Clinical Practice Guidelines:  
Management of  
Type 2 Diabetes Mellitus  
(5th Edition) 2015  

**Topic 13:**  
Management of Chronic Complications 1
Overview

Microvascular Complications:
• Retinopathy
• Nephropathy
• Neuropathy

Macrovascular Complications:
• Coronary Heart Disease
• Cerebrovascular Disease

Combination of Micro- and Macrovascular complications:
• Diabetic Foot
• Erectile Dysfunction
Diabetic Retinopathy (DR): Introduction

• Prevalence of DR is linked to the duration of diabetes.

• At diagnosis, less than 5% will have retinopathy while the prevalence rises to 40–50% after 10 years. About 60% patients with T2DM have some degree of retinopathy after 20 years of the disease.

• In Malaysia, the prevalence of DR from the 2007 Diabetic Eye Registry was 36.8%. However, other unpublished local data obtained from primary care screening centres showed a prevalence ranging between 12.3% and 16.9%.

• Screening and early treatment can prevent substantial visual loss in many cases.
Retinopathy: Screening

• Initial assessment should be conducted at time of diagnosis of T2DM and annually thereafter.

• Pregnant women with T2DM should have retinal examination during each trimester.

• DR screening is not required for GDM. However, if GDM is diagnosed in the first trimester of pregnancy, screening should be as per pre-existing DM.
Eye Examination

- Visual acuity assessed with Snellen chart and any refractive error corrected with pinhole in addition to asking patient to wear bifocals or glasses for presbyopia.

- Non-mydriatic fundus camera should be used as a screening tool.

- Two field fundus photo (central and peripheral) assessment should be performed.

- When there is no access to fundus camera, ophthalmoscope should be used for screening of DR.

- Tropicamide 1% should be used for pupillary dilatation in selected cases by trained personnel.
DIABETIC RETINOPATHY

- Hemorrhages
- Abnormal growth of blood vessels
- Aneurysm
- "Cotton wool" spots
- Hard exudates
Referral to Ophthalmologist

1. Severe Non-Proliferative DR

2. Any level of Diabetic Maculopathy

3. Any Proliferative DR

4. Unexplained visual loss

5. If screening examination cannot be performed including ungradable fundus photo
# Urgent Referral to Ophthalmologist

<table>
<thead>
<tr>
<th>Urgency of referral</th>
<th>Ocular features</th>
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<tbody>
<tr>
<td>Emergency (same day referral)</td>
<td>• Sudden severe visual loss</td>
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<tr>
<td></td>
<td>• Symptoms or signs of acute retinal detachment</td>
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<tr>
<td>Appointment within 1 week</td>
<td>• Presence of retinal new vessels</td>
</tr>
<tr>
<td></td>
<td>• Preretinal haemorrhage</td>
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<tr>
<td></td>
<td>• Vitreous haemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Rubeosis iridis</td>
</tr>
<tr>
<td>Appointment within 4 weeks</td>
<td>• Unexplained drop in visual acuity</td>
</tr>
<tr>
<td></td>
<td>• Any form of maculopathy</td>
</tr>
<tr>
<td></td>
<td>• Severe NPDR</td>
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<tr>
<td></td>
<td>• Worsening retinopathy</td>
</tr>
</tbody>
</table>

*Adapted from Screening of Diabetic Retinopathy. Malaysia: Ministry of Health Malaysia and Academy of Medicine Malaysia; 2011 ²⁵³ (Level III)
Retinopathy: Treatment

• Mainstay of current treatment involves risk factor modification by controlling:
  – tight blood glucose
  – blood pressure
  – serum lipids

• Other modalities of risk factor modification include:
  – diet,
  – Exercise
  – stop smoking.
The presence of retinopathy is not a contraindication to aspirin therapy for cardiovascular disease prevention, as this therapy does not increase the risk of retinal bleeding.

Laser photocoagulation remains the standard practice for treating DR.

# Intra-ocular anti vascular endothelial growth factor (anti-VEGF) is a novel therapy for DR.

Stages of DR which require treatment includes severe Non-Proliferative DR, Proliferative DR, Advance Eye Disease and Diabetic Macular Oedema (DME).
Recommendations: Retinopathy

1. The initial assessment should be conducted at the time of diagnosis of T2DM and annually thereafter. [Grade C]
2. Examination schedule and urgency of referral to an ophthalmologist should be based on the grade and severity of diabetic retinopathy as well as the presence of risk factors. [Grade C]
Nephropathy: Introduction

- Diabetic nephropathy is a major cause of chronic kidney disease (CKD) contributing to 58% of new patients requiring dialysis in 2012 in Malaysia. It is also major risk factor for cardiovascular morbidity and mortality.

