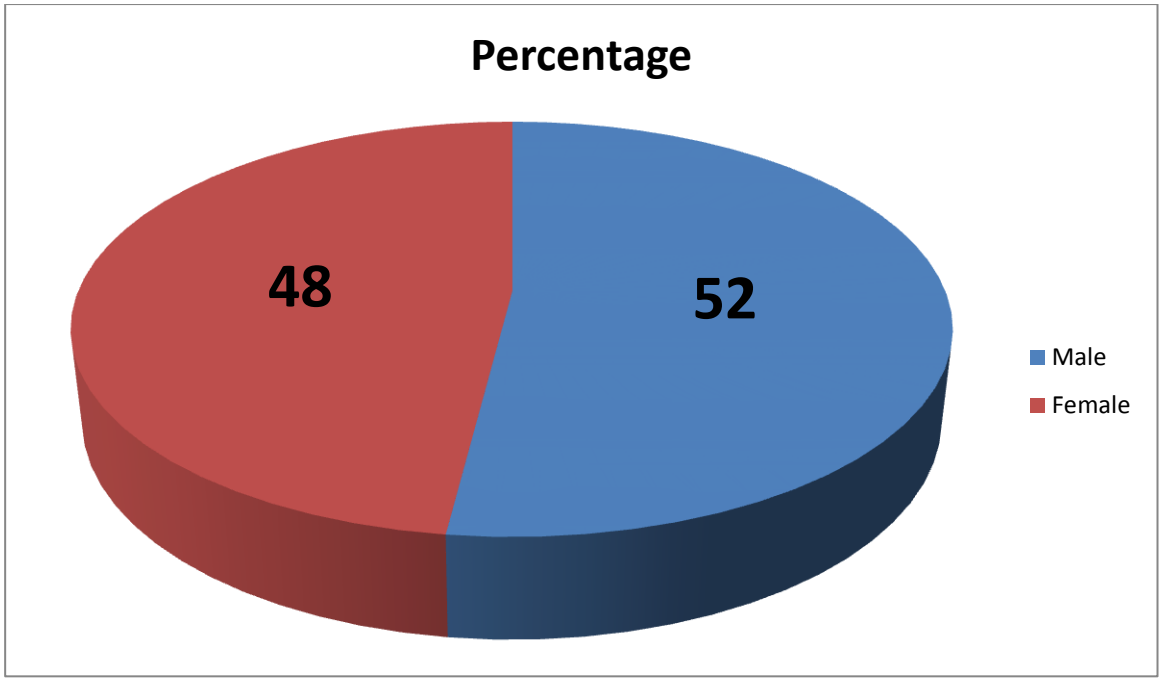

Figure 11 : Gender distribution of the study population

Table 3 : Incidence of Diabetic retinopathy in study population with anemia (n = 39)

Anemia	**Diabetic retinopathy (Present)**	**Diabetic retinopathy (Absent)**	**Total**
< 6 gms	6	4	10
6-8 gms	18	3	21
>8 – 12 gms	6	2	8
Total	30	9	39

Comment : Among the 39 patients with anemia 30 patients have Diabetic retinopathy

