Table IV: Classification of skin and soft tissue infection proposed by Infectious Disease Society of America (IDSA)

Class	Type of infection	Management
Class I	Superficial skin infections like impetigo, ecthyma	Oral (rarely topical) antibiotics +/- drainage
Class 2A	Purulent SSTIs like abscess, furuncle, carbuncle Erysipelas and cellulitis Traumatic wounds like post- operative/animal bites Systemically well, No SIRS	Oral/outpatient based parenteral antibiotics
Class 2B	Class 2A infections in a systemically unwell patient but no SIRS	Oral/outpatient based parenteral antibiotics; may need short course of admission
Class 3	Necrotising SSTI like necrotizing fasciitis/gas gangrene/pyomyositis	Urgent hospitalization

Abbreviation: SIRS-systemic inflammatory response syndrome
SSTIs-Skin and soft tissues infections

A furuncle is deep infection of hair follicle and surrounding tissue. Multiple furuncles may coalesce to form an inflammatory mass, termed carbuncle. This mass usually drains on to the skin surface with multiple pus points. The most common sites are the back, nape of the neck and buttocks. Staphylococcus aureus is the usual causative organism. Management involves prompt surgical debridement, administration of appropriate antibiotics and control of hyperglycemia.

Necrotising fasciitis (NF) is a rare invasive SSTI characterised by extensive local tissue destruction, microvascular thrombosis and systemic toxicity. The infection is generally polymicrobial and clinical features includes severe local pain and tenderness with associated swelling and erythema, crepitus, skin necrosis, bullae and features of systemic inflammatory response syndrome (SIRS). NF involving scrotal and perineal region is known as Fournier gangrene. It may begin in scrotal region and spread rapidly to involve penis, perineum, and anterior abdominal wall; however, testicles are spared due to separate blood supply.

NF is an acute surgical emergency and aggressive surgical debridement combined with parenteral antibiotics may be lifesaving. Like ROCM, prompt surgery holds the key since antibiotic penetration may be poor due to microvascular thrombosis[68]. Empirical antibiotic therapy should include a combination of clindamycin or metronidazole and a broad-spectrum penicillin plus beta-lactamase inhibitor (as piperacillin-tazobactam or ampicillin-sulbactam).

Insulin site infections

Injection site abscesses are a result of poor hygiene at injection site, repeated use of the same needle, repeated injections at same site, use of contaminated insulin and failure to change catheter at recommended interval in patients using continuous subcutaneous insulin infusion (CSII). Most common microorganisms implicated are Staphylococcus aureus and Streptococcus pyogenes; however, rarely atypical mycobacteria (as Mycobacterium chelonae and fortuitum) have been implicated in its causation[69,70]. Treatment involves incision and drainage of the abscess along with antimicrobial therapy guided by the results of pus culture.

Genitourinary infections

Genitourinary infections are the commonest infections among patients with diabetes. As already mentioned, not only are patients with diabetes at increased risk of recurrent genitourinary infections, they are also likely to have a more complicated course, compared to the general population. Factors predisposing to increased risk of genitourinary infections in these patients include presence of hyperglycemia, metabolic acidosis, cystopathy with significant post-void residual urine and obstruction due to calculi, papillary necrosis, fungal ball etc. Various genitourinary infections in patients with DM have been listed in Table V.

Table V: Genitourinary infections in patients with diabetes mellitus

Bacterial	Fungal
Cystitis Emphysematous cystitis Pyelitis Pyelonephritis Emphysematous pyelonephritis Perinephric abscess	Vulvovaginal candidiasis Invasive candidiasis Renal actinomycosis

Among the bacterial causes, E.coli accounts for the majority of UTIs followed by other Gram negative bacilli such as Proteus, Klebsiella, Acinetobacter and Pseudomonas. Enterococci, coagulase negative staphylococcus, beta-hemolytic streptococci and Staphylococcus aureus are other important microorganisms implicated. All UTIs in T1DM merit treatment and in recurrent cases, imaging should be obtained to exclude obstructive etiology.

