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Corresponding Author
Suchandra Das,
Department of Ophthalmology, Sarat Chandra Chattopadhyay Government Medical College and Hospital (Uluberia Station Road, Bazarpara, Howrah), West Bengal 711316, India
suchandradas495@gmail.com

Author Designation
[1]Assistant Professor
[2]Senior Resident

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Evaluation of Ocular Changes in Patients with Type-2 Diabetes Mellitus with More than 20 Years of Disease Duration

[1]Bijan Mallick and [2]Suchandra Das
[1,2]Department of Ophthalmology, Sarat Chandra Chattopadhyay Government Medical College And Hospital, Uluberia Station Road, Bazarpara, Howrah, West Bengal 711316, India

ABSTRACT
Diabetes mellitus (DM) is a critical risk factor for avoidable blindness globally, primarily due to diabetic retinopathy (DR), an ocular condition with serious implications if left unmanaged. The risk of DR progression is closely linked to diabetes duration, blood glucose control, and other modifiable factors like blood pressure, hyperlipidemia, and smoking. While laser photocoagulation has been the conventional treatment, advances have integrated pharmacotherapy and early surgical interventions. Multiple studies, including the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the EURODIAB Prospective Complications Study, have underscored the influence of diabetes duration, HbA1c levels, and early onset on DR progression. Despite extensive research in type 1 diabetes, studies on type 2 diabetes, particularly for patients with over 20 years since diagnosis, are limited. This study examines the prevalence of DR and other ocular complications in type 2 DM patients with prolonged disease duration. Findings from global studies emphasize the need for effective metabolic control to mitigate DR progression. This investigation highlights the substantial public health burden posed by DR, underscoring the necessity of modifiable risk management to preserve ocular health in diabetic patients.

INTRODUCTION

Diabetes mellitus is a major cause of avoidable blindness in both the developing and the developed countries. Significant technological advances have taken place to improve the diagnostic accuracy of diabetic retinopathy. In the last three decades, the treatment strategies have been revised to include, besides laser photocoagulation, early surgical interventions and phar-macotherapies. The prognosis of some of the most prevalent conditions seems to be intricately related to myriad risk factors, largely modifiable but often leading to irreversible complications when left unmanaged. Risk factors of DR include duration of diabetes, pregnancy, renal disease, age, smoking, alcohol, hyperlipidemia and antioxidants. Among the independent risk factors for severity of Diabetic Retinopathy (DR) has been duration of diabetes mellitus (DM), HbA1c, male gender, macro-albuminuria and insulin therapy[1]. Of all these independent parameters, the most important is the duration of the disease. There have been many studies on the duration of disease and the incidence of retinopathy in type I disease[2]. The WESDR study has shown that the 25-year cumulative rate of progression of DR was 83%, progression to proliferative DR (PDR) was 42% and improvement of DR was 18%. Progression of DR was more likely with less severe DR, male sex, higher glycosylated hemoglobin, an increase in glycosylated hemoglobin level and an increase in diastolic blood pressure level from the baseline to the 4-year follow-up. The Finn-Diane Study Group has studied DR up to 30 years and has shown a decline in DR but again in type 1 disease.

Another study done on duration of the disease along with other parameters was the EURODIAB Prospective Complications Study (PCS) which included a large cohort of patients but again with Type I (insulin-dependent) diabetes mellitus. The Baseline data were collected between 1989 and 1991 on 3250 patients who were recalled for follow-up. Physical examination, biochemical tests and assessment of complications were done on both occasions. In particular, 1249 patients had retinal photographs taken both basally and after an average of 7.3 years. Proliferative retinopathy had developed in 157 patients (cumulative incidence 17.3/1000 patient-years; 95%-Cl: 13.6-21.1). HbA1c (standardized regression estimate-SRE = 3.03, CI 2.49- 3.69), diabetes duration (1.71, 1.42-2.06), age at diagnosis <12 (1.66, 1.11-2.50), diastolic blood pressure less than or equal to 83 (1.50, 1.03-2.20) and waist-to-hip ratio (1.50, 1.03-2.20) were all independent predictors for progression to PDR when entered simultaneously into a logistic regression model. Including retinopathy at baseline maintained the effects of metabolic control and pre-pubertal onset only. Including the albumin excretion rate maintained the effect of control but reduced SRE for pre-pubertal onset to 1.49 (0.94-2.33). There was no evidence for a threshold effect for HbA1c concentrations at baseline and progression to proliferative retinopathy. Metabolic control and duration of diabetes were strong indicators of progression to proliferative retinopathy. Onset of diabetes before puberty could be an additional independent risk factor.

One of the Wisconsin studies had studied the rate of proliferative diabetic retinopathy and found that the same varied from 2.0% in persons who had diabetes for less than five years to 15.5% in persons who had diabetes for 15 or more years. By using the Cox regression model, the severity of retinopathy was found to be related to longer duration of diabetes, younger age at diagnosis, higher glycosylated hemoglobin levels, higher systolic BP, use of insulin, presence of proteinuria and small body mass[3].

An important reason for the lack of studies in type 2 DM patients could be the late onset of the disease. However with younger onset of age and better management of cases with DM, there are now cases available who are surviving 20 years after the diagnosis of the disease. Interesting feature in this XXII report of WESDR has been the improvement of DR in 18% of the study population and in the FinnDiane Study Group, though both are in type 1 disease.

In the GEDAPS study 65 health centers (433 health professionals) took part from 1993 to 2003. 34 workshops on consensus guidelines and feedback referring to the variables that needed to be improved were carried out[4]. Data collection was obtained concerning, socio-demographic information and disease characteristics and complications from patients with type 2 diabetes mellitus (DM). They found that retinopathy had decreased by 40.7% ($p<0.001$). However more reports on the same and from our country are lacking.

It would therefore be interesting to study the ocular manifestations in patients with longer duration of disease after diagnosis. Hence a study was conducted to study the effects of diabetes in patients with more than twenty years of disease duration.

AIMS AND OBJECTIVES

Aims of study:

- To detect incidence of retinopathy in patients with type 2 DM of more than 20 years after diagnosis
- To detect other ocular manifestations in patients with type 2 DM of more than 20 years after diagnosis

Objective of study: To evaluate the effect of disease duration of more than 20 years on the ocular manifestations patient of type2 DM.

REVIEW OF LITERATURE

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors.

Global prevalence: The epidemiology of DM has been studied by different workers at different parts of the world like Wild *et al*.[5], Saidkot *et al*.[6], Yanko *et al*.[7], Williams *et al*.[8], Wong *et al*.[9] and Wang *et al*.[10].

To examine the global prevalence and major risk factors for Diabetic Retinopathy (DR) and vision-threatening diabetic retinopathy (VTDR) among people with diabetes the Meta-Analysis for Eye Disease (META-EYE) Study Group was constituted. A pooled analysis using individual participant data from population-based studies around the world was performed. A systematic literature review was conducted to identify all population-based studies in general populations or individuals with diabetes who had ascertained DR from retinal photographs. Studies provided data for DR end points, including any DR, proliferative DR, diabetic macular edema and VTDR and also major systemic risk factors. Pooled prevalence estimates were directly age-standardized to the 2010 World Diabetes Population aged 20-79 years.

