Table III: International Clinical Disease Severity for Diabetes Retinopathy

Proposed disease severity level	Findings on dilated ophthalmoscopy
DIABETIC RETINOPATHY (DR)	
No apparent retinopathy	No abnormalities.
Mild nonproliferative DR (NPDR)	Microaneurysms only.
Moderate NPDR	Microaneurysms with other signs such as dot and blot haemorrhages, hard exudates and cotton wool spots, but less than severe NPDR.
Severe NPDR	Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in 2+ quadrants; prominent intraretinal microvascular abnormalities in 1+ quadrant AND no signs of PDR.
PDR	One or more of the following: neovascularization on the optic disc and/or elsewhere, and vitreous/preretinal haemorrhage.
DIABETIC MACULAR EDEMA (DME)	
DME apparently absent	No apparent retinal thickening or hard exudates in macula.
Non-central involving DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter.
Central involving DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter.

Abbreviations: PDR- Proliferative diabetic retinopathy

The sensitivity of screening by direct ophthalmoscopy may be lower, especially when performed by non-eye care professionals. The highest sensitivity is provided by mydriatic retinal imaging using more than two fields of view.

Figure 2: Image of normal retina, showing the optic disc in blue circle, and fovea in yellow circle

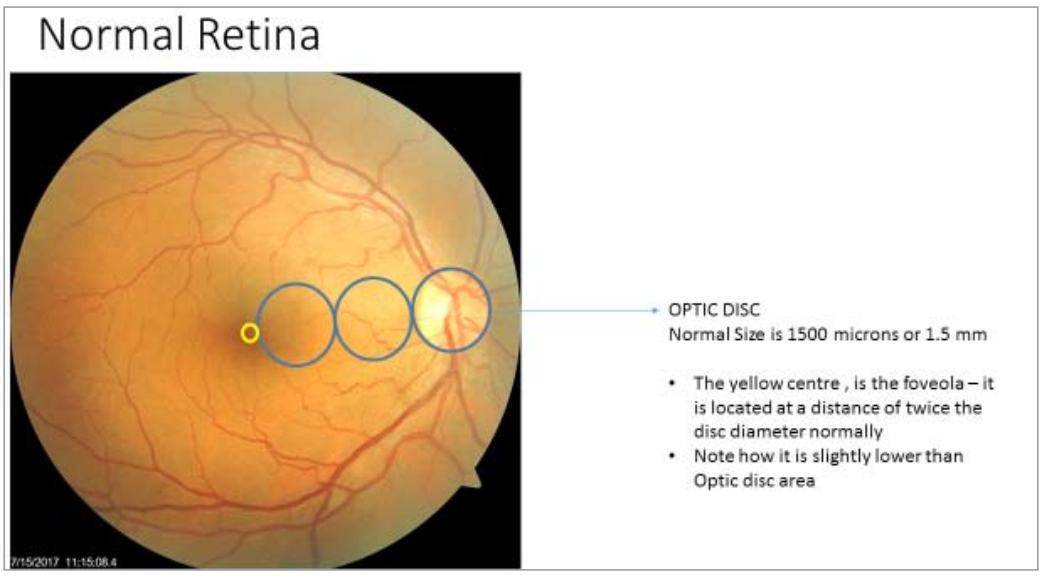
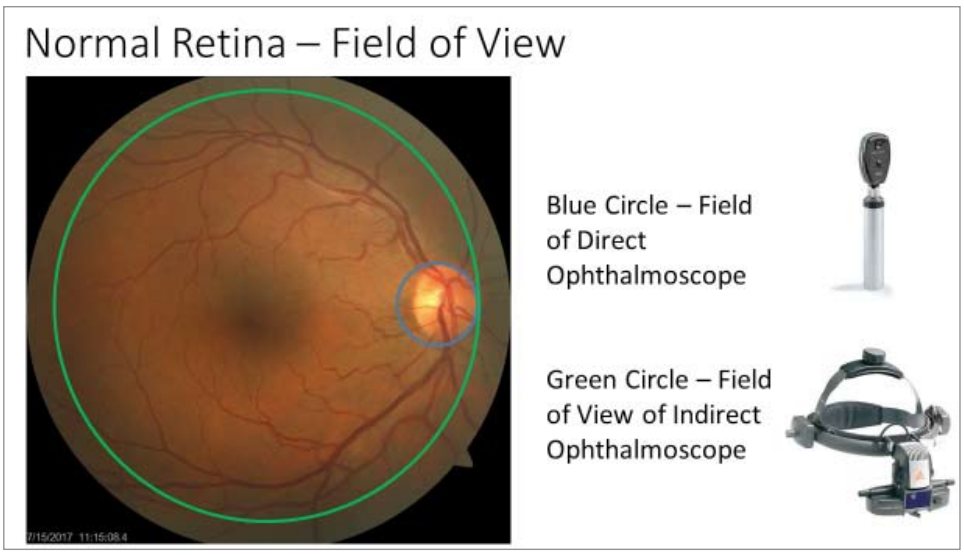


Figure 3: Image showing the field of view of the direct and indirect ophthalmoscopes. Further, by asking the patient to look in different directions, or with examiner changing the position, more areas of the fundus can be seen using the either technique



Investigations

A detailed investigative work-up for DR would include:

A. Fundus Photography
B. Fundus Fluorescein Angiography (FFA)
C. Optical Coherence Tomography (OCT)
D. B-Scan Ultrasonography