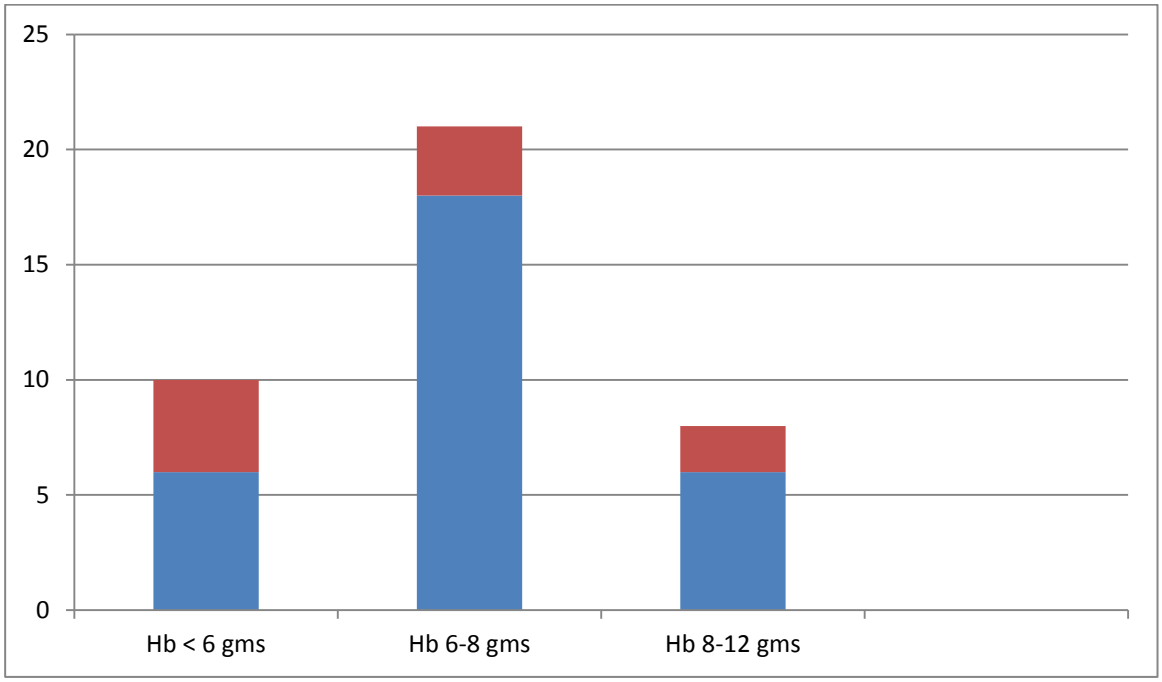

Figure 12 : Diabetic retinopathy Incidence in study population with anemia (n = 39)

Table 4: Incidence of Diabetic retinopathy in study population with systemic Hypertension (n = 30)

Hypertension	**Diabetic retinopathy (Present)**	**Diabetic retinopathy (Absent)**	**Total**
Stage 1	14	4	18
Stage 2	9	3	12
Total	23	7	30