Urinary tract candidiasis

Urinary tract candidiasis may be seen in patients on broad spectrum antibiotics and in those with prolonged indwelling catheter. Although often asymptomatic, it may present with cystitis, pyelonephritis, renal abscesses, and rarely formation of fungal ball. Candida albicans is the most common pathogen identified, followed by Candida glabrata. The infection can be acquired through genitourinary tract (ascending infection), from the gut or via hematogenous spread[71].

Asymptomatic candiduria in presence of indwelling catheter frequently resolves (20-40% cases) on removing or changing the catheter[72]. Stopping the antibiotics which are not necessary is also helpful. If candiduria fails to clear despite these measures, deep seated infection should be suspected and imaging of kidney and collecting system should be done. All symptomatic cases should be treated with oral fluconazole with or without flucytosine for 2 – 3 weeks. Fungal ball needs removal via cystoscope or ureteroscope or rarely, an open surgical intervention. Renal candidiasis should be treated with amphotericin B +/- flucytosine. Surgical intervention in the form of drainage or even nephrectomy may be rarely required.

Perinephric abscess

Perinephric abscess may be a complication of acute pyelonephritis and should be suspected in patients who fail to improve on conventional therapy. About 30-40% patients with perinephric abscess have diabetes[73,74]. Clinical features include flank pain, nausea, vomiting,

dysuria and polyuria. Most commonly implicated microorganisms include E.coli, Klebsiella and Proteus species. Samples for blood culture, urine culture and pus culture (obtained via USG or CT guided aspiration) should be collected, followed by institution of empirical antimicrobial therapy. Duration of antibiotics should be at least 2 to 3 weeks, and should be adjusted based upon improvement of clinical and laboratory parameters and resolution of abscess[75]. Percutaneous drainage of abscess should be done and any obstruction (as calculi) should be removed. Rarely, in advanced cases, nephrectomy may be required[76].

Renal papillary necrosis (RPN)

RPN, characterised by coagulative necrosis of renal medullary pyramids and papillae has been postulated to occur due to marginal changes in vascular supply leading to infarction of the renal papillae[77]. It should be suspected in patients with recurrent pyelonephritis or difficult to treat pyelonephritis, recurrent renal colic, gross hematuria and unexplained renal failure. Acute presentation is usually unilateral and is dominated by symptoms of fever, flank pain, renal colic and hematuria. A chronic presentation is, however, more common and is often bilateral. Intravenous urography (IVU) is the most sensitive investigation, but is rarely used due to associated renal dysfunction. Aggressive antibiotic treatment with relief of obstruction from sloughed papillae is the recommended treatment.

Emphysematous pyelonephritis (EPN) and emphysematous cystitis

Upto 90% of patients presenting with emphysematous urinary tract infections have diabetes. The presence of gas forming organisms, high level of blood glucose and impaired renal perfusion (contributing to gas accumulation) are the three prerequisites for emphysematous kidney disease[78]. Emphysematous pyelonephritis (EPN) is a severe, necrotizing form of multifocal bacterial infection with gas formation within the kidney parenchyma. Its presentation is usually similar to acute pyelonephritis with fever, flank pain, nausea and vomiting. Rarely, a palpable mass or crepitus may be appreciated. Acute presentation with sepsis, septic shock, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) is also reported, but DKA is surprisingly rare. The causative microorganisms include gram negative bacilli such as E.coli (most common), Klebsiella and Proteus[78]. Radiograph of kidney, ureter and bladder (KUB) region may show gas overlying the renal fossa while ultrasonography may reveal enlarged kidney with hyperechogenic foci within. CT abdomen is the imaging modality of choice to identify and stage the anatomical extent of abnormal gas accumulation. A radiological grading system based on CT findings proposed by Heung and Tseng is as follows[79]:

Grade 1 : Gas confined to the collecting system
Grade 2 : Gas in renal pelvis
Grade 3a : Perinephric collection
Grade 3b : Extension of gas beyond Gerota's fascia
Grade 4 : Bilateral involvement or EPN in a single kidney

Grade 1 and grade 2 EPN can be managed conservatively with intravenous antibiotics (cefoperazone-sulbactam, piperacillin-tazobactam, meropenem, levofloxacin) with or without percutaneous drainage. Grade 3 EPN may be managed conservatively with intravenous antibiotics and percutaneous drainage, however, may require nephrectomy if poor prognostic factors (such as thrombocytopenia, DIC, shock, acute kidney injury) emerge while grade 4 EPN (especially with associated poor prognostic factors) often require nephrectomy[80].