A. Fundus Photography

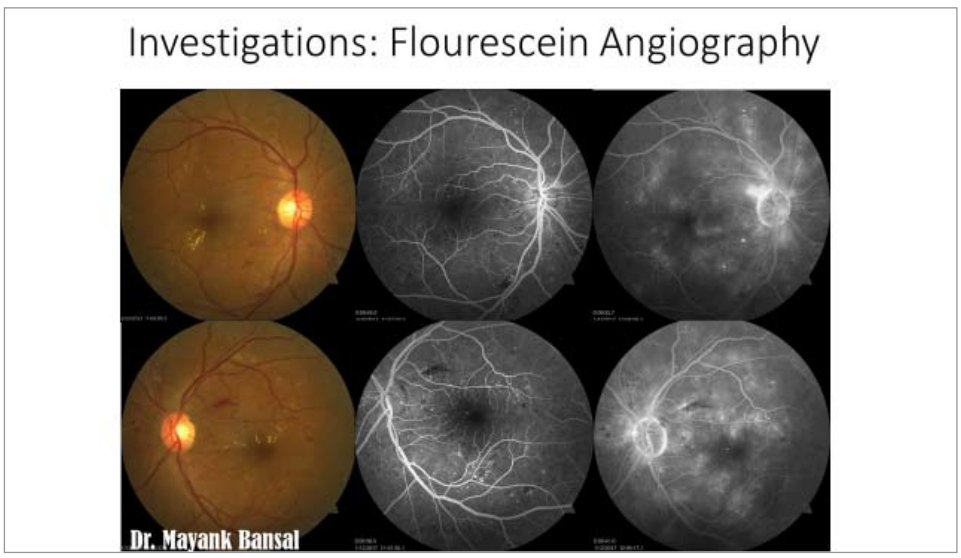
Fundus photography is a valuable tool which helps to document the status of DR, and monitor changes over a period of time. It is also useful to store data for subsequent clinical studies. A variety of portable, low cost fundus photography tools are now available. Ultra-wide field fundus imaging is a relatively new retinal imaging technique that allows imaging of the peripheral retina[20].

B. Fundus Fluorescein Angiography (FFA)

An essential part of DR investigation is FFA which involves the injection of sodium fluorescein (3ml of 20% or 5ml of 10%) dye intravenously. Following injection of dye, images of the retina are taken using the FFA camera. The images are observed for presence of hyperfluorescent and hypofluorescent areas. Hyperfluorescense typically caused by leaking microanuerysms and neovascularization (Figure 4), while hypofluorescence results from areas of non-perfusion/ischemia to the retina. Another common cause of the latter is blocked fluorescence due to haemorrhage (pre-retinal/retinal). Ultra-wide field fluorescein angiography (UWFA) is a relatively new modality which allows visualization of peripheral retinal non-perfusion areas, as well as NVEs, thus aiding with targeted retinal photocoagulation[21]. Complications of FFA include painful extravasation of dye and allergic reactions which can range from mild to severe; resuscitation equipment should be available when FFA is done. The use of FFA is contraindicated in a patient with history of allergic

hypersensitivity to fluorescin. In the present day, the indications for use of FFA are gradually dwindling, with the advent of Optical Coherence Tomography (OCT).

Figure 4: Fundus Fluorescein Angiography (FFA) showing leaking microanuerysms at the posterior pole



C. Optical Coherence Tomography (OCT)

This investigation uses a laser light source to image the layers of retina (Figures 5 and 6). The resolution provided is of the order of 5 to 30 microns (depending on the advancement of the system). The importance of OCT in evaluation of DR has been increasing. The clear advantage is that it is a non-invasive investigation which images the presence of DME, classifies it as center-involving or non-center involving and also quantifies its degree of severity. The cause of DME can be ascertained, and response to treatment can be followed up on an OCT (Figure 7)[22].

OCT Angiography (OCTA) is a recent advancement in ophthalmic imaging which allows visualization of retinal vasculature, without the use of any dye. Its role is being increasingly established in various retinal conditions[23,24]. However currently, it is not considered an important component of DR management.

Figure 5: Optical coherence tomography (OCT) of a normal eye showing the central foveal dip

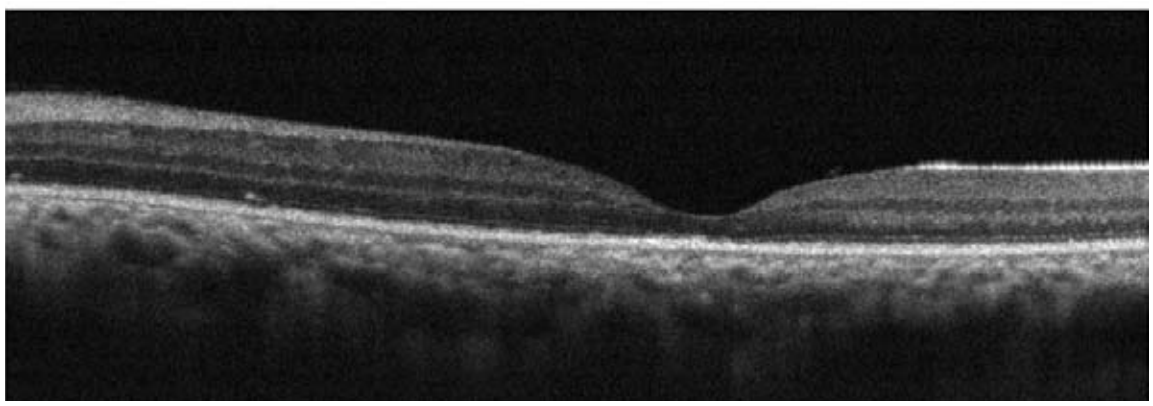


Figure 6: Optical coherence tomography (OCT) of a patient with diabetic macular edema (DME) showing loss of central foveal dip, with hypo-reflective fluid filled spaces at the macula. There is a co-existing hyper-reflective membrane at the surface of the retina, the epi-retinal membrane (ERM)