Comment : Stage 1 Hypertension : 140/90 mmHg – 160/100 mmHg

Stage 2 Hypertension : >160/100 mmHg – 180/110 mmHg

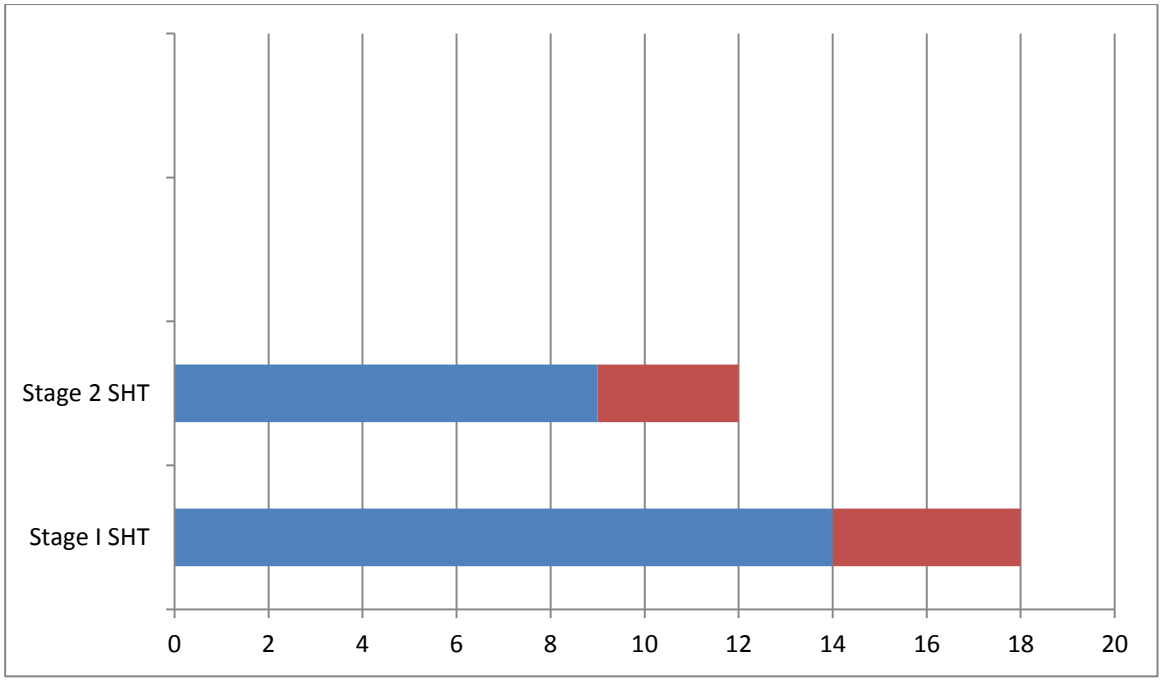

Figure 13 : Diabetic retinopathy Incidence in study population with systemic Hypertension (n = 30)

Table 5: Diabetic retinopathy Incidence with Longer duration of Diabetes in study population (n = 100)

Duration	**Diabetic retinopathy (Present)**	**Diabetic retinopathy (Absent)**	**Total**
<5 years	6	50	54
5 – 15 years	18	6	24
>15 years	16	4	20
Total	40	60	100

Comment : Among 100 patients with diabetes 34 patients have diabetic retinopathy if duration of diabetes more than 5 years

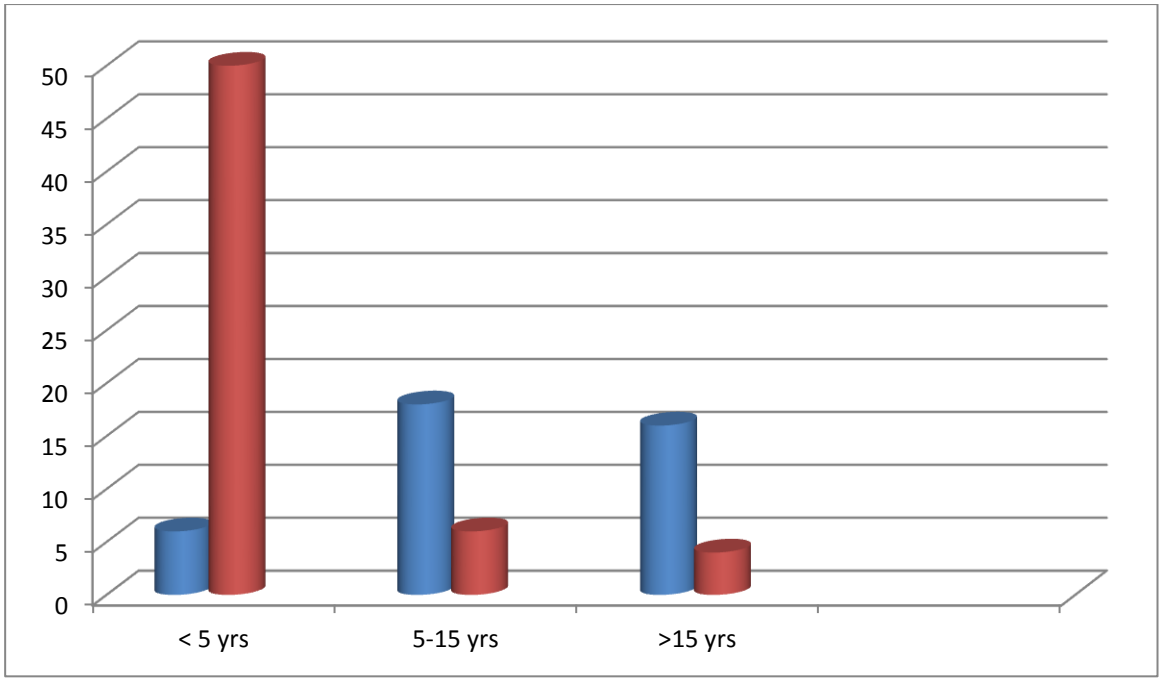

Figure 14 : Diabetic retinopathy Incidence with Longer duration of Diabetes in study population (n = 100)