A total of 35 studies (1980-2008) provided data from 22,896 individuals with diabetes. The overall prevalence was 34.6% (95% CI 34.5-34.8) for any DR, 6.96% (6.87-7.04) for proliferative DR, 6.81% (6.74-6.89) for diabetic macular edema and 10.2% (10.1-10.3) for VTDR. All DR prevalence end points increased with diabetes duration, HbA1C and blood pressure levels and were higher in people with type 1 compared with type 2 diabetes.

There are approximately 93 million people with DR, 17 million with proliferative DR, 21 million with diabetic macular edema and 28 million with VTDR worldwide. Longer diabetes duration and poorer glycemic and blood pressure control are strongly associated with DR. These data highlight the substantial worldwide public health burden of DR and the importance of modifiable risk factors in its occurrence. This study is only limited by data pooled from studies at different time points, with different methodologies and population characteristics. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. The metabolic dysreguation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system[11]. DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT).

India shelters the most number of people with diabetes mellitus worldwide. From 31 million in the year 2000, the number of persons with diabetes mellitus in India would register a 2.5 fold increase over the next 30 years so as to reach an alarming level of estimated 80 million by the year 2030[9]. The only published nationally representative study on burden of diabetes mellitus in India is Prevalence of Diabetes in India Study.

PODIS (2002), a multi-centric study (49 urban and 59 rural centers) on 41,000 Indian people. PODIS has estimated the age and gender standardised prevalence of diabetes mellitus in India to be 3.3 percent. The prevalence estimates ranged from 5.6 to 12.4 percent in urban area and 2.4-2.7% in rural area[9].

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be 45-64 years of age.

Screening: Widespread use of the FPG as a screening test for type 2 DM is recommended. The ADA recommends screening all individuals >45 years every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) >25 km/m^2] and have one additional risk factor for diabetes. In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM[12].

Type 2 DM: Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Insulin resistance precedes an insulin secretory defect but that diabetes develops only when insulin secretion

becomes inadequate. Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. Insulin resistance, as demonstrated by reduced glucose utilization in skeletal muscle, is present in many nondiabetic, first-degree relatives of individuals with type 2 DM. The disease is polygenic and multifactorial since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified but recent genome-wide association studies have identified several genes that convey a relatively small risk for type 2 DM (relative risk of 1.1-1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with type 2 diabetes in several populations and with impaired glucose tolerance in one population at high risk for diabetes. Genetic polymor-phisms associated with type 2 diabetes have also been found in the genes encoding the peroxisome proliferators-activated receptor-inward rectifying potassium channel expressed in beta cells, zinc transporter expressed in beta cells, IRS and calpain 10.

The mechanisms by which these genetic alterations increase the susceptibility to type 2 diabetes are not clear but several are predicted to alter insulin secretion. Investigation using genome-wide scanning for polymorphisms associated with type 2 DM is ongoing.

Criteria for the Diagnosis of Diabetes Mellitus
Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL) or
Fasting plasma glucose 7.0 mmol/L (126 mg/dL) or
HbA1C > 6.5% or
Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

Ocular manifestations of diabetes: The incidence of all ocular manifestations of DM increases with age and duration of the disease, whether type 1 or type 2[13]. Approximately 5% of the population with DM may develop glaucoma, compared with about 2% of the general population. Glaucoma also has a higher prevalence in groups at known risk for DM, including African Americans, Native Americans and older persons. Cataracts are 2-4 times more prevalent, occur at younger ages and progress more rapidly in patients with DM than in the general population (Table 1).

Ocular conditions directly associated with diabetes

Cataract: Cataract is a major cause of vision impairment in people with diabetes. Numerous studies have documented an association between diabetes and cataracts. This association is supported by an abundance of data from Rowe *et al*.[14] Both cross-clinical epidemiological studies and basic science studies, the Beaver Dam Eye Study, the Blue Mountains Eye Study and the Visual Impairment Project, have documented associations between diabetes and both prevalent and incident posterior sub capsular cataract and, less consistently, with prevalent and incident cortical cataracts but not nuclear cataract. The Blue Mountains Eye Study showed that impaired fasting glucose, in the absence of clinical diabetes, was also a risk factor for the development of cortical cataract[14]. There is additional evidence that the risk of cataract increases with increasing diabetes duration and severity of hyperglycemia. Deposition of advanced glycation end products in the lens has been postulated as one possible pathogenic mechanism for diabetic cataract[15]. In individuals with diabetes, cataract occurs at a younger age and progresses more rapidly, resulting in higher rates of cataract surgery at a relatively young age. In the W isconsin Epidemiologic Study of Diabetic Retinopathy, the 10-year cumulative incidence of cataract surgery was 8% in those with type 1 diabetes and 25% in those with type II diabetes. Predictors of cataract surgery included older age, greater severity of diabetic retinopathy and baseline proteinuria in type 1 diabetes and older age and use of insulin in type II diabetes.

While the overall outcomes of cataract surgery are excellent, patients with diabetes may have poorer

Table 1: Ocular manifestations of diabetes mellitus[14]

Functional	Tritan color vision deficiencies refractive error changes accommodative dysfunction visual field defects
Extraocular muscle	Mononeuropathies (third, anomalies fourth, or sixth cranial nerves) Pupillary reflexes Sluggish Pupillary reflexes Bulbar Conjunctiva Conjunctival microaneurysms
Tear film	Dry Eye Syndrome
Cornea	Reduced corneal sensitivity Reduced corneal wound- healing ability Basement membrane abmnormalities resulting in frequency increased of abrasions or recurrent erosion syndrome Descemet's membrane wrinkling Endothelial cell morphology changes, resulting in increased corneal thickness Iris Depigmentation Rubeosisiridis, possibly with associated ectropion, uvea and peripheral anterior synechiae
Lens	Higher prevalence of cataracts Reversible opacities and snowflake
Vitreous	Hemorrhage (PDR)
Retina	Retinopathy
Optic nerve	Papillopathy Ischemic optic neuropathy Higher incidence of open-angle glaucoma

vision outcomes than those without diabetes and the worst outcomes may occur in operated eyes with active proliferative retinopathy and/or preexisting macular edema. To improve cataract surgical outcomes in patients with diabetes, adequate control of diabetic retinopathy with laser treatment before cataract surgery is necessary[16].

The most devastating postoperative complication is endophthalmitis, a severe intraocular infection, with several studies showing that patients with diabetes have an increased risk of developing this complication, resulting in poorer outcomes. with Patients endophthalmitis characteristically present with pain, redness, discharge, decreased vision, eyelid edema, proptosis and conjunctival injection, with anterior chamber inflammation and vitritis. Management of endophthalmitis consists of inpatient admission for a combination of intravitreal, subconjunctival and topical antibiotics and steroids and possibly ocular surgery. In patients with diabetes, treatment may need to be more aggressive, with surgery performed earlier rather than later.

Anterior ischemic optic neuropathy: Anterior ischemic optic neuropathy (AION) is an acute vascular condition of the optic nerve. Studies suggest that up to 25% of patients with AION have a history of diabetes. In patients with diabetes, diabetic microvascular disease affecting the anterior part of the optic nerve is thought to cause the ischemia.

The optic disc in the contra-lateral eye of patients with AION is typically small in diameter with a small or absent cup, referred to as a "disc at risk." Patients with AION usually present with moderate loss of vision upon awakening, presumably related to nocturnal systemic hypotension. Visual acuity is better than 20/200 in 60% of cases at presentation. Untreated, AION generally remains stable and recurrence in the same eye is unusual. Good recovery of vision was observed in 43% of patients in the Ischemic Optic Neuropathy Decompression Trial.