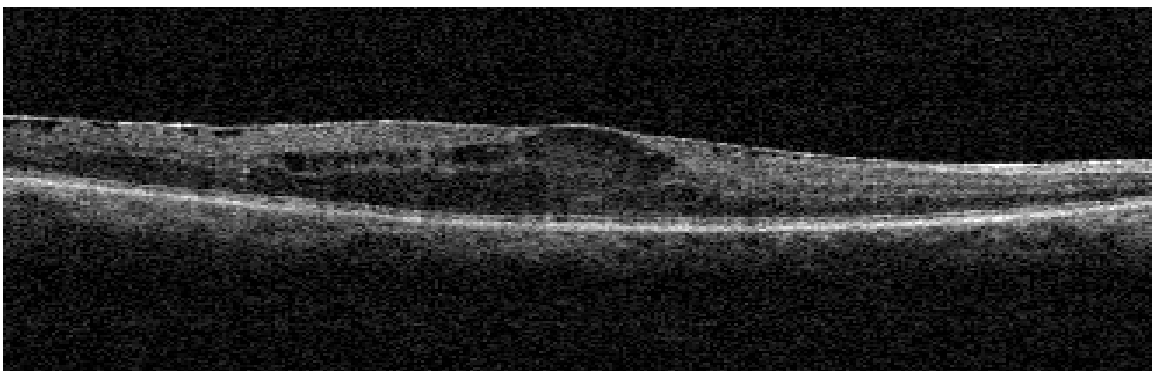
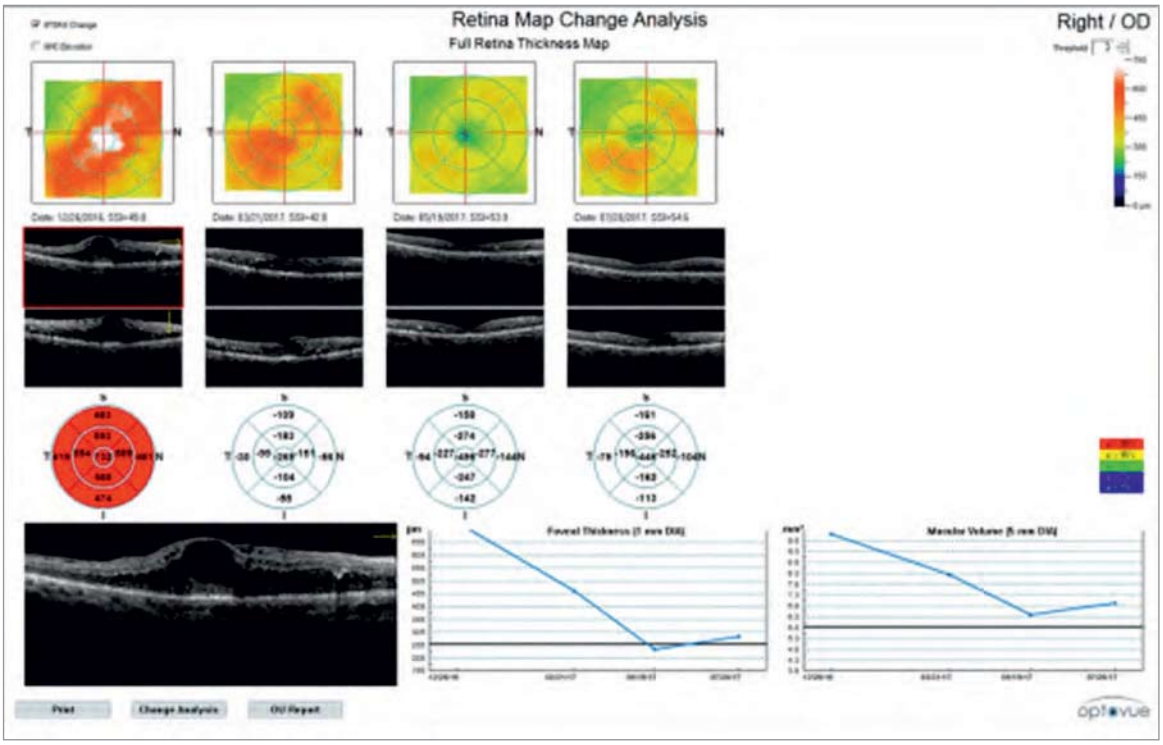


Figure 7: Optical coherence tomography (OCT) change analysis of a patient showing resolving macular edema following treatment with intra-vitreal injections.



D. B-Scan Ultrasonography:

B-Scan Ultrasonography can be used for imaging of retina and serve as an important preoperative tool for surgical planning in patients with hazy media such as due to dense cataract or vitreous hemorrhage.

Overview of management, referral and follow up plan

Glycemic control remains paramount in management, as established by DCCT. There is strong evidence to suggest that controlling hyperglycemia is associated with reduction in the incidence as well as progression of DR. In DCCT, each 10 percent proportional decline in HbA1c (for instance, from 9.0 to 8.1%) was associated with a 39 percent reduction in the

risk of DR. Besides, the benefits of early glycemic control on microvascular complications including DR persist in the long-term even after deterioration in blood glucose control, as was shown in the DCCT follow-up study-EDIC (legacy effect or metabolic memory). There is some risk of early worsening of DR with glycemic control, especially in those who have higher baseline HbA1c; however serious vision loss is rare and evidence for long term benefits is quite clear. In addition, control of blood pressure, lipids, proteinuria and cessation of smoking is helpful.In T1DM, evidence for reduction in the incidence of DR with intensive blood pressure lowering is modest; however, considering other benefits such as reduction in risk of cardiovascular disease and nephropathy, optimal control of hypertension control should be actively pursued. There is no conclusive evidence to support the specific use of agents blocking renin angiotensin aldosterone system in patients with DR. Similarly, the use of lipid lowering medications has not been found to reduce the risk of DR; however, optimal lowering should be targeted for cardiovascular benefits.