Table 6: Prevalence of retinopathy in patients with Hb <8 gms, SHT, Duration of diabetes > 5 years

Predictors	**Diabetic retinopathy (Present)**	**Diabetic retinopathy (Absent)**	**Total**	**'p' value**
Hb < 8 gms	24	7	31	0.021
Systemic Hypertension	23	7	30	0.028
Duration>5 years	34	10	44	0.005

Comment : Prediction of diabetic retinopathy by Hb < 8 gm/dl , Systemic hypertension and longer duration of diabetes are statistically significant.

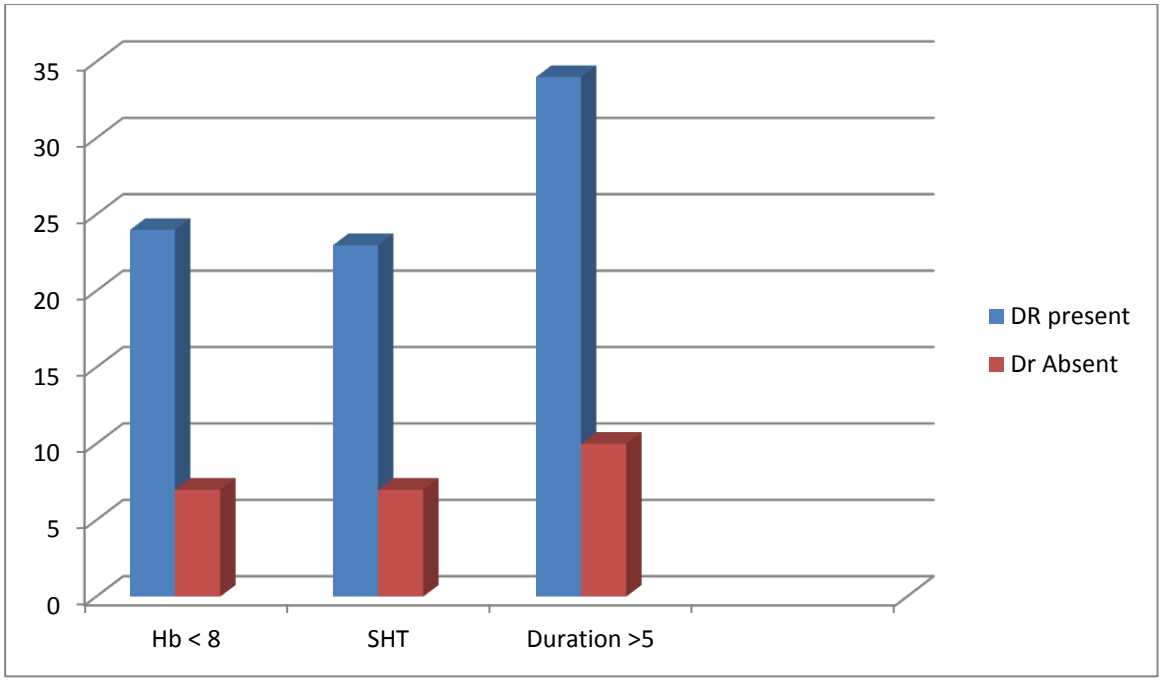

Figure 15 :Prevalence of retinopathy in patients with Hb <8 gms, SHT, Duration of diabetes > 5 years

DISCUSSION

Diabetic retinopathy is a specific microvascular complication related to sight threatening problem in diabetes. DR is characterized by progressive alterations in microvasculature of retina, leading to hypoperfusion of retina, increased vascular permeability and retinal vessels proliferation.

Normoalbuminuria does not imply normal renal function. In type 2 diabetes mellitus, concordance rate with albuminuria and glomerular filtration rate is much less when compared to type 1 diabetes mellitus. Hence many type 2 diabetes patients may have decreased glomerular filtration rate, which itself is a risk factor for DR without albuminuria.