There are no proven treatments for AION and the Ischemic Optic Neuropathy Decompression Trial revealed no benefit of optic nerve decompression surgery. Currently, neuroprotective agents are being investigated for nonarteritic AION (NAION) and appear to be beneficial against secondary neuronal degeneration in animal models of ischemic retinal ganglion cell damage and optic nerve crush injury. There is no proven prophylaxis for AION and the evidence for the efficacy of aspirin therapy is limited.

Diabetic papillopathy: Diabetic papillopathy is an uncommon optic nerve condition characterized by acute disc edema and mild vision loss[17]. Diabetic papillopathy is a risk factor for the progression of diabetic retinopathy and in rare instances, papillopathy can precede the development of AION. Early investigators postulated a toxic effect of abnormal glucose metabolism on the optic nerve in individuals with diabetes; subsequent studies have suggested that diabetic papillopathy may be a mild and reversible form of AION[18].

The significance of this condition is twofold. First, this condition may be misdiagnosed as papilledema. Second, telangiectasia at the optic disc in diabetic papillopathy may be mistaken as neovascularization in the opitc disc as part of proliferative diabetic retinopathy, leading to unnecessary laser photocoagulation. Diabetic papillopathy spontaneously improves within a year and vision prognosis is usually good. In most patients, vision recovers to a level = 20/30. Tightening diabetes control and treating coexistent hypertension and renal dysfunction may help with resolution of this condition.

Ocular movement disorders: Extraocular motility disorders may occur in patients with diabetes, secondary to diabetic neuropathy, involving the third, fourth, or sixth cranial nerve. Rarely, simultaneous palsies of multiple extraocular nerves can occur. Diabetes is the underlying cause in 25-30% of patients aged 45 years and older who develop acute extraocular muscle palsy. In one study, 1% of patients with diabetes were found to have cranial nerve palsies, compared with only 0.13% of control subjects. Of these cases, 41% had a third nerve palsy. In another population-based study, patients with sixth cranial nerve palsy were six times more likely to have diabetes[19].

Patients with extraocular palsies present with binocular diplopia. Pupil sparing is an important diagnostic feature in diabetes-related third cranial nerve palsy, distinguishing it from surgical causes, such as intracranial aneurysm or tumor. In diabetic cranial nerve palsies, recovery of extraocular muscle function generally occurs within 3 months. Recurrences can be common and may involve the same or other cranial nerves. The presence of other focal neurological signs, progressive deterioration, or palsy in a patient younger than 45 years should be investigated to exclude a compressive lesion. In these instances, a neurology or ophthalmology consultation is recommended.

Ocular conditions for which diabetes is a known risk factor

Glaucoma: Glaucoma is a progressive optic neuropathy associated with typical optic disc changes and visual field defects. Elevated intraocular pressure is the major risk factor for glaucoma, although a proportion of patients with glaucoma do not have raised intraocular

pressure. Patients with diabetes are at risk of two major types of glaucoma: Primary glaucoma and neovascular glaucoma.

- **Primary glaucoma:** Several large epidemiological studies have reported positive associations between diabetes with Primary Open Angle Glaucoma (POAG), the most common form of primary glaucoma, or elevated intraocular pressure in the absence of glaucomatous optic neuropathy. Glaucoma occurs more often in patients with diabetes (5%) than in the general population (2%). The risk of glaucoma has been reported to be 1.6-4.7 times higher in individuals with diabetes than in non-diabetic individuals. In the Blue Mountains and Beaver Dam Eye studies, participants with diabetes were twice as likely to have glaucoma as those without. However, not all population-based studies have identified such an association[20]

There are clear biologically plausible mechanisms supporting an association between diabetes and POAG. First, microvascular damage from diabetes could impair blood flow to the anterior optic nerve, resulting in optic nerve damage. Diabetes also impairs the autoregulation of posterior ciliary circulation, which may exacerbate glaucomatous optic neuropathy. Second, patients with diabetes often have concomitant cardiovascular risk factors (e.g., hypertension) that may affect vascular perfusion of the optic nerve head. Finally, relative to those without diabetes, individuals with diabetes may be more vulnerable to elevated intraocular pressure with more severe visual field loss at the same intraocular pressure level[21]

It is important to screen for POAG among individuals with diabetes, as POAG can be asymptomatic until the late stages, when decreased vision and/or constricted visual fields are noted. Treatment involves lowering intraocular pressure through topical eye drops and laser and surgical procedures. Primary Angle Closure Glaucoma (PACG), the other common primary glaucoma, is characterized by narrow or closed anterior chamber angles, which impedes drainage of aqueous humor and leads to raised intraocular pressure. Patients with PACG appear to be more likely to have abnormal glucose tolerance than those with POAG or those without glaucoma. Diabetes may be associated with PACG via systemic autonomic dysfunction or increased lens thickness as a result of sorbitol overload. Patients with PACG may present with an acute attack, which is associated with severe ocular pain, headaches and nausea, with substantially elevated intraocular pressure. Acute PACG requires urgent referral and treatment.

- **Neovascular glaucoma:** Studies have shown a consistent association between diabetes and neovascular glaucoma, with proliferative retinopathy the leading cause of this type of secondary glaucoma. Between 32 and 43% of neovascular glaucoma cases are caused by proliferative diabetic retinopathy. Neovascularization of the iris, an early precursor of neovascular glaucoma, is commonly seen in patients with long-standing poorly controlled diabetes. Hypoxia in the retina and other ocular tissue causes an increased expression of Vascular Endothelial Growth Factor (VEGF), which stimulates new vessel formation in the iris or in the anterior chamber angle. Neovascular glaucoma requires aggressive intervention to lower intraocular pressure with medication, followed by surgery[22]. Regression of neovascularization following pan-retinal laser photocoagulation can occur if treated early.

Ocular ischemic syndrome: Ocular ischemic syndrome (OIS) is an uncommon vascular problem that results from chronic hypo- perfusion of the eye, most commonly caused by ipsilateral internal carotid or ophthalmic artery occlusion. Patients with OIS typically present with vision loss and dull ocular pain. The prevalence of diabetes in patients with OIS is higher than in the general population, with one study reporting that more than 50% of patients with OIS have diabetes. Diabetes is a major risk factor for carotid artery stenosis and plaque formation, the underlying causes of OIS.

The 5-year mortality rate among patients with OIS has been reported to be 40% or higher. Coexisting cardiovascular and cerebrovascular diseases are the main causes of death. Carotid ultrasonography is useful to delineate the presence and severity of carotid artery stenosis. Although, carotid endarterectomy lowers the risk of stroke in patients with symptomatic carotid stenosis, it is unclear whether this procedure alters vision prognosis in eyes with OIS. The coexistence of diabetes with OIS may be an indicator of poorer vision prognosis, due to the higher incidence of secondary glaucoma. Pan-retinal laser photocoagulation is indicated in eyes with ocular neovascularization.