Ophthalmologic management depends on severity of DR at the time of screening. Early treatment of PDR and DME is crucial because it can prevent vision loss and lead to stabilisation or improvement in visual acuity. The management plan for various stages of DR is as follows:

- For absent DR or mild NPDR, annual screening is adequate.
- For moderate NPDR and severe NPDR, follow-up is advisable at 6 months and 4 months-interval, respectively.
- For PDR, 3 monthly follow up is advised (this decision is also based on treatment response), while DME requires frequent monthly follow-up to look for progression and treatment response. Generally speaking, eyes with moderate NPDR or worse are more likely to have associated DME.

The reasons for vision loss in a patient with DR include CSME, PDR causing pre- retinal hemorrhage, or tractional retinal detachment, and neovascular glaucoma (resulting from neovascularization of iris causing blockage of aqueous humor outflow). While DME is a more common cause of vision loss and leads to loss of central vision, PDR can result in more severe visual impairment, such as loss of perception in both eyes. Once PDR with high risk characteristics is present (NVD ≥ 1/3 disc area, any NVD with vitreous or pre-retinal hemorrhage or NVE ≥ 1/2 disc area with vitreous or pre-retinal hemorrhage), laser treatment is required. The indications and side effects of various modalities of treatment for DR have been summarized in Table IV.

Laser

Following types of laser are used in management of a patient with DR:

Grid/focal laser photocoagulation: Grid/focal lasers are primarily used for treatment of DME. However, the indications for the use of these lasers are gradually diminishing with the availability of pharmacotherapy for DME. While effective in controlling DME, these lasers do cause collateral damage / burn to retinal tissue (Table IV).

Panretinal photocoagulation: Panretinal photocoagulation (PRP) is the gold standard in management of PDR with high risk characteristics. The role of laser photocoagulation in DR was established by the Diabetic Retinopathy Study[25]. PRP involves administration of 1200-

Table IV: Indications and side effects of various treatment modalities for diabetic retinopathy[34,35]

Treatment	Indications	Side effects/ Complications	Remarks
Laser PRP	PDR Severe NPDR, especially when close follow-up is not possible	Pain during treatment, constriction of peripheral visual field with delayed dark adaptation, transient loss of central vision due to macular edema, VH if neovascularisation present.	Non-invasive, completed in 1-2 visits. Retreatment can be done if incomplete regression of vessels.
Focal/grid laser photo-coagulation	DME	Paracentral scotomas and permanent central scoto-ma due to inadvertent laser burns close to or at fovea, expansion of laser scar, and choroidal neo-vascularisation. Transient decrease in central vision may occur.	Given as a one-off treatment which can be repeated, if needed. Use diminishing, being replaced by intravitreal VEGF and/or steroid injections. Preferred in pregnancy with DME.
Intravitreal VEGF	DME PDR	Invasive, risk of complications such as cataract, retinal tear and endophthalmitis. Worsening of traction, increased risk of intraocular inflammation.	Requires multiple visits, especially during the first year. Higher cost compared to laser. Most popular for DME. Also used in combination with laser PRP (one week or immediately before laser PRP) to reduce DME. Can be used as a primary treatment for PDR.
Intravitreal steroids	DME	Invasive, risk of complications such as cataract, glaucoma and infectious endophthalmitis.	Requires multiple visits. Useful for DME that does not respond to other treatment.
Vitrectomy	Non resolving VH Tractional RD involving or threatening macula Tractional rhegmatog-enous detachment PDR which does not respond to aggressive laser PRP.	Recurrent VH, retinal tear or RD, vision loss, infectious endophthalmitis, cataract.	Better outcomes and safer procedure with the advancement in the surgical techniques and instrumentation for VR surgery.

Abbreviations: DME-Diabetic macular edema; NPDR- Non-proliferative diabetic retinopathy; PDR- Proliferative diabetic retinopathy; PRP- Pan retinal photocoagulation; RD-Retinal detachment; VH- Vitreous hemorrhage; VR- Vitreoretinal

1800 laser burns to the peripheral retinal tissue, destroying the outer photoreceptor and retinal pigment epithelium. The principle is to convert the hypoxic retina, which is releasing VEGF and other growth factors into anoxic retina by laser ablation. PRP is typically done in 2 to 3 sessions. The side effects of decreased peripheral field of vision and night vision must

be explained to the patient. PRP may exacerbate pre-existing macular edema and hence focal treatment of macular edema (clinically significant or not) should be considered in patients who may require PRP in future.

Vitrectomy

The Diabetic Retinopathy Vitrectomy Study (DRVS) was the initial study to lay down indications for vitrectomy in eyes with DR[26]. In general, vitrectomy is required when there is non-resolving vitreous haemorrhage (typically, vitreous haemorrhage present for more than 3 months), tractional retinal detachment involving or threatening macula, tractional rhegmatogenous detachment or PDR which does not respond to aggressive laser PRP. As technology evolves, results of vitrectomy are becoming increasingly predictable, and surgical results have improved. However, they depend on various patient-related factors, which include macular perfusion, and duration of macular detachment. Prior to any surgical procedure (i.e., vitrectomy, and intravitreal injections), patient's blood glucose must be adequately controlled to reduce chances of infection.

Other pharmacotherapy: Anti-VEGF, corticosteroids, systemic management

In the recent past, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has extensively studied the role of pharmacotherapy and laser in management of DME[27], the results of which would be exhaustive for this chapter. It is important to mention here that there is good evidence available which suggest that DME with preserved visual acuity can be managed conservatively, and treatment can be considered in cases with progression of vision loss. Besides, treatment for DME should only be considered after exclusion of ischemic maculopathy, as inappropriate treatment can lead to further loss of vision. The characteristic feature of ischemic maculopathy is capillary dropout at fovea, with enlargement of foveal avascular zone. The treatment modalities for management of DME have been addressed below:

Intravitreal Anti-VEGF agents are used primarily for DME, although recently their use has also been reported in PDR. These include Ranibizumab, Aflibercept and Bevacizumab[28,29]. The use of these agents in DME has been found to provide better functional and structural outcomes compared to laser treatment.