Hence, even in type 2 diabetes patients with normoalbuminuria, presence of other predictors like low haemoglobin, systemic hypertension and longer duration of diabetes can identify high risk individuals who develop diabetic retinopathy.

This study was conducted among 100 patients attended Department of General Medicine in Government Rajaji Hospital, Madurai. Gender distribution was almost equal with 52% were males and 48% were females. Most of the study group was in the age group of 35 to 65 years (67%), rest of the study group was at age groups 18-35 and 65-85 years(33%).

Anemia of haemoglobin < 8 grams was present in 31 patients in the study group. Out of which 24 patients had diabetic retinopathy which was statistically significant with the ‘p’ value of 0.021.

Systemic hypertension was seen in 30 patients in the study group. Out of which 23 patients had diabetic retinopathy which was statistically significant with the ‘p’ value of 0.028.

In the study group, 44 patients had more than 5 years duration. Out of which 34 patients had diabetic retinopathy which was statistically significant with the ‘p’ value of 0.005.

Even though type 2 diabetes mellitus patients have normoalbuminuria, they may still have diabetic retinopathy. Hence the other predictors of diabetic retinopathy like low haemoglobin, systemic hypertension, and longer duration of diabetes should be carefully monitored in every patient with type 2 diabetes for early identification and efficient treatment of diabetic retinopathy.

CONCLUSIONS

In patients of type 2 DM, inspite of normoalbuminuria diabetic retinopathy is very much common. Absence of albuminuria should not be the criteria to defer for screening of diabetic retinopathy. Various predictors for the determination of DR are the estimated levels of haemoglobin, diabetes duration, and associated systemic hypertension.

. Hence, even in type 2 diabetes patients with normoalbuminuria, presence of other predictors like low haemoglobin, systemic hypertension and longer duration of diabetes can identify high risk individuals who develop diabetic retinopathy.

Large number of diabetic individuals could be anemic. Anemia identification and treatment will make a great change in the progression of diabetic complications like retinopathy.

By early identification and timely intervention of diabetic retinopathy, many sight threatening complications can be avoided.

SUMMARY

In this study, the level of hemoglobin in DM patients with DR was lower than those without DR. The prevalence of anemia was higher in patients with more advanced DR. Concerning the exclusion of patients with creatinine more than 2 mg/dl in our study, lower hemoglobin level in patients with DR compared to patients without DR.

Qiao et al. in Finland on 1691 DM patients found that the DM patients with hemoglobin level lower than 8 mg/dl were two times more likely to develop DR . Consistently, we found that anemic DM patients were 2.4 times more likely to develop DR.

Chronic hyperglycemia is involved in the pathogenesis of anemia by mean of creating abnormalities in RBCs, oxidative stress, autonomic neuropathy and renal sympathetic denervation. These conditions put the renal inerstitium in a hypoxic state and consequently, the production of erythropoietin by peri tubular fibroblasts is impaired

In type 1 diabetes, the independent risk factor for the development of diabetic retinopathy is microalbuminuria.

This is not true in case of type 2 diabetes. So it should be noted that retinopathic changes may occur in type 2 diabetes inspite of normal albuminuria..

There was about 20 to 30 percent estimated prevalence of diabetic retinopathy in patients with normal excretion of albumin in urine. But there are only limited number of studies to show the predictors and the prevalence of DR in such kind of patients with normal albuminuria.

Hence, even in type 2 diabetes patients with normoalbuminuria, presence of other predictors like low haemoglobin, systemic hypertension and longer duration of diabetes can identify high risk individuals who develop diabetic retinopathy.

In our study, the diabetic retinopathy estimated prevalence in patients with normoalbuminuric type 2 diabetes mellitus is around 40%. Hence in normoalbuminuric type 2 diabetes individuals, presence of other predictors like anemia (Hb < 8 gms), systemic hypertension and longer duration of diabetes can identify the individuals with diabetic retinopathy which was statistically significant in our study.