Ocular conditions where diabetes is a possible risk factor

Retinal vein occlusion: Retinal Vein Occlusion (RVO) is a retinal vascular condition characterized by dilated tortuous retinal veins with retinal hemorrhages, cotton wool spots and macular edema. Central RVO occurs at the optic disc, whereas branch RVO occurs at retinal venular branches, usually at the site of arterio-venous crossing. Central RVO may be subdivided further into

nonischemic and ischemic types, the latter associated with poorer vision prognosis. Although it has been thought that diabetes is a major risk factor for RVO, epidemiological studies have not shown a consistent relationship between diabetes and the presence of RVO, with some studies reporting a positive association and others finding no association[23]. The importance of RVO in. patients with diabetes is that the retinal signs (e.g., hemorrhages or cotton wool spots) may "mimic" diabetic retinopathy. Thus, when patients with diabetes present with acute vision loss and asymmetric signs of "diabetic" retinopathy, RVO should be considered.

The management of RVO depends upon the site of occlusion (central or branch), degree of ischemia, presence of macular edema, visual acuity level and complications. Approximately 30% of central RVO cases are initially nonischemic but ~10% progress to ischemia within 6 months. The two major complications of RVO are secondary neovascular glaucoma and macular edema. Pan-retinal laser photocoagulation has been shown to prevent neovascular glaucoma. No treatment has proven effective for macular edema in patients with central RVO, although focal laser treatment may be useful in patients with macular edema and branch RVO. Clinical trials are on-going to assess the intraocular administration of pharmaceutical agents, such as steroids or antivascular endothelial growth factor agents. The vision prognosis with central RVO, particularly ischemic central RVO, is poor but that of branch RVO is relatively good, with nearly half of patients maintaining visual acuity better than 20/40. Patients with diabetes who develop RVO are more likely than their nondiabetic counterparts to develop retinal neovascularizatio, neovascular glaucoma and vitreous hemorrhage. More importantly, recent studies suggest that, among those with diabetes 43-69 years of age, the presence of RVO is associated with double the risk of cardiovascular mortality.

Management of concomitant medical conditions (e.g. hypertension and dyslipidemia) may be important to prevent a recurrence of RVO. There is no good evidence that tight glycemic control can alter the course or improve the prognosis of RVO.

Retinal arteriolar emboli: Retinal arteriolar emboli are discrete plaque-like lesions lodged in the lumen of retinal arterioles. The majority of emboli are asymptomatic and transient, although patients infrequently present with episodes of sudden, painless, monocular blindness (amaurosis fugax), a transient ischemic attack, or stroke[24].

Population-based studies show that asymptomatic retinal emboli occur in 1.3-1.4% of adults 40 years of age and older. Studies show that retinal arteriolar emboli are associated with carotid artery disease, hypertension, other cardiovascular risk factors and an increased risk of stroke and stroke-related and all-cause mortality. However, there are no consistent data on whether retinal arteriolar emboli occur more commonly in people with diabetes. In the Beaver Dam Eye Study, participants with type 2 diabetes were found to have a twofold higher prevalence of retinal emboli[24].

Once an embolus has been detected, a full cardiovascular and cerebrovascular risk assessment is recommended, including carotid artery ultrasound and echocardiography to assess the source of the emboli. Treatment of concomitant cardiovascular risk factors is v ital and should include improved control of hyperglycemia, hypertension and hyperlipidemia, cessation of smoking and carotid endartarectomy, if indicated. Low-dose aspirin can be recommended to prevent retinal artery occlusion.

Retinal artery occlusion: Retinal Artery Occlusion (RAO) is a retinal vascular condition similar to emboli. The hallmark of RAO is sudden, unilateral, painless loss of vision associated with a visual field defect. Patients with central RAO usually present with a dramatic loss of vision, an afferent pupillary defect, diffuse retinal whitening and the resultant classic "cherry spot" on the macula. The fundoscopic findings with branch RAO, which occur at a branch, usually consist of a focal wedge-shaped area of retinal whitening; vision loss also tends to be much milder. As for emboli, there is no clear evidence that patients with diabetes are at higher risk of RAO. However, the prevalence of diabetes among patients with RAO has been reported to be as high as 21%, which is higher than in the general population of the same age.

Patients with RAO should be referred immediately to an ophthalmologist for management. In the acute phase (within 24 hrs), a variety of treatments have been proposed, such as ocular massage (to dislodge the embolus) and intravenous acetazolamide injection (to lower intraocular pressure). However, there is no evidence from randomized trials regarding the efficacy of these treatments. It is important for physicians to measure the erythrocyte sedimentation rate to exclude giant cell arteritis. Regardless of treatment, however, the vision prognosis of central RAO is poor.

Corneal diseases: Patients with diabetes are known to exhibit abnormalities of the corneal epithelium, leading to corneal erosion, persistent epithelial defect, or corneal ulcers. Recurrent corneal erosions in patients with diabetes are usually posttraumatic and the result of apparently mild epithelial breakdown following cataract or vitreoretinal surgery[25]. Areduction in hemidesmosomes may contribute to a weakness in the adhesion of diabetic corneal epithelium to the underlying stroma. In addition, erythrocyte aldose

reductase increase has been reported in patients with type 2 diabetes, leading to high accumulation of sorbitol, which can damage the corneal epithelium. In one study, corneal abnormalities (gerontoxon, limbal vascularization, punctate keratopathy, endothelial dystrophy, recurrent erosion and ulcers) were detected in up to 73.6% patients with diabetes. Patients with corneal disease often present with pain, photophobia, blurred vision and hyperemia. However, patients with diabetes often have reduced corneal sensitivity as part of diabetes complication in peripheral nerves and limbalvasculopathy.

Patients with diabetes who wear contact lenses must take extra hygiene care and be warned to seek advice early if any irritation symptom develops to prevent vision loss from microbial keratitis. Treatment of corneal disease includes topical antibiotics and topical cycloplegic (short term) and corneal patching for 24 hrs is indicated if the original insult is of nonorganic nature (not from plant or soil sources), for large corneal lesions (>2 mm) and in non-contact lens users. Contact lens-related conditions including corneal ulcers and large abrasions need urgent referral to the ophthalmologist. All other corneal cases need to be reviewed the next day by the primary care physician.

Lipemia retinalis: Lipemia retinalis, a relatively rare disorder that develops primarily in ketotic diabetic patients with severe hypertriglyceridemia, is characterized by creamy white-colored retinal blood vessels. The condition is not usually associated with long-term visual changes if treatment for hyperlipidemia and ketoacidosis if indicated, is administered appropriately. If blood lipid levels are extremely high, the aqueous humor itself may also take on such an appearance.

Wolfram syndrome: Wolfram syndrome also called as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) is a rare condition characterized by Type 1 diabetes and optic atrophy; progressive impairment of hearing has also been associated with this condition. The estimated prevalence of Wolfram syndrome is approximately 1 in 770,000 in the general population and 1 in 150 cases of Type 1 diabetes. The key ophthalmologic finding in these patients is optic atrophy, although low VA, color vision defects and visual field defects have also been described[26].

Cranial nerve palsies: Cranial nerve mononeuropathies are a well-documented diabetic complication, specifically those affecting the third, fourth, sixth and seventh cranial nerves; multiple neuropathy has been less commonly reported . Watanabe et al. found a 1% incidence of cranial nerve palsy in diabetic subjects over a 25-year period, which represented a 7.5-fold increase in incidence compared with non-diabetic subjects. Interestingly, diabetic patients with cranial nerve palsies were reported to have significantly less diabetic retinopathy. Cranial nerve mono-neuropathy classically presents with an abrupt onset and is characterized by transient pain, absence of other neurologic involvement and spontaneous recovery in 3-6 months, although a-lipoic acid has been shown to significantly accelerate recovery.