Intraocular Corticosteroids have been used in the management of DME for a long period of time; their use should be especially considered in DME that does not respond to other treatment. The risk of cataract and increase in intra-ocular pressure must be explained to the patient when prescribing steroids[30]. Steroids are typically preferred in pseudophakic eyes, and eyes without a prior history of glaucoma. The various routes and formulations of corticosteroids are:

- Posterior sub-tenon injection of triamcinolone acetonide (PST): duration of action is 4 to 6 weeks
- Intra-vitreal injection of triamcinolone acetonide (IVTA): duration of action is 4 to 6 weeks
- Intra-vitreal dexamethasone implant (Ozurdex): Injected using a 23G system, the advantage of this implant is sustained action for upto 6 months
- Intra-vitreal fluocinolone acetonide implant (Illuvein): duration of action is upto 3 years.

Cataract surgery and diabetic retinopathy

Individuals with type 1 diabetes are likely to develop cataract at a younger age. It is important to remember that DR (especially severe NPDR, PDR or CSME) may worsen following cataract surgery. Ideally, stable and effective control of the retinopathy and maculopathy should be achieved for at least three months prior to cataract surgery. Post-operative inflammation should be minimised using topical non-steroidal anti-inflammatory drugs (NSAID) or steroids and intra-operative or early postoperative PRP, intravitreal VEGF inhibitors or intravitreal steroids should be considered in selected cases[31-33].

Pregnancy and diabetic retinopathy

Among women with pre-existing diabetes and DR (which was present before conception or was detected early in pregnancy), DR is known to progress faster compared to non-pregnant women. DME is also known to develop or progress during pregnancy. Besides, the progression of DR can continue in postpartum period up to a duration of 12 months. Accordingly, a close watch for DR should be kept in pregnant women with T1DM. Ideally, a dilated retinal examination should be carried out in preconception period for all women with T1DM planning pregnancy. If the same was not possible, a dilated retinal examination should be performed as early in pregnancy as possible; follow-up examinations should be performed at least once in each trimester (the frequency may vary according to severity of DR on initial examination and status of risk factors control). Dilated retinal examination should continue after delivery for patients with DR of any severity and for those with DME, initially at 1-2 months postpartum and subsequently at regular intervals for the next 10-12 months[34, 35].

Intravitreal injections of anti-VEGF agents and triamcinolone are contraindicated in pregnancy due to their teratogenic potential. For women with PDR, laser PRP should be considered within 4 weeks of the diagnosis. For women with severe NPDR, a close follow-up at 1-month interval should be considered; however, laser PRP should be offered for patients with single eye. For non-center involving DME, a close observation is warranted, while for center-involving DME, focal/grid laser photocoagulation should be considered[34,35]. A close collaboration between endocrinologist/diabetologist, ophthalmologist and obstetrician is needed to ensure optimal outcomes.

Conclusion

Screening and regular follow-up, along with systemic control, form the backbone of DR prevention. Patients are often unaware of retinal changes or ignorant of it until vision loss occurs. Retinal changes occur much before vision loss, therefore, providing us with a lead time; this highlights the role of retinal screening in prevention of DR. Once vision loss occurs, the retinopathy has already progressed, although various treatment options exist even at this stage. With improving technology, and availability of non-invasive investigations such as OCT, more accurate diagnosis and treatment of DR has been made possible. Laser PRP is the gold standard for treatment of PDR with high-risk characteristics, while intra-vitreal injections of VEGF and/or corticosteroids are preferred for treatment of DME. In advanced DR, surgical management maybe required, where advances in vitreo-retinal surgery have improved surgical outcomes.

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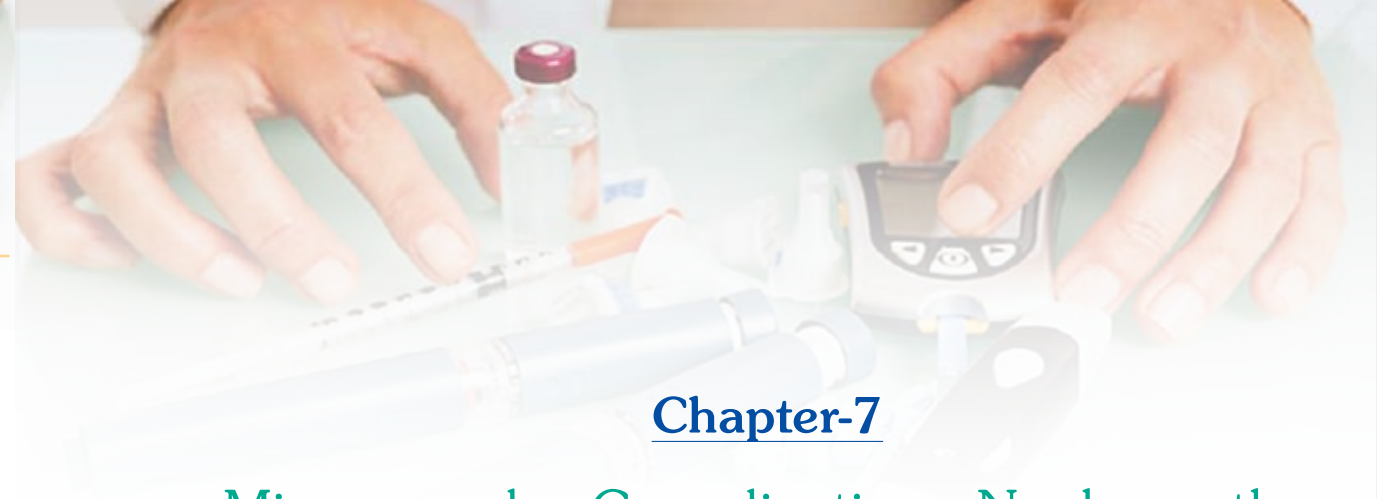