LIMITATIONS OF THE STUDY

1. Our study has smaller study group.

2.More studies are further needed to identify the predictors and the prevalence of diabetic retinopathy in type 2 diabetes with normal albumin excretion.

ANNEXURES

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PROFORMA

Name: Age/Sex: Occupation:

Presenting complaints:

H/o Blurring of vision, easy fatiguability,etc..

Past history:

H/o Type 2 Diabetes mellitus

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy, hydration status

Vitals: PR,BP,RR,SpO2.

Systemic examination:

CVS:

RS:

ABD

CNS:

Laboratory investigations:

Hemoglobin estimation

Fundus Examination

Urine albumin

Renal function test

Liver function test

Lipid profile

RBC, PCV

Peripheral Blood Smear

ABBREVIATIONS

AGE- Advanced Glycation End products

CHD- Coronary Heart Disease

CSME- Clinically Significant Macular Edema

DCCT- Diabetes Complications and Control Trial

DM- Diabetes Mellitus

DR- Diabetic Retinopathy

HBA1C- Glycosylated Hemoglobin

IDF- Indian Diabetes Federation

PKC- Protein Kinases C

ROS- Reactive Oxygen Species

UKPDS- United Kingdom Prospective Diabetes Study

NAME	AGE	SEX	HEMOGLOBIN in gms					BLOOD PRESSURE in mmHg		DURATION in years			DRP
			< 6	6 to 8	8 to 12	> 12	NORMAL	stage 1	stage 2	< 5 years	5 to 15	>15	
RAMAN	M	49	5.8				100/70					18	P
PRABU	M	53				14	110/80					19	P
SHEELA	F	39		7.8			130/80			4			A
KARUPAYEE	F	62		6.8				146/94		4			P
MEENA	F	53	5.6				112/78					21	P
ARUN	M	71				14	112/76			4			A
SUBBIAH	M	54		7.5					170/102	3			P
INDHIRANI	F	61				15	126/82					23	P
RAJU	M	64			10.8			142/94		3			A
GEETHA	F	51				14	118/76					18	P
FATHIMA	F	34			11.2		120/72			4			P
VASUNDRA	F	69				15	124/86			2			A
SABARISH	M	45		6.4				148/100			12		P
KOMANAVALI	F	33				14.8	112/66				6		A
SIVAKAMI	F	60				15	120/84			3			A
PONMALAR	F	60			8.8				164/102		14		P
MURUGESAN	M	61				14	114/84					23	P
GOPINATH	M	49	5.8				116/74			4			A
MANIKANDAN	M	64				15	122/76					21	P
YAZHINI	F	58				14.8	118/82			3			A
SENTHIL	M	72		7.8				156/98			13		P
ANNAMALAI	M	68				14.4	122/68			4			P
NILA	F	69		7.2				144/96			13		P
MANICKAM	M	43				15	114/76			4			A
PAPPA	F	60				14	122/86				9		A
HYDER ALI	M	66				15.6	118/66					22	P
CHINNASAMI	M	41				14	118/82			2			A
LAVANYA	F	55		6.8					172/106		12		P
RAMANI	M	40				15	116/86			4			A
GURU	M	39				15	120/80			4			A
KIRUBA	M	71				14.8	110/86					16	A
AISHWARYA	F	46				15	120/82			4			A
MURUGESWAR	F	49				15	110/68			3			A
SAMPATH	M	55		6.6				152/94			11		P
ISMAIL	M	38				14	122/64				12		A