- Diagnosis is made clinically by the presence of proteinuria. “Moderately increased albuminuria” and “severely increased albuminuria” are new term for microalbuminuria and overt proteinuria respectively.

- Progression to ESRD requiring renal replacement therapy occurs in majority of patients, particularly those with poor diabetic and blood pressure control.
Progression of CKD in T2DM

Stage of CKD

Pre 1
Incipient 2
Overt 3
ESRD 4 5

eGFR (mL/min/1.73m²)

0 30 60 90

Years of T2DM

0 25+

Urine protein excretion (mg/d)

2000 3000

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; T2DM = type 2 diabetes mellitus

Williams ME. Semin Dial. 2010;23(2):129-133.
Slide courtesy of Clifford J. Bailey, PhD.
Nephropathy: Screening

• Standard urine dipstick test for proteinuria should be performed in all diabetic patients at diagnosis and annually.

• If the test is negative, it is recommended to screen for microalbuminuria using the first morning urine sample or random urine sample without excessive water intake.

• Microalbuminuria is the earliest sign of diabetic nephropathy and predicts increased cardiovascular mortality and morbidity and ESRD.

• If microalbuminuria is detected, a repeat test should be done within 3 to 6 months for confirmation. If it is negative, annual screening should be continued.
Nephropathy: Screening

- A more sensitive and specific test called the Urine Albumin Creatinine Ratio (ACR) may be performed in those with negative microalbuminuria.

- ACR - is defined as a urinary albumin:creatinine ratio >2.5 mg/mmol in men and >3.5 mg/mmol in women, which is equivalent to a 24 hour urine collection level of >20 mg/L.

- This should be performed on an early morning urine sample to minimise the effect of posture and exercise on urine albumin excretion.
Nephropathy: Screening

• Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present.

• Measurement of GFR could easily be performed by using the MDRD formula which can be accessed at http://www.mdrd.com.
Recommendations for Screening Nephropathy

1. Screening for proteinuria should be performed at diagnosis and annually with conventional dipstick on an early morning urine specimen. [Grade C]
2. If urine dipstick for proteinuria is negative, screening for microalbuminuria should be [Grade C]
3. If microalbuminuria is detected, confirmation should be made with further tests within 3 to 6 months. [Grade C]
4. If microalbuminuria is not detected, re-screening should be performed annually. [Grade C]
5. Regardless of the degree of the proteinuria, serum creatinine level should be measured annually to determine GFR. [Grade C]
Nephropathy: Management

• BP and glycaemic control crucial in preventing or retarding progression of diabetic nephropathy.

• Dose adjustment of anti-diabetic agent may be necessary

• The presence of microalbuminuria or overt proteinuria should be treated even if the BP is <135/75 mm Hg. An ACEI or ARB is preferred. In a proportion of patients, microalbuminuria may be normalised by ACEIs or ARBs even if the BP is optimally controlled with close monitoring of potassium level.

• Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate.
Nephropathy: Management

• Decrease protein intake to 0.8 g/kg body weight per day in individuals with diabetes at stage III and IV CKD and to 0.6–0.75 g/kg body weight per day in ESRD. Reduction in protein intake may delay progression of renal impairment.

• ACEIs or ARBs should be initiated unless contraindicated to slow progression of diabetic nephropathy.

• Other measures:
  – Lipid control
  – Stop smoking
  – Weight reduction
  – Moderate protein and salt restriction
# Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m² body surface area)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>End Stage Renal Disease</td>
<td>15 or dialysis</td>
</tr>
</tbody>
</table>

* Kidney damage defined as abnormalities on pathological, urine, blood, or imaging tests.
* Adapted from National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease 276 (Level III)
# Staging of Chronic Kidney Disease

**CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.**


## Persistent albuminuria categories

<table>
<thead>
<tr>
<th>Description and range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
<td>30-300 mg/g 3-30 mg/mmol</td>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
</tr>
</tbody>
</table>

## GFR categories (mL/min/1.73 m²)

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²)</th>
<th>Description and range</th>
<th>Previous NKF CKD stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 G1</td>
<td>Normal or high</td>
<td>≥90</td>
</tr>
<tr>
<td>2 G2</td>
<td>Mildly decreased</td>
<td>60-89</td>
</tr>
<tr>
<td>3 G3a</td>
<td>Mild to moderately decreased</td>
<td>45-59</td>
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<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30-44</td>
</tr>
<tr>
<td>4 G4</td>
<td>Severely decreased</td>
<td>15-29</td>
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<tr>
<td>5 G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category**

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
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<tbody>
<tr>
<td>A1 if CKD</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>4+</td>
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CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.