Chapter-7

Microvascular Complications-Nephropathy

Dr. Arunkumar Subbiah, Dr. Sanjay Kumar Agarwal

Introduction

Diabetic Kidney Disease (DKD) is the most common cause of chronic kidney disease (CKD) in India and worldwide. It is characterised by a combination of albuminuria, reduction of glomerular filtration rate (GFR), and hypertension with increased risk for cardiovascular diseases. A number of studies have revealed the presence of non-albuminuric diabetic nephropathy, which as the name suggests retains all other features of the disease apart from albuminuria. Although type 2 diabetes is the most common cause for diabetic nephropathy in terms of absolute numbers, nephropathy develops in around 25% - 40% of patients with type 1 Diabetes Mellitus (T1DM). End Stage Renal Disease (ESRD) remains the major cause of morbidity and premature mortality in patients with T1DM. Early diagnosis coupled with optimal glycemic control and blood pressure management has improved the prognosis of these patients in the last couple of decades. Herewith we present an overview of nephropathy in T1DM, its pathogenesis, risk factors, management options and outcome.

Epidemiology

Diabetic nephropathy is the single most common cause for CKD in India and worldwide[1]. Though type 2 diabetes mellitus is largely responsible for CKD burden, the incidence of type 1 diabetes mellitus (T1DM) causing CKD is increasing in India. The prognosis of patients with T1DM has improved significantly with better access to healthcare facilities, health education and therapeutic options[2]. This has increased the risk of nephropathy in T1DM patients due to their longer disease duration. Prior epidemiologic studies have shown that 20% – 30% of T1DM patients develop microalbuminuria at around 5 – 10 years after diagnosis[3]. Classically, ESRD is seen in 4% to 17% patients after 20 years of diagnosis of T1DM. In the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, after 25 years of diabetes, the incidence of ESRD was 2% and 1% respectively in the conventional and intensively treated groups[4].

Recent studies have shown that the risk of ESRD ranges between 2.5 – 7.8% at around 30 years of T1DM duration (Table I)[5]. In the study by Bhatia et al, out of 160 diabetic patients, 81% had T1DM and at a mean disease duration of 10.2±4.6 years, 18% developed nephropathy[6]. Ramachandran *et al* reported nephropathy in 7.1% patients with T1DM while in the study by Jevalikar et al 13.4% had nephropathy at a median duration of 10.5 years[2]. A study from North India on 512 T1DM reported hypertension in 11.7%, microalbuminuria in 10.3%, and gross albuminuria in 3% patients with median diabetes duration of 102 months[7]. Non-albuminuric phenotype of diabetic nephropathy has been

reported mainly in T2DM; in a Finnish study, this was present in 2% of T1DM patients[8]. Though this study demonstrated an increased risk for cardiovascular mortality, further studies would be needed to ascertain the exact risk posed by the non-albuminuric phenotype in T1DM.

Table I: Epidemiology of nephropathy in T1DM

Ref.	Year	Author	No of cases	DOD (Yr)	Prevalence
4	2009	DCCT Trial	1602	25	▪ ESRD 2%
4	2009	EDIC Study	1602	25	▪ ESRD 1%
5	2010	Mollsten A et al.	11681	30	▪ ESRD 2.5 – 7.8%
6	2004	Bhatia V et al.	160	10.2	▪ Nephropathy 18%
2	2019	Ramachandran et al.	617	10.5	▪ Nephropathy 7.1%
2	2019	Jevalikar et al.	577	10.5	▪ Nephropathy 13.4%
7	2019	Sudhanshu S et al.	512	8.5	▪ Microalbuminuria 10.3% ▪ Overt proteinuria 3%
8	2015	Thorn LM et al.	3809	21.2	▪ Non-albuminuric nephropathy 2%

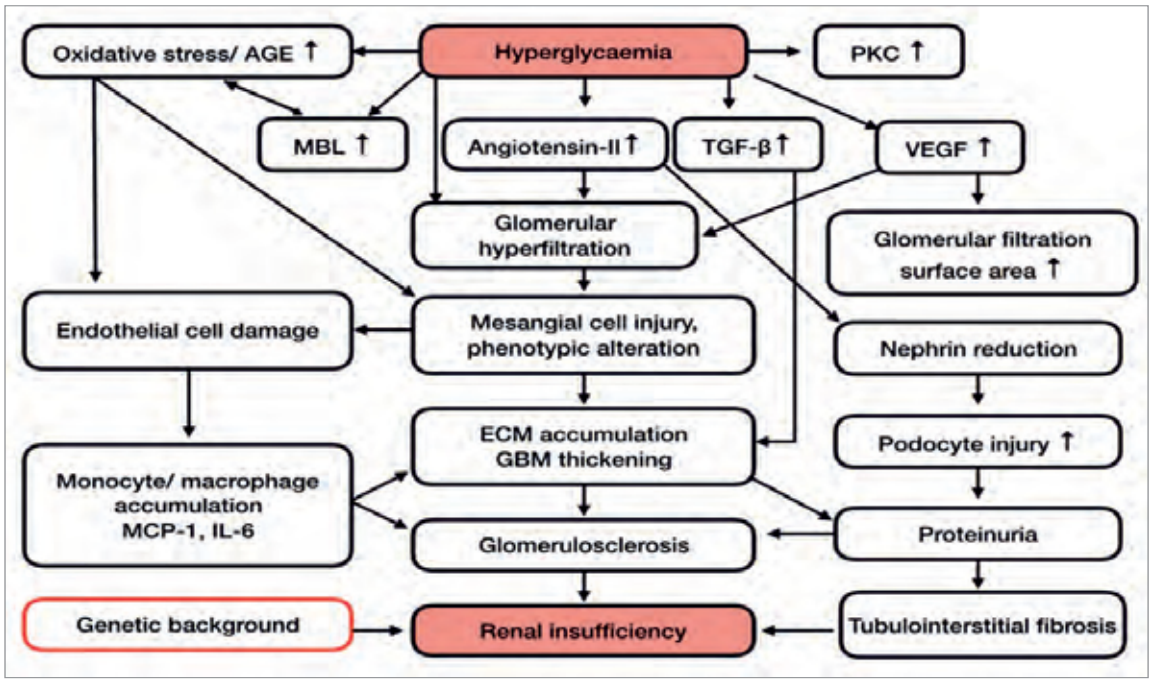
Abbreviations: T1DM-type 1 diabetes mellitus, Yr-year, DCCT- Diabetes Control and Complications Trial, DOD-Duration of disease; EDIC-Epidemiology of Diabetes Interventions and Complications