VELLAMMAL	F	68				15	118/84			3			A
VASU	M	49	5.8				122/68			4			A
SRINI	M	31		7.8					174/106		13		P
CHIDABARAM	M	56		7				148/98			9		P
MARI	M	30				14	110/82					17	A
SETHU	M	61				15	110/64			4			A
THENMOZHI	F	41				14	122/78			2			A
DURAI	M	46	5					150/98				21	P
PUSPAM	F	56		6.8			122/86			4			A
KAYAL	F	57		6.6				142/94			12		P
KARTHI	M	34				15	116/78			3			A
CHITHRA	F	71			11				178/102	4			A
ANANDHI	F	43				14	112/78			3			A
VEENA	F	34			11.8		124/78			4			P
GAYATHRI	F	45				15	116/82			3			A
DHANAPAL	M	72				14	122/74			4			A
MAHESH	M	70				15	132/84			3			A
RAM	M	62			10				166/104		14		P
PREMA	F	42		7.6				150/98		4			P
VIDHYA	F	49				15	128/74			3			A
KAVIARASU	M	34				14	114/68				6		A
VALLI	F	41				15	134/76			4			A
GOWRI	F	44				15	132/84			3			A
MADHESWARI	F	72		7.4			122/68					16	P
SHAHJAHAN	M	33		6.8					176/108		7		P
ILAVARASI	F	42				14	134/68			4			A
PERUMAL	M	55				15	122/78			3			A
MYTHILI	F	41				15.4	112/82			4			A
PREM	M	57				15	132/86			3			A
KAVITHA	F	43				14.8	124/68			4			A
GUNA	M	47		7.2				142/96			14		P
SHENBAGAM	F	64				14	132/84			4			A
CHELLIAH	M	59				15	110/68			4			A
THANGAM	F	44				15	120/84			3			A
SENGOTTUVEI	M	58	5.6					154/92				19	P
ANAND	M	72				15		150/98		4			A
PANDI	M	69	5.8				120/68					23	P

VAIRAVEL	M	72			9		132/68					19	P
NANCY	F	36				15	122/68			3			A
NEELAMMAL	F	52				14			174/102	4			A
BABU	M	69				15	124/88					18	P
SAILAJA	F	39				14	132/78			3			A
GOMATHI	F	37				15	112/66			4			A
KUPPAMMAL	F	54		7.4			122/68			3			A
PERIYASAMY	M	64		6.8				150/98				17	P
MUTHAMMAL	F	44				15	132/66					16	P
PAPPATHI	F	41				14	122/66				14		A
RAJIV	M	32				15	118/78			4			A
GEETHA	F	67				14	122/64				7		A
KANNAN	M	34	5.6				112/84			3			A
PRABAKAR	M	34			9				166/108		6		P
VELLAIAMMA	F	59		7				142/92			12		P
PECHI	F	66				15	120/84			4			A
LINGAM	M	67				15	112/86			4			A
DIVAKAR	M	40		7.6					174/106		13		P
SOORI	M	58	5				112/68				14		P
DIVYA	F	43				14	112/68			3			A
MURUGAN	M	51				15	110/88			4			A
RAJI	F	44				15	114/84			3			A
DINESH	M	53				15		144/98		4			A
SUNDAR	M	69				14			178/104			19	A
KALYANI	F	31				15		150/96		3			A
VIJAY	M	63	5.8				118/84			4			A
MARUTHU	M	34		6.6				142/98			7		P
LEELA	F	40				15			176/102		9		P

Ref.No.6506/E1/5/2014

Madurai Medical College,
Maduai -20 Dated: 19.08.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for August 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 05th August 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member ecretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the Ethical Committee

Name of P.G.	Course	Name of the Project	Remarks
Dr.S.Irsath drirsath@yahoo.co.in	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai	**Predictors of diabetic retinopathy in patients with type 2 diabetes mellitus with normoalbuminuria**	**Approved**

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical Committee

19.8.14
DEAN/Convenor
Madurai Medical College & Govt.
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The above Applicant
-thro. Head of the Department concerned

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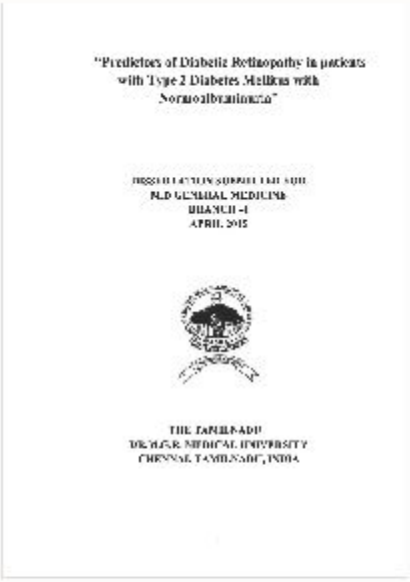