Referral to nephrologist

1. Estimated GFR <30 ml/min or serum creatinine >200 μmol/L
2. Heavy proteinuria (urine protein ≥3 g/day or urine protein: creatinine ratio (uPCR) ≥0.3 g/mmol)
3. Haematuria
4. Rapidly declining renal function (loss of glomerular filtration rate/GFR >5 ml/min/1.73 m$^2$ in one year or >10 ml/min/1.73 m$^2$ within five years)
5. Resistant hypertension (failure to achieve target blood pressure despite 3 antihypertensive agents including a diuretic)
6. Suspected renal artery stenosis
7. Suspected other causes of CKD (primary glomerular disease, genetic or uncertain cause of CKD)
8. Pregnant or when pregnancy is planned

*Adapted from Malaysian Clinical Practice Guidelines for the Chronic Kidney Disease in Adults
Recommendations: Management of Nephropathy

1. ACEIs or ARBs should be initiated in patients with microalbuminuria or proteinuria. [Grade A]
2. Urine protein-creatinine index (UPCI) or ACR should be used to monitor treatment directed against proteinuria. [Grade C]
3. Protein restriction should be instituted according to degree of renal impairment [Grade C]
Neuropathy: Introduction

• The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse.

• The most prevalent neuropathies are peripheral neuropathy (DPN) and autonomic neuropathy (DAN) particularly cardiovascular AN (CAN).
Diabetic peripheral neuropathy

• DPN may be defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

• DPN may be asymptomatic in a large proportion of cases (up to 50%) and requires clinical examination to document/unveil its existence. It causes or contributes to significant morbidity and mortality.

• Studies from tertiary centres showed that prevalence of DPN ranged between 50 to 80%.
Neuropathy: Screening

• Neuropathy should be assessed with a 10-g monofilament; and one other modality:
  a) Pin prick
  b) Vibration sense using 128 Hz tuning fork
  c) Ankle reflexes
  d) Vibration perception threshold testing using a biothesiometer

• The above increases the sensitivity of detecting peripheral neuropathy by 87%.

• These bedside tests should be performed at least annually.
Neuropathy: Treatment

• Tight glycaemic control has not shown any benefit in preventing DPN but has modest effect in slowing progression without neuronal loss reversal.

• No pharmacology therapy has been shown to be effective in treating DPN.

• Drugs approved for pain associated with DPN include pregabalin, gabapentin, amitriptyline, duloxetine, and venlafaxine as first line therapy; tramadol as second line therapy.

• Topical treatment (e.g. capsaicin cream, lidocaine 5% patch) may be added to systemic treatment at any time.
Diabetic Autonomic Neuropathy

• DAN results in significant morbidity and may lead to mortality in some patients with diabetes. In particularly CAN, is an independent risk factor for cardiovascular mortality.

• Clinical manifestations of DAN include:
  – resting tachycardia,
  – exercise intolerance,
  – orthostatic hypotension,
  – gastroparesis, constipation,
  – erectile dysfunction,
  – sudomotor (sweat glands) dysfunction
  – impaired neurovascular function
  – autonomic failure in response to hypoglycaemia.
DAN: Treatment

- Intensive control of cardiovascular modifiable risk been shown to reduce the progression and development of CAN among patients with T2DM.

- Avoid drugs causing orthostatic hypotension. Midodrine has been approved as medical therapy for orthostatic hypotension.

- Prokinetic agent such as erythromycin aids in relieving gastroparesis symptoms.

- Short term metoclopramide (maximum for 5 days) may be used in severe cases.
Recommendations: Neuropathy

1. Assessment for peripheral neuropathy should be performed at diagnosis and annually. [Grade C]
2. Drugs approved for neuropathic pain include pregabalin, gabapentin, amitriptyline, duloxetine, and venlafaxine as first line therapy; tramadol as second line therapy [Grade B]
3. Tight control of blood sugar and have been shown to reduce the progression and development of autonomic neuropathy [Grade B]