Pathogenesis

Hyperglycemia is the sine qua non for development of kidney disease in diabetes mellitus. In T1DM, this is the sole initiating factor for nephropathy while in T2DM, apart from hyperglycemia, risk for renal structural injury is often concomitantly contributed by ageing, effects of hypertension, obesity and dyslipidemia[9]. Hyperglycemia alters both blood flow and glomerular vascular permeability. The increase in renal blood flow and intra glomerular capillary pressure reduces nitric oxide synthesis in efferent vessels which in-turn increases its sensitivity to angiotensin II. Also, hyperglycemia stimulates mesangial matrix expansion and promotes apoptosis of mesangial cells. This causes a profibrotic milieu which in the early stages is potentially reversible. In addition to these rheologic effects, hyperglycemia induced mitochondrial superoxide production offsets the cellular redox balance resulting in oxidative stress. The resulting mitochondrial DNA damage initiates a vicious cycle of persistent reactive oxygen species (ROS) production. Furthermore, there is a concomitant increase in synthesis of advanced glycation end-products (AGEs). The AGEs interact with receptor for AGE (RAGE) to induce expression of TGF-β and other profibrotic cytokines thereby promoting tubulointerstitial fibrosis. The various pathways involved in development and progression of diabetic nephropathy are depicted in Figure 1.

Hyperglycemia, AGEs, ROS activate protein kinase C (PKC) which promotes glomerular basement membrane thickening. T1DM is associated with raised prorenin activity. Prorenin activates mitogen-activated protein kinase (MAPK) which is fibrogenic. Activation of inflammatory cytokines promotes matrix expansion in T1DM. Downregulation of expression of the transmembrane protein, nephrin is associated with improper filtration and albuminuria seen in T1DN. The role of toll-like receptors and ubiquitin proteasome system (UPS) in promoting progression of diabetic kidney lesions and renal fibrosis is being evaluated[10].

Figure 1: Pathophysiology of diabetic kidney disease. Central role of hyperglycemia and downstream effects leading to renal insufficiency.



Abbreviations: AGE-advanced glycation end products; ECM-extracellular matrix; GBM,-glomerular basement membrane; MCP-monocyte chemoattractant protein; PKC- Protein Kinase C; TGF-β- transforming growth factor; VEGF- vascular endothelial growth factor, IL6-Interleukin 6. MBL - Mannose binding lectin

Risk Factors

Risk factors for nephropathy in T1DM can be grouped as modifiable and non- modifiable and can also be grouped as risk factors for initiation and progression of nephropathy.

A. Factors for initiation of nephropathy

- Genetic factors
- Hyperglycemia

B. Factors for progression of nephropathy

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Proteinuria

Recent data stress on the role of genetic variables in conferring susceptibility or protection from nephropathy in T1DN. The different time durations for development of DN in transplanted patients reaffirms the role of a genetic predisposition to kidney disease. Diabetic nephropathy is a complex genetic disease involving multiple genetic loci and not explained by any Mendelian inheritance model[11]. The importance of genetic background in T1DN was first shown by Seaquist et al who concluded that there was a four-fold increased risk of DN in patients whose siblings had T1DM and nephropathy. Familial clustering of cases suggests a genetic basis for the disease.

Susceptibility genes reported in DN of T1DM are:

1. FRMD3 gene
2. CARD gene
3. AFF3 gene
4. Intergenic SNP on chromosome 15q26 between the genes RGMA and MCTP2
5. Intronic SNP in the ERBB4 gene

The role of genetic factors in progression of DN is under study and may throw light on the approaches to contain and reverse DN. Recent studies highlight the importance of epigenetic modifications including DNA methylation and histone post translational modification (PTMs) in susceptibility to DN.

Poor glycemic control is an important predictor of both initiation as well as progression of diabetic kidney disease[12]. There is a "legacy effect" or "metabolic memory" wherein patients with initial poor glycemic control tend to develop progressive diabetic complications even after they have achieved better glycemic control in the later stages. This highlights the importance of early glycemic control in preventing microvascular and macrovascular complications of diabetes.

Glomerular volume and number are also believed to determine nephropathy risk. Lower the number of glomeruli, higher is the risk for progression of diabetic nephropathy. Patients with higher glomerular volumes develop DN later than those with lesser volumes. Other risk factors for progression of DN include an increased body mass index (BMI), smoking and oral contraceptive pill (OCP) use. Older age, female sex and longer duration of T1DM has been shown to be a risk factor for DN in non-albuminuric patients[8].