The study by Watanabe found that the most common mononeuropathies in diabetic patients were oculomotor and facial nerve palsies. By contrast, a Mayo Clinic study reported that the most commonly acquired cranial nerve palsy independent of etiology involved the abducens nerve, followed sequentially by the oculomotor and trochlear nerves. While the Mayo Clinic study did not specifically categorize the frequency of cranial nerve palsies in diabetic patients, a more recent study that did, found that the abducens nerve was most f requently involved (50.0%), followed by the oculomotor (43.3%) and trochlear (6.7%) nerves.

The development of sixth nerve palsies in diabetic patients is often attributed to the patients' history of microvascular ischemia. Similarly, third nerve mononeuropathy with pupil sparing is largely associated with diabetic microvascular disease and helps to distinguish it from intracranial tumour or aneurysm. A prospective study by Jacobson found pathological anisocoria in ten out of 26 patients with diabetic oculomotor nerve palsy; the degree of anisocoria was typically less than 1 mm and the pupil always remained reactive. In light of the fact that pupil involvement in third nerve palsy is typically seen in aneurysmal palsies, in an editorial accompanying Jacobson's study, Trobe suggested that catheter angiography be performed in patients with acquired third nerve palsy who have an anisocoria greater than 2 mm.

Diabetic retinopathy (DR): Diabetic Retinopathy (DR) is the most common microvascular complication of diabetes and remains one of the leading causes of blindness worldwide among adults aged 20-74 years[26]. The two most important visual complications of DR are Diabetic Macular Edema (DME) and Proliferative DR (PDR). The prevalence of DR increases with the duration of diabetes and nearly all people with Type 1 diabetes and more than 60% of those with Type 2, have some retinopathy after 20 years.In the Wisconsin Epidemiologic Study of Diabetic Ret- inopathy (WESDR), 3.6% of younger onset patients (Type 1 diabetes) and 1.6% of older onset patients (Type 2 diabetes) were legally blind (Table 2).

Etiopathogenesis of diabetic retinopathy: Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) established that

Table 2: Incidence of diabetic retinopathy by type and duration of diabetes[40]

Diabetes	Duration of disease	Incidence of diabetic retinopathy (%)
Type 1	0-4 years	27
	5-9 years	71
	10-14 years	54
	15+ years	38
Type 2	0-4 years	31
	5-9 years	32
	10-14 years	38
	15+ years	51

hyperglycemia is the initiating cause of retinal damage[27,28]. Underlying biochemical mechanisms associated with hyperglycemia and identified in diabetic retinas include activation of PKC, increased formation of Advanced Glycation End Products (AGES), polyol formation, increased hexosamine fluxes, activation of the renin-angiotensin System (RAS) and production of excess Reactive Oxygen Species (ROS)[29]. Numerous studies suggested that increase in fluxes through these pathways may lead to a cascade of events, such as promotion of apoptosis, inflammation and angiogenesis, which may, in turn, induce damage to a diabetic retina, leading to DR. Although, the pathophysiological processes responsible for the various lesions of DR and maculopathy are not fully understood, various individual retinal lesions indicate the risk for progression of DR and vision loss. Biochemical changes in the retina and alteration in retinal blood flow are early changes resulting from diabetes. Loss of intramural pericytes, either preceding or secondary to the development of capillary nonperfusion, weakens the retinal capillary walls. The result is saccularoutpocketing of these capillaries called microaneurysms (Ma), which are frequently the earliest clinical sign of DR.

Ruptured microaneurysms, leaking capillaries and Intraretinal Microvascular Abnormalities (IRMA) result in intraretinal hemorrhages. The clinical appearance of these hemorrhages reflects the architecture of the retinal layer in which the hemorrhage occurs. Hemorrhages in the nerve fiber layer of the retina have a flame-shaped appearance and coincide with the structure of the nerve fiber layer that lies parallel to the retinal surface. Hemorrhages deeper in the retina, where the arrangement of cells is more or less perpendicular to the surface of the retina, assume a pinpoint or dot shape and are more characteristic of DR. Intraretinal microvascular abnormalities represent either new vessel growth within the retina or, more likely, pre-existing vessels with endothelial cell proliferation that serve as "shunts" through areas of nonperfusion. IRMA are frequently adjacent to cotton wool spots. Whereas multiple IRMA mark a severe stage of nonproliferative retinopathy, frank neovascularization is likely to occur on the surface of the retina or optic disc within a short time. Venous caliber abnormalities are indicators of severe retinal hypoxia. These abnormalities can take the form of venous dilation, Venous Beading (VB), or loop formation. Large areas of nonperfusion can appear adjacent to these abnormal veins. VB is a significant risk factor for progression to proliferative retinopathy. Proliferative DR is marked by the proliferation of endothelial cell tubules. The rate of growth of these new vessels, either at or near the optic disc (neovascularization of the disc, or NVD) or elsewhere in the retina (neovascularization elsewhere, or NVE), varies. Adjacent to the new vessels, translucent fibrous tissue often appears. This fibroglial tissue becomes opaque and begins adhering to the adjacent vitreous. Although PDR is responsible for the most severe vision loss, macular edema is the most common cause of reduced visual acuity in persons with DM.

Diabetes alters the structure of the macula, thereby significantly altering its function, in any of the following ways:

- The collection of intraretinal fluid in the macular portion of the retina, with or without lipid exudates and with or without cystoid changes (macular edema)
- Nonperfusion of parafoveal capillaries, with or without intraretinal fluid
- Traction in the macula by fibrous proliferation, causing dragging of the retinal tissue, surface wrinkling, or detachment of the macula
- Intraretinal or preretinal hemorrhage (PRH) in the macula. Lamellar or full-thickness hole formation.
- Any combination of the above
- Diabetic macular edema can be present with any level of diabetic retinopathy. When it involves or threatens the center of the macula, it is called CSME (Clinically Significant Macular Edema). CSME is defined by the presence of any one of the following:

    - Retinal thickening at or within 500 µm of the
    - Hard exudates with adjacent retinal thickening at or within 500 µm of the fovea
    - An area of retinal thickening 1500 µm or more in diameter, any part of which is within 1500 µm of fovea[30]

CSME is a clinical diagnosis that is not dependent on visual acuity or results of ancillary testing such as fluorescein angiography. It is diagnosed with the help of +90D lens using slit lamp biomicroscopy (Table 3-6).