Emphysematous pyelitis refers to the abnormal gas collection localized to the collecting system. It is most often a result of underlying obstruction. CT scan is the imaging modality of choice. Treatment requires broad spectrum intravenous antibiotics and percutaneous drainage. Emphysematous cystitis is less common than EPN, but portends a better prognosis. It presents with dysuria, abdominal discomfort and hematuria. Pneumaturia is a rare finding but is highly specific for this entity. Radiograph of KUB region reveals curvilinear or mottled areas of increased radiolucency in the region of bladder. CT is the imaging modality of choice as it defines the abnormal gas collection and its anatomic extent. Treatment involves administration of broad spectrum intravenous antibiotics.

Gastrointestinal infections

Gastrointestinal dysmotility in addition to immune dysfunction increases the predisposition to infection with several enteric pathogens in patients with diabetes. Emphysematous cholecystitis is a dreaded complication of acute cholecystitis, wherein, air fills the lumen and walls of gall bladder, leading to 30 times increased risk of perforation and 10 times increased risk of gangrene. The most common causative organisms include anaerobic gas forming bacteria, such as Clostridium perfringens and Clostridium welchii, followed by aerobes, such as Escherichia coli. Treatment requires an emergent cholecystectomy[81].

Respiratory tract infections

Pulmonary infections due to various microorganisms (such as pneumococcus, influenza) implicated in community acquired pneumonia (CAP) are associated with increased morbidity and mortality in patients with diabetes. Additionally, people with diabetes are also more prone to infections with organisms like Mycobacterium tuberculosis, Staphylococcus aureus, gram negative bacilli and fungi (such as Cryptococcus, Candida, Mucor).

Diabetes and Tuberculosis

Epidemiology

Diabetes and tuberculosis share a bidirectional relationship with each other and together they form a deadly syndemic. Patients with diabetes are not only at increased risk of tuberculosis but are also likely to have poorer outcomes with treatment. On the other hand, tuberculosis can lead to worsening of glycemic control giving rise to a vicious cycle of synergism[82].

Patients with diabetes are at 3.5-5.0-fold higher risk of developing tuberculosis, and the risk is especially high in patients with T1DM[83,84]. In a study involving 151 subjects with T1DM who were screened for pulmonary tuberculosis (PTB), prevalence of sputum culture positive PTB was found to be 10.6%[85].

Studies have shown that diabetes may influence the clinical features, radiological manifestations, sputum conversion rates, drug resistance patterns and treatment outcomes among patients with PTB. PTB might progress rapidly in diabetic patients, especially in patients with uncontrolled hyperglycemia and delayed diagnosis in such cases is associated with increased mortality. Multi-lobar disease, preferential involvement of lower lobe and multi-cavitary disease is also more common in patients with diabetes. Despite higher bacterial load, sputum negativity is common. Patients with diabetes show delayed mycobacterial clearance with treatment and are also at increased risk of relapse following the treatment[86,87]. Additionally, multidrug-resistant tuberculosis (MDR-TB) has been found to be more common in patients with diabetes[88].

Pathophysiology of the association between DM and tuberculosis

There is evidence of impaired cell-mediated immunity, micronutrient deficiency, pulmonary microangiopathy and renal insufficiency in patients with diabetes, all of which predispose to PTB. Stress due to a chronic infectious disease such as TB which causes considerable catabolism may increase insulin resistance and increase the demand for insulin secretion. When the increased demand cannot be met (due to a pre-existing low beta-cell mass), as is often the case in poor TB patients with associated malnutrition, the potential underlying risk of diabetes may be unmasked. Regardless of the direction of the association, the common diabetes–tuberculosis comorbidity presents clinical challenges: first, as a result of stress-induced hyperglycemia, and second, because rifampicin [one of the key drugs in any anti-tuberculosis treatment (ATT) regimen] may in itself have hyperglycemic effects[89,90].