Clinical features and Staging

The natural history of diabetic kidney disease is a little different in T1DM and T2DM. The classic history of DN in T1DM is divided into five stages and was initially described by Mogensen[13]. Most patients with T2DM do not follow the classic pattern of DN progression from albuminuria to macroproteinuria to renal dysfunction, as seen in T1DM.

Stages of diabetic nephropathy (figure 2)

Stage 1: Hyperfiltration stage – The earliest preclinical stage associated with glomerular hypertrophy with resultant increase in GFR.

Stage 2: Silent stage – This is characterised by near normal GFR and also no overt clinical features. Characteristic pathological structural changes seen in renal glomeruli are basement membrane thickening and mesangial expansion. This occurs after 5 – 8 years of diabetes and can be associated with mild hypertension detected by ambulatory blood pressure monitoring (ABPM)[14].

Stage 3: Microalbuminuria (MA) stage or Incipient nephropathy – It is characterised by urinary albumin excretion in the range of 20 to 200 µg/min or 30 to 300 mg/24 h. The onset is usually 5 – 15 years after onset of T1DM and this is the earliest measurable marker of diabetic kidney disease. In the present classification this is referred to as 'moderately increased albuminuria'. Initially MA was considered to be a marker for progressive glomerular damage. This concept has lost favour with recent evidence showing that MA is often transient and reversible in a subset of patients with good glycemic and blood pressure control. In the DCCT/EDIC cohort of patients, after 10 years of onset of

MA, 40% reverted back to normoalbuminuria; 28% developed overt proteinuria while 4% progressed to ESRD[15]. In the Oxford Regional Prospective Study, 52% of patients exhibited 'intermittent' microalbuminuria. Therefore, as a marker of progressive diabetic nephropathy, MA should be persistent.

Stage 4: Macroalbuminuria stage or Overt nephropathy – This stage has urinary albumin excretion greater than 300 mg/24 h. In the present classification, this stage is referred to as 'severely increased albuminuria'. This stage is usually associated with development of hypertension and the GFR starts reducing from this stage.

Stage 5: Renal impairment – Progressive decrease in GFR occurs in 25 – 40% of T1DM resulting in worsening CKD and ESRD which is the final common endpoint of kidney disease progression.

Microalbuminuric T1DM patients have a median risk ratio of 21 for developing DN. Sequential progression of DN in T1DM does not always occur. It has now been observed that like in T2DM, patients can have renal dysfunction without albuminuria, the so called non-albuminuric phenotype. Also, in the second Joslin Kidney Study it was seen that even in the microalbuminuric stage, over one-third of patients had renal dysfunction. Apart from MA and glycemic control, the other risk factors for progression of DN include familial clustering, ethnicity, smoking, dyslipidemia and hypertension.

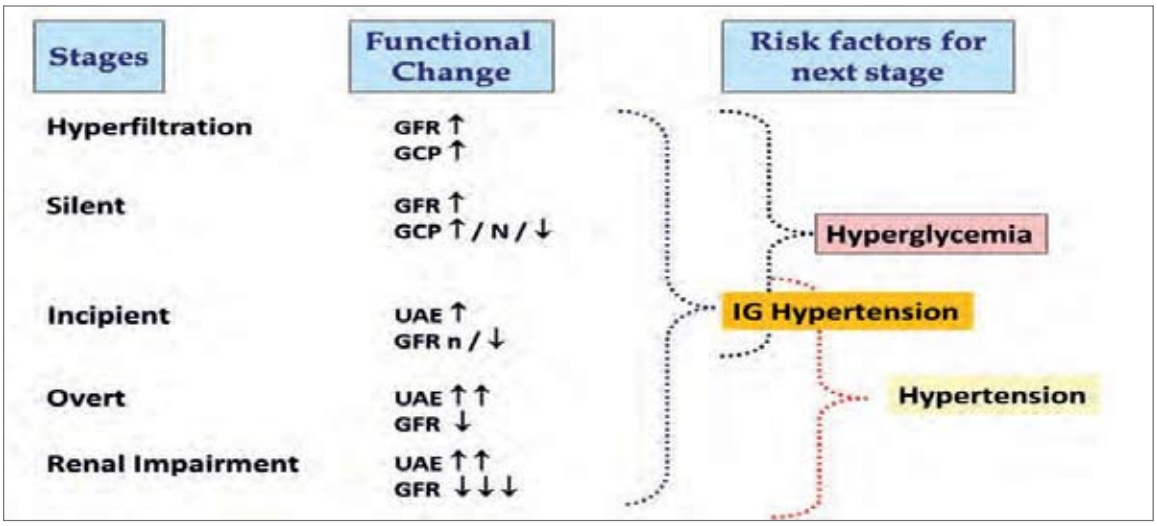


Figure 2: Salient features of stages of nephropathy in T1DM

Abbreviations: T1DM-Type 1 Diabetes Mellitus, GFR-glomerular filtration rate, GCP-glomerular capillary pressure, UAE-urinary albumin excretion, IG-intraglomerular, n and N-Normal

Diabetes affects the glomeruli, interstitium and the vascular component of the kidney. The classical pathological feature of diabetic nephropathy is diffuse or nodular glomerulosclerosis. This is however a late feature of DN. Early changes include mesangial expansion and glomerular basement membrane thickening, which are the most common lesions in DN. The histopathological classification of DN (both T1DM and T2DM) developed by Tervaert et al[16] is as follows:

Class I: Isolated glomerular basement membrane (GBM) thickening
Class II: Mesangial expansion (II a <25%; II b >25%)
Class III: Nodular mesangial matrix expansion with Kimmelstiel-Wilson lesion
Class IV: Advanced diabetic glomerulosclerosis (involving >50% glomeruli)