Table 3: classification of diabetic retinopathy in the early treatment of diabetic retinopathy study

Disease severity level	Findings observable upon dilated ophthalmoscopy
Mild nonproliferative retinopathy	At least one microaneurysm and definition not met for moderate non-proliferative retinopathy, severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Moderate nonproliferative retinopathy	Hemorrhages and/or microaneurysms = standard photograph 2A*; and/or soft exudates, venous beading, or intraretinalmicrovascular abnormalities definitely present; and definition not met for severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Severe nonproliferative retinopathy	Soft exudates, venous beading and intraretinalmicrovascular abnormalities all definitely present in at least two of fields four through seven; or two of the preceding three lesions present in at least two of fields four through seven and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intraregional micro vascular abnormalities present in each of fields four through seven and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy (see below)
Early proliferative retinopathy (i.e., proliferative retinopathy without Diabetic Retinopathy Study high-risk (see below) characteristics)	New vessels and definition not met for high-risk proliferative retinopathy
High-risk proliferative retinopathy (proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics)	New vessels on or within one disc diameter of the optic disc (NVD) >standard photograph 10A* (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/ or preretinal hemorrhage accompanied by new vessels, either NVD <standard photograph 10A or new vessels elsewhere (NVE) >one-quarter disc area

Table 4: International Clinical Diabetic Retinopathy (DR) Disease Severity Scale[30]

Proposed disease severity level	Findings observable with dilated ophthalmoscopy
No apparent DR	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	More than "mild" but less than "severe"
Severe nonproliferative DR	Any of the following: (a) 20 or more intraretinal hemorrhages in 4 quadrants (b) Definite venous beading in 2 or more quadrants (c) Prominent IRMA in 1 or more quadrants and no neovascularization
Proliferative DR	One or more of the following: (a) Definite neovascularization and (a) Preretinal or vitreous hemorrhage

Table 5: International Clinical Diabetic Macular Edema (DME) Disease Severity Scale[30]

Proposed disease severity level	Findings on dilated ophthalmoscopy
DME absent	No retinal thickening or hard exudates present in posterior pole
DME present	Some retinal thickening or hard exudates present in posterior pole

Table 6: If DME is present, it can be categorized as follows:

Proposed disease severity level	Findings observable on dilated ophthalmoscopy*
Mild DME	Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
Moderate DME	Retinal thickening or hard exudates approaching the center of the macula but not involving the center
Severe DME	Retinal thickening or hard exudates involving the center of the macula

International classification of diabetic retinopathy: In an effort to simplify classification and standardize communication, the American Academy of Ophthalmology initiated a project to establish a consensus International Classification of DR and DME. This International Classification of DR and DME described five clinical levels of diabetic retinopathy: no apparent retinopathy (no abnormalities), mild NPDR (microaneurysms only), moderate NPDR (more than microaneurysms only but less than severe NPDR), severe NPDR (any of the following: <20 intraretinal hemorrhages in each of four quadrants, definite VB in two or more quadrants, prominent IRMA in one or more quadrant and no PDR) and PDR (one or more of retinal neovascularization, vitreous hemorrhage,or preretinal hemorrhage)[30].

The International Classification identified two broad levels of DME: Macular edema apparently absent (no apparent retinal thickening or Hard Exudates (HE) in posterior pole) and macular edema apparently present (some apparent retinal thickening or HE in posterior pole); if present, macular edema was subclassified as 'mild DME' (some retinal thickening or HE in posterior pole but distant from center of the macula), 'moderate DME' (retinal thickening or HE approaching the center of the macula but not involving the center), or 'severe DME' (retinal thickening or HE involving the center of the macula)[30].

Ocular changes after long duration of disease: A total of 955 insulin-taking persons living in an 11-county area in southern Wisconsin with type 1 diabetes diagnosed before age 30 years who participated in a baseline examination (1980-1982) and at least 1 of 4 follow-up (4-, 10-, 14- and 25-year) examinations or died before the first follow-up examination (n = 64) were subjected to stereoscopic colour. fundus photographs which were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme[2].

The main outcome measures were to assess the progression and regression of DR status.

The 25-year cumulative rate of progression of DR was 83%, progression to proliferative DR (PDR) was 42% and improvement of DR was 18%. Progression of DR was more likely with less severe DR, male sex, higher glycosylated hemoglobin, an increase in glycosylated hemoglobin level and an increase in diastolic blood pressure level from the baseline to the 4-year follow-up. Increased risk of incidence of PDR was associated with higher glycosylated hemoglobin, higher systolic blood pressure, proteinuria greater body mass index at baseline and an increase in the glycosylated hemoglobin between the baseline and 4-year follow-up examinations. Lower glycosylated hemoglobin and male sex, as well as decreases in glycosylated hemoglobin and diastolic blood pressure during the first 4 years of follow-up, were associated with improvement in DR. Persons diagnosed most recently with a similar duration of diabetes had a lower prevalence of PDR independently of glycosylated hemoglobin level, blood pressure level and presence of proteinuria.

These data showed a relatively high 25-year cumulative rates of progression of DR and incidence of PDR. The lower risk of prevalent PDR in more recently diagnosed persons possibly reflects improvement in care over the period of the study[4].

In this issue of Diabetes Care, Kytö described the 20- to 30-year decline in cumulative incidence of laser photocoagulation to prevent blindness in cohorts of patients with type 1 diabetes. The authors attribute these reductions in complications to the no-cost or low-cost glucose testing and insulin available in Finland. Even more striking are the reductions in type 1 diabetes complications found in the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort that followed the Diabetes Control and Complications Trial (DCCT) population. Complication rates fell in the group with tight glycemic control including peripheral neuropathy, autonomic neuropathy, retinopathy and nephropathy[31].

The study looked at 3,781 patients diagnosed with type 1 diabetes (1939-2005), median age at onset 13 (interquartile range [IQR] 9-21) years and duration of diabetes 19 (IQR 13-27) years. The severe retinopathy was based on a history of laser treatment. Patients were divided into <1975, 1975-1979, 1980-1984 and =1985 cohorts according to the diagnosis of diabetes. The results showed that the cumulative incidence of severe retinopathy had declined ($p<0.0001$). After 20 years of duration, the cumulative incidence was 23% (95% CI 21-25) and 33 (30-35) in the earliest cohorts, 18 (15-21) in the next cohort and 6 (4-9) in the recent cohort. After 30 years, the cumulative incidence was 52 and 48% in the earliest cohorts, while it was 62% after 40 years in the earliest cohort. It was concluded that the cumulative incidence of severe retinopathy has declined in patients with type 1 diabetes.

DR and nephropathy[32]: Diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy and affects approximately 40% of type 1 and type 2 diabetic patients. It increases the risk of death, mainly from cardiovascular causes and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Diabetic nephropathy is categorized into stages: microalbuminuria (UAE >20 microg/min and < or = 199 microg/min) and macroalbuminuria (UAE > or = 200 microg/min). Hyperglycemia, increased blood pressure levels and genetic predisposition are the main risk factors for the development of diabetic nephropathy. Elevated serum lipids, smoking habits and the amount and origin of dietary protein also seem to play a role as risk factors. Screening for microalbuminuria should be performed yearly, starting 5 years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control. In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease. Achieving the best metabolic control (A1c <7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 hrs and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system and treating dyslipidemia (LDL cholesterol <100 mg/dL) are effective strategies for preventing the development of microalbuminuria, in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes.

Retrospective review of medical records of 39 patients aged 26 to 70 years, (20 females, 78 eyes) with type 1 diabetes controlled by the same ophthalmologist from 1971 to 2008 was done in a Chilean population. A questionnaire was sent to each patient and their treating physician to request information about the evolution of the disease and metabolic control[33].