"Predictors of Diabetic Retinopathy in patients with Type 2 Diabetes Mellitus with Normoalbuminuria"

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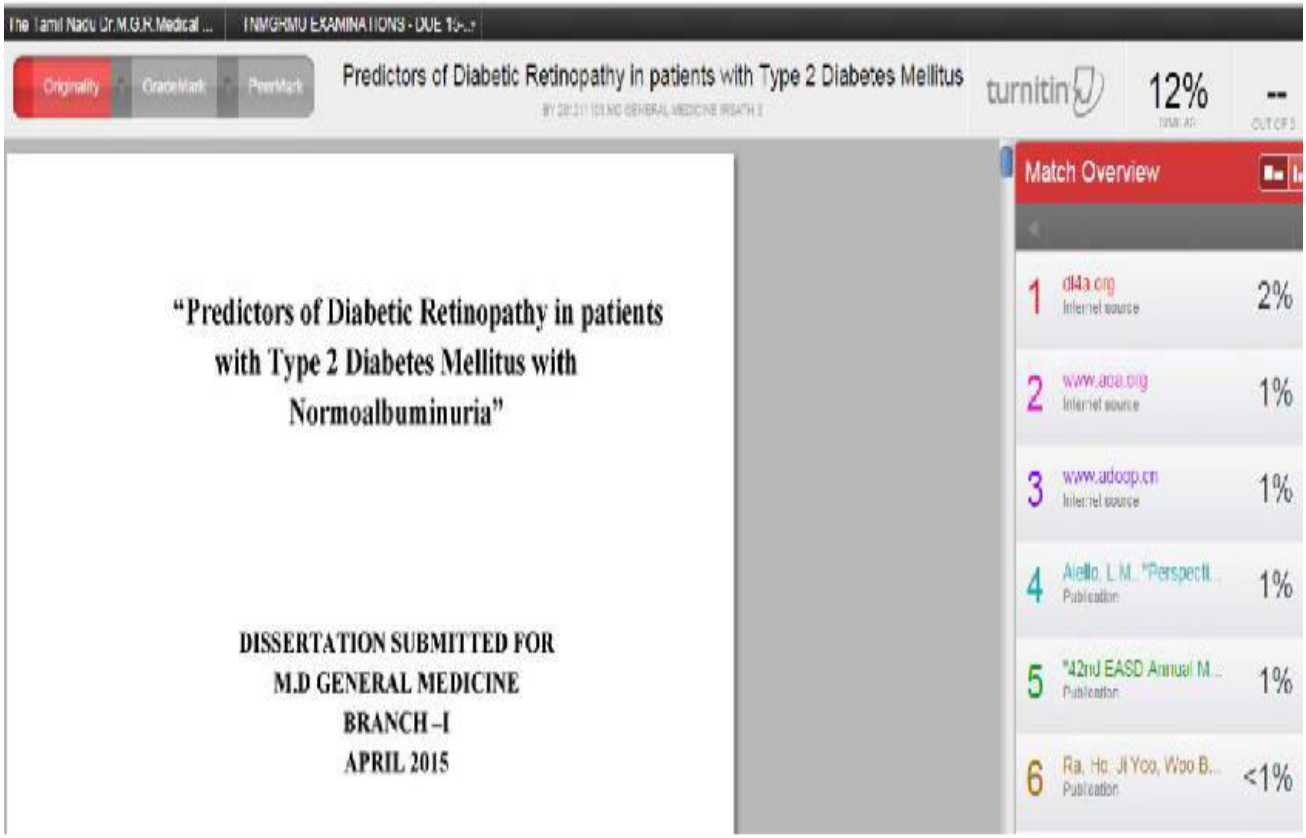
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