Management of patients with tuberculosis and DM

Tuberculosis in patients with diabetes is associated with increased relapse rates. New cases of PTB with diabetes should be treated for 6 months (as per the standardized WHO regimen) Whether treatment in such cases should be extended to a total duration of 9 months needs an evidence-based justification. The recommended treatment for management of tuberculosis includes the standard four drug regimen- isoniazid along with pyridoxine, rifampicin, ethambutol and pyrazinamide. Whether patients with extensive cavitary disease should receive an additional drug (possibly a quinolone like moxifloxacin) to rapidly reduce sputum AFB load remains an unanswered question[82]. Tight glycemic control makes anti-tubercular drugs more effective and leads to better clinical, radiological and bacteriological resolution of the disease. Due to worsening of glycemic control with acute infection, insulin doses may need up-titration during the initial phase, requiring close follow-up with the treating physician.

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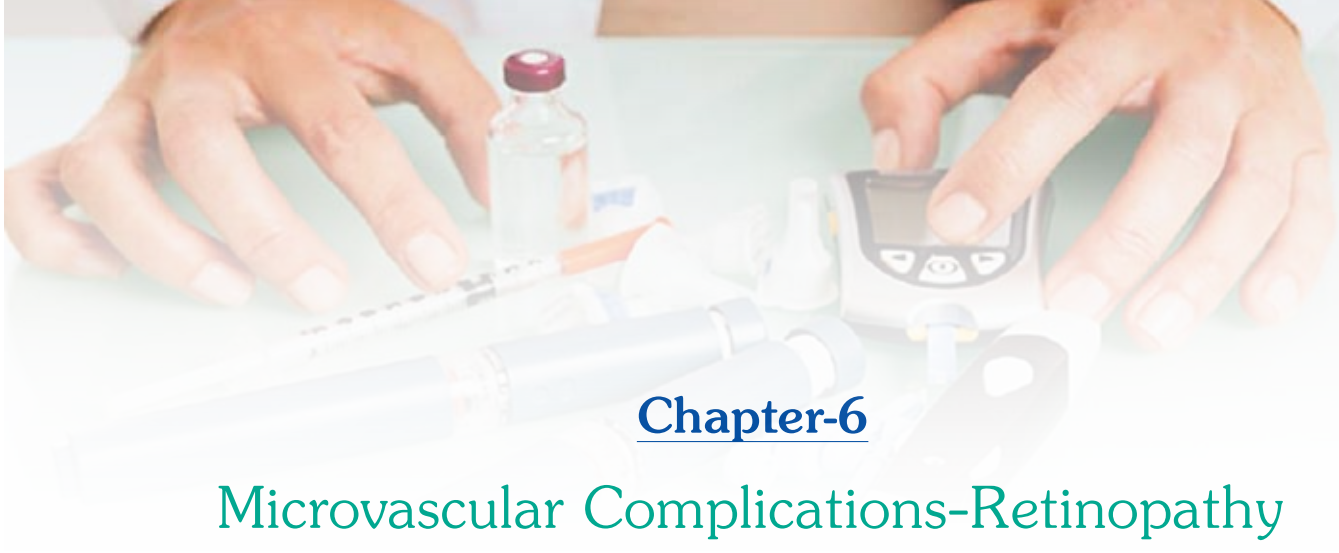

Chapter-6

Microvascular Complications-Retinopathy

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Introduction

Diabetic retinopathy (DR) is one of the most common microvascular complication of type 1 diabetes mellitus (T1DM) and a leading cause of blindness in adults[1]. It is a progressive disease which if untreated can lead to severe visual loss. With the advent of better insulin regimens and intensive management of diabetes, there is evidence for decrease in the occurrence of sight threatening proliferative DR (PDR)[2]. However, poor glycemic control continues to be a problem in many patients with T1DM, putting them at risk of complications. Significant improvement has been seen in the past couple of decades with regard to screening methods and treatment of DR. Patients with T1DM are also at a higher risk of developing other eye diseases such as cataract, glaucoma, retinal vein occlusion, and cranial nerve palsies. Besides, cataract surgery may run a complicated course and can be associated with worse visual outcomes in such patients. This chapter reviews epidemiological and clinical aspects of DR with emphasis on clinical practice guidelines for detection and management of sight threatening DR.