The questionnaire was answered by 24 patients (62%) and 21 attending physicians (54%). Small hard drusen were observed in 25 patients (64%). In 12 cases the drusen were detected before the development of any type of retinopathy. Eleven women became pregnant and retinopathy progressed in four of them. Twenty three patients (59%) developed Proliferative Diabetic Retinopathy (PDR). Patients with PDR had a significantly longer duration of diabetes and worse

glycemic control. There was a higher frequency of diabetic nephropathy in the PDR group but only 13 patients out of 23 with PDR had nephropathy. The retinopathy progressed to high risk PDR two years after successful kidney-pancreas transplantation in one patient.In patients with type 1 diabetes mellitus, small hard drusen may be the initial manifestation of diabetic retinopathy. Risk factors for progression to PDR were duration of diabetic and poor glycemic control. Nephropathy was more prevalent in patients with PDR but a significant group of PDR patients did not have demonstrable nephropathy[34].

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia. The latter complications of diabetes mellitus include microvascular complications the major microvascular complications, are the more important causes of retinopathy and nephropathy, blindness and end-stage renal disease in Europe. Different risk factors such as diabetes duration, blood pressure and lipid control have consistently been shown to correlate with both microvascular complications for diabetes. Despite the efforts of studies to correlate the two major diabetes mellitus microvascular complications, retinopathy and nephropathy, the relationship has not so far been clearly described. However, the currently literature data suggest that the presence of a pre-existing microvascular complication (retinopathy or nephropathy) may contribute to the development of another, especially in DM1 patients. More prospective studies are needed if we are to know the exact mechanism of how these diabetic microvascular diseases correlate and if we are to develop a scoring system for predicting the development of those complications that will allow us to identify the patients at risk, with its consequent positive impact on patients' quality of life[35].

This is a 15-year follow-up study of a cohort of 112 consecutive Type I (insulin-dependent) diabetes mellitus without diabetic retinopathy or nephropathy who were enrolled in 1990. The incidence of diabetic macular edema and its risk factors were studied. The epidemiological risk factors included in the study were as follows: Gender, diabetes duration, glycated hemoglobin (HbA1c) levels, arterial hypertension, macroangiopathy, triglyceride levels, fractions of cholesterol [high-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol] and cigarette smoking.

The incidence of diabetic macular edema after 15 years was as follows: The focal form of diabetic macular edema was present in 13 (11.6%) patients and the diffuse form of macular edema was present in 10 (8.9%) patients, among 23 (20.5%) patients. The following factors were significant in the development of diabetic macular edema: high levels of LDL-cholesterol ($p = 0.013$), high levels (>7.5%) of HbA1c ($p = 0.021$), the presence of macroangiopathy ($p = 0.022$), the severity of diabetic retinopathy ($p = 0.029$), the presence of arterial hypertension ($p = 0.037$) and the presence of overt nephropathy ($p = 0.047$). Microalbuminuria was not significant in logistic regression ($p = 0.587$) and cigarette smoking was not significant ($p = 0.976$). The relationship between diabetic macular edema and duration of diabetes presented two peaks of incidence: First in patients with 15-20 years' duration of diabetes mellitus and second in patients with >35 years' duration.

This data suggest that better control of glycemia, LDL-cholesterol levels and blood pressure in Type I diabetes mellitus patients may be beneficial in reducing the incidence of diabetic macular edema. This data validates the current guidelines for ophthalmologic care for the detection of diabetic macular edema over the long-term course of diabetes.

Genetics and DR[36]: Diabetic retinopathy affects a third of persons with diabetes and is the most frequent cause of blindness in working aged adults.

Although, diabetic retinopathy blindness appear to have fallen in the developed world, the rapidly increasing number of persons with diabetes worldwide has lead to a continuing increase in the global burden of this disease. The major risk factors for diabetic retinopathy include duration of diabetes, hyperglycemia and hypertension but these factors account for only a small amount of the variation in the risk of diabetic retinopathy. Research into new markers for retinopathy including including genetics, genetics, blood biomarkers and retinal imaging will further our understanding of the risk factors and pathogenesis of diabetic retinopathy[36].

There are many reasons to suspect a genetic influence on the development and progression of diabetic retinopathy, including substantial variability in disease severity among patients with similar risk factors. Linkage studies have suggested associations with chromosomes 1, 3, 12 and others. The most studied individual genes are those encoding vascular endothelial growth factor, aldose reductase and the receptor for advanced glycation end products, all of which have shown statistically significant associations in multiple series from various parts of the world. At this time, no definite genetic associations with diabetic retinopathy have been consistently reported. This may be due to small sample sizes, differences in study design, underlying genetic differences between study populations, or other factors. As we continue to collect data, these relationships may become clearer.

Genetics and nephropathy[37]: The aim of the study was to explore the association of the Angiotensin-converting Enzyme (ACE) gene I/D polymorphism and the methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism with development of diabetic nephropathy in type 2 diabetes mellitus. Three groups were recruited during 2007-2011: 232 normal controls, 185 type 2 diabetics without nephropathy and 407 type 2 diabetics with nephropathy. The ACE I/D and MTHFR C677T polymorphisms were examined using PCR and PCR-RFLP methods. No significant association of the ACE I/D polymorphism with diabetic nephropathy in genotype, allele, dominant and recessive models was found. However, a significant association of MTHFR C677T with development of diabetic nephropathy in type 2 diabetics was observed. The MTHFR C677T polymorphism plays a significant role in predisposition of renal insufficiency in diabetic patients.

MATERIALS AND METHODS

Study area: Department of Ophthalmology, Command Hospital (Eastern Command), Kolkata.

Study population: Diagnosed patients of type 2 DM coming to Ophthalmology OPD for eye checkup.

Study period: January 2012 to December 2012.

Sample size: 50 patients.

Study design: Cross-sectional, observational, hospital-based, study.

Parameters to be studied:

- Complete ophthalmic examination including best corrected visual acuity, iris neovascularization (NVI), intra-ocular pressure (IOP) by applanation tonometry (ATN), assessment of lens status and fundus evaluation
- Blood pressure measurement
- Estimation of Blood sugar levels, Serum urea/ creatinine, HbA1C, lipid profile and urinalysis.

Study technique: After taking clearance from Ethical committee of the institute, study was conducted in the Department of Ophthalmology, Command Hospital (EC). A thorough history of the subjects ware taken with reference to the duration of the disease, medications being taken and the presence of other co-morbidities.

Patients diagnosed with type 2 DM at endocrine/ Medicine OPDS with disease duration of more than 20 years were enrolled in the study.

The duration of the disease was ascertained from the documents available with the patients.

The enrolled patients were then be subjected to complete ocular examination.

- Visual acuity in both eyes (unaided and aided)
- Detailed anterior segment evaluation with diffuse illumination and by slit lamp biomicroscopy in particular for NVI
- Evaluation of anterior v itreous by slit-lamp biomicroscopy
- Fundus examination by direct and 90 D slit lamp bio-microscopy
- Measurement of Intra Ocular Tension with Goldmannapplanation tonometer
- Fundus photography using Zeiss FF 450 Fundus Camera
- Fundus fluorescein angiography

A complete medical history for any of the following disorders was obtained:

- Renal disease
- Hypertension
- Coronary arterial disease
- Cerebro-vascular disease
- Systemic or ocular medications.

Procedure of fundus fluorescein angiography (FFA): Informed consent was taken and the pupils were maximally dilated prior to the procedure with mydriatics. The procedure was done after fasting of at least two hours. Stereoscopic colour fundus photograph was first taken using the Carl Zeiss fundus camera FF450. An intracath was put in the arm and then 3 mL of 20% sodium f luorescein was injected. Serial fundus photographs were then taken. The fundus pictures were then analysed. The severity of DR was based on the ETDRS scale.