Epidemiology

There are limited studies on DR exclusively dealing with T1DM patients. One of the longest follow-up study is the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR). In this study, amongst 996 young subjects (<30 years) requiring insulin, the prevalence of DR varied from 17% in subjects with diabetes for less than 5 years to 97.5% in those with disease duration of 15 or more years. On the other hand, PDR varied from 1.2% in subjects with diabetes for less than 10 years to 67% in those with disease duration of 35 or more years[3]. A follow-up of the same cohort showed cumulative incidence of 59%, 89.3%, 95.9% and 97% at 4, 10, 14 and 25 years, respectively[4]. The risk of DR is higher in T1DM compared to adult-onsetT2DM. In a meta-analysis of 35 population-based studies in which fundus photographs were used to ascertain retinopathy, prevalence of any DR or PDR was higher in those with T1DM compared to adult-onset T2DM (77.3 vs. 25.2 % for any DR, 32.4 vs. 3.0% for PDR)[5].

The most significant paradigm change in T1DM treatment happened with the DCCT (Diabetes Control and Complications Trial) study. Intensive treatment and lower glycosylated haemoglobin (HbA1c) levels reduced the risk for DR by 76% and slowed the progression of existing DR by 54%. There were also marked risk reduction in development of PDR (47%), onset of macular edema (26%), and need for laser photocoagulation (56%). A follow-up of the same cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) showed lasting benefits of intensive control despite a subsequent

increase and equalization of HbA1c in both arms of treatment. Though intense glycemic control initially worsened DR, lasting benefits were evident in 1.5-3.0 years[6]. In the post-DCCT era, there is some evidence of decline in the prevalence of DR, as seen in an analysis of 1604 adolescents with T1DM stratified by four time periods between 1990-2009; retinopathy declined (53%, 38%, 23%, and 12%; $p < 0.001$) and use of multiple injection or insulin pump increased (17%, 54%, 75%, and 88%; $P < 0.001$) during this time period[7].

As opposed to adult-onset T2DM, the burden of DR is higher in patients with youth-onset T2DM compared to T1DM. Among a cohort of 1746 subjects with T1DM (mean disease duration: 7.9 years) and 272 subjects with youth-onset T2DM (mean disease duration: 7.9 years) who were a part of the SEARCH for Diabetes in Youth registry, 5.6% and 9.1%, respectively had DR. This observation suggests the aggressive nature of youth onset T2DM8. A higher burden of DR (and microvascular complications in general) in youth-onset T2DM may be governed by delayed presentation and poor glycemic control related to difficulties in accepting the diagnosis and low adherence to lifestyle measures and pharmacotherapy. Besides, a lower risk of developing ketoacidosis in the absence of adequate treatment increases the probability of exposure to sustained hyperglycemia in patients with youth-onset T2DM.

The literature on occurrence of DR in T1DM in India is limited and mainly available from hospital- based studies. These are summarized in Table I[9-14]. A variable burden of DR reported in these studies may be due to differences in diabetes duration and techniques of assessment employed in these studies. Most studies have utilized direct or indirect ophthalmoscopy for diagnosis. In a study by Rajalakshmi and colleagues which evaluated 150 subjects with T1DM using four-field digital retinal colour photography, the age and gender-adjusted prevalence of DR, DME and PDR was reported to be 62.5%, 10% and 7.3%, respectively[14].