After completing the ophthalmic examination the patients were subjected to laboratory investigations consisting of estimation of Blood sugar levels, Serum eatinine, HbA1C and lipid profile.

Duration of disease: This was based on the documents available with the patient: OPD books/ ser- vice Discharge Books.

CKD: This was based on the evaluation done from the Nephrology OPD

Inclusion criteria:

- Patients diagnosed with type 2 DM from endocrine/medicine OPD
- Patients having type2 DM 20 years or more based on available documentation

Exclusion criteria:

- Patients with less than 20 years of disease duration
- Patients with NVI and NVG

Plan for analysis of data: Data was collected as per Data Collection Protocol and was subsequently analyzed with the help of a statistician. Analysis of variance and correlation coefficient with significance levels was calculated on the data collected using an appropriate statistical test. The clinical level of significance was pegged at a difference of one line or a score of 0.1. The sample size was calculated accordingly.

Hypertension was excluded from the analysis as hypertension is a common co-morbidity and all the study population was hypertensive on treatment.

A total of 50 patients were studied.

DISCUSSION

Age distribution: The age range is from 48 years to 85 years. Since this study group was formed of patients with > 20 years of disease duration, it can be presumed that in this study group DM was detected from ages of 28-65 years. This in consonance with the global study[38].

Majority of the patients is within the age range of 61 to 70 years (52%) and these constitute half the study population. If a decade earlier is also added, this would constitute 76% of the study group. The mean age of the study group is also 65.04 years. This in itself corroborates the increasing longevity of patients with DM.

Since this study is of diabetic subjects with more than 20 years of disease duration, it would imply that majority would have had DM by the ages of 41 to 51 years. This is in consonance with the global study[38].

Age when compared with sex, lens status, renal status, retinal status and HbA1C was not significant. However when compared with duration of disease was statistically significant. This could be because of 62% (31/50) were having disease duration of 20-22 years compared to 6% (3/50) of patients with 29 years of disease duration.

Sex distribution: In this study there is a male preponderance though all studies so far have not shown any difference between the sexes. The reason for the deviation could be the sample size as also the facts that this study was conducted at a service hospital which has a male bias. However, the parameter of sex has not found to be statistically significant when compared to all other parameters. This however is in variance with studies wherein male sex has been considered to be a risk factor for DR[1].

Lens status: This observation has no importance as the study population is in the age of cataractogenesis and the same has been corroborated by the statistical analysis wherein sex has not been found to have any signifi- cance with any other parameter.

Retinal status: The distribution of various stages of DR does not confirm to the global studies[38]. The percentage of PDR is per global percentages but the total percentages of any DR which has 80% in this study is much more than 34% in the global meta-analysis. The various stages of DR also have no statistical significance amongst them.

The retinal status does not have any significance with the lens status which is obvious.

The retinal status when compared to the renal status is quite significant. This significance is for the 07cases having CKD. All these had DR and 06 of them had severe NPDR to PDR. In comparison patients with mild and moderate NPDR (excepting 01) did not have CKD.

Retinal status is also not related to age. The various stages of DR have been equally distributed across all ages.

The retinal status is also statistically significant when compared to HbA1C levels. This is in consonance with existing knowledge.

The numbers of patients with any DR are more with the disease duration of 20-22 years. As the duration of DM. With increasing duration of disease the percentage of any DR is decreasing 16% (8/50). This fact is also statistically significant. This corroborates with the studies of Finn-Diane[4].

Renal status: In this study there were only 8/50 patients with CKD (16%). This is in consonance with the studies of Verdaguer *et al*.[33].

The renal parameters were statistically not significant with age, sex, lens status or duration of disease. The association of renal disease has been seen with all duration of diseases.

However, they are statistically significant when compared with various stages of DR. It may be seen that CKD (Chronic Kidney Disease) was seen with cases with Moderate NPDR upwards which is in consonance with the available data on this aspect from various studies worldover.

The renal parameters are also statistically significant when compared to HbA1C levels. All the 08 cases of CKD had more than 6.5% of HbA1C.

Glycosylated Hb: Glycosylated hemoglobin (HbA1C) levels reflect the long term glycaemic I control. In this study group, 62% had a good control. However the difference between the two groups of <6.5% and

>6.5% has not been statistically significant. The range of HbA1C levels has been from 6.5-11% with a mean of 7.74%. This probably infers the glycaemic control of the study population as a whole.

HbA1c levels were not statistically significant when compared to age, sex and lens status.

HbA1C levels are significant when compared with retinal status, renal status and duration of disease which have already been discussed. It may be seen that higher stages of DR and CKD are associated with higher levels of HbA1C. When HbA1C is compared to the duration of disease it appears 25 years, majority of the patients a that with disease duration of 20-25 years, majority of the patients a poorer control which was statistically significant.

Duration of disease: This is the essence of this study. The range of disease duration is from 20 years to 30 years. The outer limits are certainly very encouraging. On statistical analysis it may be seen that the 62% of subjects with the rest >22 years (38%) is statistically significant.

The duration of the disease when compared to sex and lens status is not significant and this stands to reason.

The duration of disease when compared to renal status is also not significant. This would indicate that apart from glycaemic toxicity there are perhaps other features to account for renal disease in diabetics which may include concurrent morbidities and genetic predisposition also.

The duration of disease when compared to the levels of DR is significant. This means that any level of DR is less in patients with more duration of disease.

The data on the duration of disease shows a reduced percentage of patients with any DR and CKD. This is in consonance with the studies of The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII which assessed the twenty-five-year progression of retinopathy in persons with type 1 diabetes and the Finn-Diane study and the studies of James *et al*.[31] There could be various reasons for this improvement. Development of newer more effective insulins and their easy availability could be a reason. One cannot also forget the genetic factors[39].

SUMMARY AND CONCLUSION

Fifty diagnosed patients of DM with duration of diabetes more than 20 years with ages ranging from 48 years to 85 years were analysed for ocular findings along with renal function tests and HbA1c levels. Since this study group was formed of patients with 20 years of disease duration, it can be presumed that in this study group DM was detected from ages of 28-65 years. This is in consonance with the global study. Patients between 51-70 years constituted 76% of the study group. The mean age of the study group is also 65.04 years. This in itself corroborates the increasing longevity of patients with DM. Of the study group, 62% (31/50) were having disease duration of 20-22 years compared to 6% (3/50) of patients with 29 years of disease duration. This difference is statistically significant implying that majority of diabetics have an average of 22 years of disease duration. Sex had no bearing on any of the study parameters including DR. The lenticular status (PSC/pseudophakia) had no significance when compared to any other parameter. Only 16% of the study population with duration of disease more than 26 years had any DR compared to the remaining percentage seen in patients with less than 25 years of disease duration. DR was statistically significant with HbA1C levels. This is consistent with existing knowledge on the subject. Only 8/50 patients with disease duration more than 20 years had CKD. These patients had HbA1C more than 6.5% and were associated with severe NPDR and PDR. HbA1C levels were significant with levels of DR and CKD. They were < = 6.5 % in patients with disease duration >26 years. With increase in disease duration there was lesser incidence of DR as also CKD.

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