Table I: Prevalence of diabetic retinopathy among subjects with T1DM in various Indian studies[9-14]

Author, Year	Method of examination	Sample size	Duration of diabetes (years)	Prevalence of DR
Ramachandran et al, 2000	Indirect ophthalmoscopy	617	Median: 4 years Range: 3-34 years	13.4%
Bhatia et al, 2004	Direct ophthalmoscopy	50	> 5 years	22.0%
Unnikrishnan et al, 2008	Direct ophthalmoscopy	535	Mean: 5.6 years	5.0%
Kumar et al, 2008	N/A	166	N/A	8.4%
Amutha et al, 2011	Direct and indirect ophthalmoscopy	224	> 5 years	35.3% 77.3% with > 15 years duration
Rajalakshmi et al, 2014	Four field digital retinal photography	150	Mean: 12.4 years	53.3%

Abbreviations: DR- Diabetic retinopathy; N/A- Not available; T1DM-Type 1 diabetes mellitus

Risk Factors

The potential risk factors for DR are summarized in Table II. Longer diabetes duration, poor glycemic control and suboptimal blood pressure control are associated with increased risk of DR in most studies. Total number of prepubertal years seem to add to the risk of DR[15], but glycemic control during puberty is a more important determinant. The increased risk for DR after the onset of puberty may be due to increased insulin-like growth factor-1 (IGF-1), growth hormone, sex steroids, and blood pressure and deterioration of glycemic control. There is a possible role of genetic susceptibility, which could explain variations in retinal response to hyperglycemia and hence the discordance between degree of glycemic control and severity of retinal disease in certain cases (no/mild retinopathy despite long duration of poor glycemic control and severe retinopathy in a short period despite relatively good glycemic control). In an Indian study, diabetes duration, increased waist circumference and microalbuminuria were significantly associated with DR[14].

Table II: Risk factors for diabetic retinopathy

Non-modifiable factors	Modifiable factors	Novel factors of possible role
Duration of diabetes Puberty Pregnancy Family history of retinopathy	Hyperglycemia Hypertension Dyslipidemia Smoking Anemia Microalbuminuria	Inflammation Genetic polymorphism Adipose tissue hormones Oxidative stress Vitamin D

Pathophysiology

In both T1 and T2DM, chronic hyperglycemia is the most important risk factor for the development of retinopathy. The exact mechanism by which hyperglycemia causes changes in retinal vasculature is not completely clear and several mechanisms have been proposed[16]. These include changes in the polyol pathway (accumulation of sorbitol and fructose), non-enzymatic protein glycation forming advanced glycation products, activation of protein kinase (PKC), hemodynamic changes, changes in renin-angiotensin-aldosterone system (RAAS), subclinical inflammation and leukostasis. These mechanisms lead to increased reactive oxygen species (ROS), and reduced clearance of free oxygen, causing oxidative stress.

Changes in cellular architecture including endothelial cell damage and proliferation, loss of pericytes and changes in blood retinal barrier occur due to above mentioned factors; this causes leakage and edema, including DME. Loss of pericytes correlates with microaneurysm formation. Another feature of DR is the thickening of capillary basement membrane similar to changes in glomerular membrane and increased deposition of extracellular matrix components. Together, these changes lead to capillary occlusion and ischemia.

Retinal ischemia is a potent stimulant for formation of various growth factors, most important of which is vascular endothelial growth factor (VEGF). Binding of these growth factors to their receptor triggers various pathways leading to endothelial damage, increased capillary permeability and promoting angiogenesis and neovascularization. The latter leads to PDR which increases the risk of intravitreal bleed and blindness.

Clinical features and classification

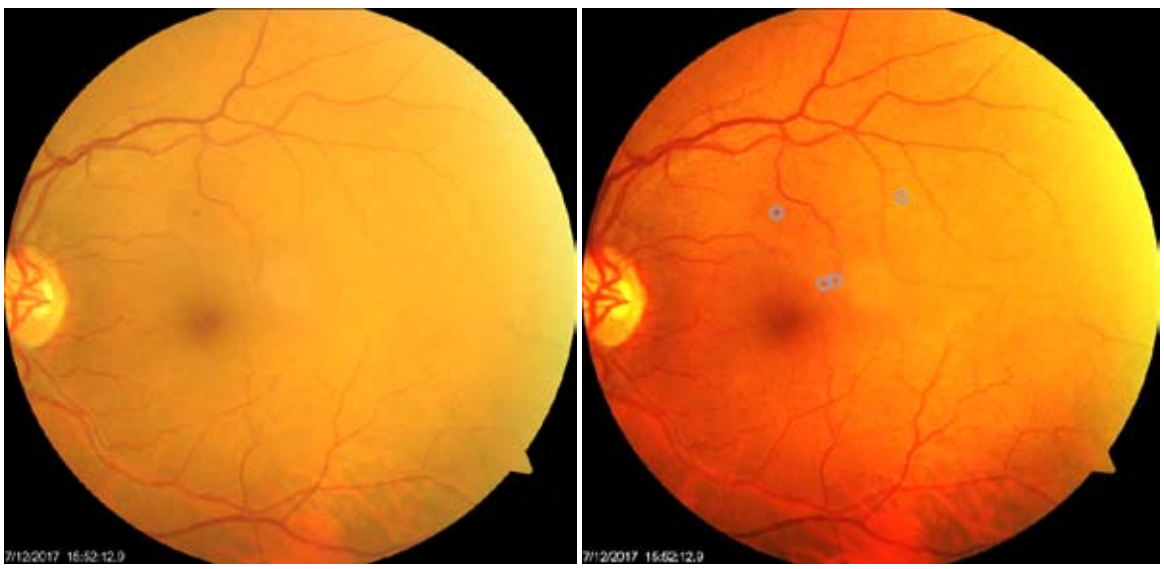
Symptoms

Most individuals with initial changes of DR are asymptomatic. The earliest change of DR is presence of microanuerysms, which we will describe in more detail in a later section. Therefore, screening at an early stage gives us a lead time before vision loss occurs. As DR progresses, some individuals may complain of blurring of vision. At this stage, swelling in the retina or DME is likely to be present. At a more severe stage, there may be presence of floaters / black moving spots in front of the eye, which are suggestive of bleeding inside the eye (vitreous haemorrhage). At a very advanced stage, there may be significant vision loss along with pain, which may be suggestive of increasing eye pressure due to advanced DR.

Signs

As mentioned earlier, the earliest sign is the presence of microanuerysms. These are seen as small deep-red dots between 25 and 100µm in diameter within the retina. These are essentially outpouchings from the retinal capillaries, caused due to pericyte loss. At this stage, the disease is classified as mild non-proliferative diabetic retinopathy (NPDR) (Figure 1).

Figure 1: On the left is the image of the fundus, showing mild NPDR; the right image is the same fundus picture, with the microanuerysms marked as blue circles



NPDR- NPDR- Non-proliferative diabetic retinopathy

As the disease progresses, presence of intra-retinal hemorrhages can be seen. These are of two types: flame shaped hemorrhages, which lie in more superficial retina (retinal nerve fibre layer) and dot-blot hemorrhages, which lie in deeper retinal layers. The type of retinal haemorrhage is not known to have a prognostic significance. Superficial retinal nerve fibre layer infarcts may be present, which are seen as yellow-white lesions with indistinct margins (cotton wool spots or soft exudates).

With further increasing severity, we see that the retinal veins have a sausage-like appearance, or beaded appearance, called venous beading. The retinal vessels may show

another sign, in which a fine abnormal vascular pattern may be seen within the retina (not elevated); this is called Intra-retinal microvascular abnormality (IRMA). In cases of extensive capillary occlusion, dot haemorrhages and IRMA may disappear and the retina may appear free of non-proliferative lesions. This entity, described as "featureless retina" is a sign of severe retinal hypoxia.

With increasing severity of DR and ischemia in the retina, there is an augmented release of VEGF inside the eye, leading to neovascularisation. These new vessels tend to grow on the surface of the retina, or into the vitreous. They may have a cartwheel, or sea-fan appearance. They are fragile, and cause pre-retinal haemorrhage seen as sub-hyaloid haemorrhage and vitreous haemorrhage. Neovascularization at the optic disc is considered as more severe and a sign of global ischemia. As this neovascularization becomes fibrotic and contracts, it leads to tractional retinal detachment.

With leakage from retinal capillaries, retinal edema develops, typically present at macula, and causing decrease in vision (DME). As the exudation from the capillaries also have lipids, their accumulation in retinal layers leads to formation of yellow waxy plaques, flecks or dots composed of lipoprotein and lipid filled macrophages (surrounding the leaking microvascular lesions in the retina). Such lesions are called hard exudates. When the macular edema involves or threatens to involve the center of the macula, it is called as clinically significant macular edema (CSME). CSME may exist with any severity of retinopathy, however, it is more common in the advanced forms, and deserves urgent attention of the ophthalmologist. CSME is defined as one of the following: a) retinal thickening at or within 500 µm of the center of the macula b) hard exudates at or within 500 µm of the center of the macula with adjacent retinal thickening c) zone or zones of retinal thickening one- disc area or large in size, any part of which is located within one-disc diameter of the center of the macula. The Early Treatment Diabetic Retinopathy Study (ETDRS) found that untreated CSME is associated with 30% risk of moderate vision loss over three years, and the risk can be reduced by 50% using focal laser photocoagulation. Evaluation for DME requires three dimensional assessment, best performed using a dilated slit lamp biomicroscopy and/or stereo fundus photography.

Classification:

The ETDRS study group has proposed a classification of DR which uses the Modified Airlie House classification to label fundus picture areas from 1 to 7[17]. As per the ETDRS classification, DR can be classified as follows:

- **MILD NPDR**

  At least one microaneurysm, AND criteria not met for more severe retinopathy.

- **MODERATE NPDR**

  Hemorrhages/microanuerysms ≥ standard photograph 2A AND/OR cotton-wool spots, venous beading, or IRMA definitely present; AND criteria not met for more severe retinopathy.

- **SEVERE NPDR**

  Cotton-wool spots, venous beading, and IRMA definitely present in at least two of photographic fields 4–7; OR two of the three preceding features present in at least two of fields 4–7 and hemorrhages/microanuerysms present in fields 4–7 ≥ standard

photograph 2A in at least one of them; OR IRMA present in each of fields 4–7 and ≥ standard photograph 8A in at least two of them; AND criteria not met for more severe retinopathy.

- **EARLY PDR**

  New vessels; AND criteria not met for high-risk PDR.

- **HIGH-RISK PDR**

New vessels on or within one disc diameter of the optic disc [neovascularization of the disc (NVD)] ≥ standard photograph 10A (approximately 1/4– 1/3 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) ≥ 1/2 disc area.

ETDRS classification is complex, requires comparison with standard photographs and is difficult to remember or apply in clinical setting; however, it is best suited for research studies. A simpler and clinically useful classification is the International Classification of Diabetic Retinopathy and Diabetic Macular Edema (the International Classification) (Table III)[18].

Differentiation from non-diabeteic retinopathy

Although a co-existing hyperglycemia is suggestive in almost all cases, differential diagnosis of DR would include:

1. Retinal vein occlusion: Typically, unilateral presentation; co-existing diabetes may be present
2. Ocular ischemic syndrome: Typically, unilateral presentation; a carotid doppler shows occlusion
3. Sickle cell retinopathy: Blood investigations are confirmatory of sickle cell disease
4. Radiation Retinopathy: History of radiation is present

Screening

Screening for DR fulfills all important pre-requisites for a screening program, i.e., the disease is an important public health problem, natural history of disease is well understood, long latent phase is present, acceptable and cost-effective tests for diagnosis are available, treatment is available and is known to improve outcomes, facilities for diagnosis and treatment are available and case finding is likely to be a continuous process and not just "once and for all" project.

Annual screening for DR in T1DM is recommended in individuals more than 10 years of age, with a disease duration of 5 years or more[19].

Screening can be done by various fundus examination techniques, which include (Figures 2 and 3):

a) Direct Ophthalmoscope

b) Indirect Ophthalmoscope

c) Slit Lamp Fundus Exam (Biomicroscopy)

d) Fundus cameras (mydriatic or non-mydriatic)