

# NATIONAL CLINICAL GUIDELINES

## CHRONIC COMPLICATIONS OF DIABETES MELLITUS

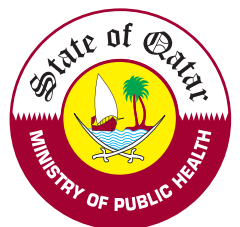
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المبادئ الإرشادية السريرية لدولة قطر  
NATIONAL CLINICAL GUIDELINES FOR QATAR



## Version History

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1.0	Final	15 <sup>th</sup> June 2017	Guidelines Team	Final version for publication.
2.0	Final	24 <sup>th</sup> February 2021	Guidelines Team	Updated Final version for publication.

## Citation

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## Abbreviations

The abbreviations used in this guideline are as follows:

<b>ACC/AHA</b>	American College of Cardiology / American Heart Association
<b>ACE</b>	Angiotensin Converting Enzyme
<b>ACR</b>	Albumin-Creatinine Ratio
<b>ACS</b>	Acute Coronary Syndrome
<b>ARB</b>	Angiotensin Receptor Blocker
<b>ASCVD</b>	Atherosclerotic Cardiovascular Disease
<b>BP</b>	Blood Pressure
<b>CCB</b>	Calcium Channel Blocker
<b>CKD</b>	Chronic Kidney Disease
<b>DASH</b>	Dietary Approaches to Stop Hypertension
<b>DPN</b>	Diabetic Peripheral Neuropathy
<b>DSPN</b>	Distal Symmetric Polyneuropathy
<b>eGFR</b>	Estimated Glomerular Filtration Rate
<b>ESRD</b>	End-Stage Renal Disease
<b>HbA<sub>1c</sub></b>	Glycated Haemoglobin
<b>HDL</b>	High-Density Lipoprotein
<b>IRMA</b>	Intraretinal Microvascular Abnormalities
<b>LDL-C</b>	Low Density Lipoprotein-Cholesterol
<b>MI</b>	Myocardial Infarction

<b>NPDR</b>	Non-Proliferative Diabetic Retinopathy
<b>PCSK9</b>	Proprotein Convertase Subtilisin/Kexin Type 9
<b>PDR</b>	Proliferative Diabetic Retinopathy
<b>PTH</b>	Parathyroid Hormone
<b>SGLT2i</b>	Sodium-Glucose Cotransporter 2 Inhibitor
<b>T1DM</b>	Type 1 Diabetes Mellitus
<b>T2DM</b>	Type 2 Diabetes Mellitus

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# 1 Information about this Guideline

## 1.1 Objective and Purpose of the Guideline

The purpose of this guideline is to define the appropriate management of the common complications of both type 1 and type 2 diabetes mellitus in adults and the elderly. The objective is to improve appropriate investigation, prescribing and referral of patients presenting to provider organisations in Qatar. It is intended that the guideline will be used primarily by physicians, nurses, and health educators in primary care.

## 1.2 Scope of the Guideline

Aspects of care covered in this guideline include the following:

- Chronic complications of type 1 and 2 diabetes in adults and elderly, including the following:
  - Diabetic retinopathy.
  - Diabetic kidney disease.
  - Diabetic neuropathy.
  - Atherosclerotic cardiovascular disease.
  - Diabetic foot disease.

Aspects of care not covered in this guideline include the following:

- Acute complications of type 1 and 2 diabetes in children and adolescents
- Management of the acute complications of diabetes e.g. hyperglycaemic emergencies (HONK, HHS) and hypoglycaemia.

## 1.3 Editorial Approach

This guideline document has been developed and issued by the Ministry of Public Health of Qatar (MOPH), through a process which aligns with international best practice in guideline development and localisation. The guideline will be reviewed on a regular basis and updated to incorporate comments and feedback from stakeholders across Qatar.

The editorial methodology, used to develop this guideline, has involved the following critical steps:

- Extensive literature search for well-reputed published evidence relating to the topic.
- Critical appraisal of the literature.
- Development of a draft summary guideline.
- Review of the summary guideline with a Guideline Development Group, comprised of practising healthcare professionals, subject matter experts and patient representatives, from across Qatar.
- Independent review of the guideline by the National Clinical Guidelines & Pathways Committee, appointed by the MOPH, from amongst stakeholder organisations across Qatar.

Whilst the MOPH has sponsored the development of the guideline, the MOPH has not influenced the specific recommendations made within it.

## 1.4 Sources of Evidence

The professional literature has been systematically queried using specially developed, customised, and tested search strings. Search strategies are developed to allow efficient yet comprehensive analysis of relevant publications for a given topic and to maximise retrieval of articles with certain desired characteristics pertinent to a guideline.

For each guideline, all retrieved publications have been individually reviewed by a member of the Editorial Team and assessed in terms of quality, utility, and relevance. Preference is given to publications that:

1. Are designed with rigorous scientific methodology.
2. Are published in higher-quality journals.
3. Address an aspect of specific importance to the guideline in question.

Further information about the literature search and appraisal process is included in the appendix.

## 1.5 Evidence Grading and Recommendations

Recommendations made within this guideline are supported by evidence from the medical literature and where possible the most authoritative sources have been used in the development of this guideline. In order to provide insight into the evidence basis for each recommendation, the following evidence hierarchy has been used to grade the level of authoritativeness of the evidence used, where recommendations have been made within this guideline.

Where the recommendations of international guidelines have been adopted, the evidence grading is assigned to the underlying evidence used by the international guideline. Where more than one source has been cited, the evidence grading relates to the highest level of evidence cited:

- **Level 1 (L1):**
  - Meta-analyses.
  - Randomised controlled trials with meta-analysis.
  - Randomised controlled trials.
  - Systematic reviews.
- **Level 2 (L2):**
  - Observational studies, examples include:
    - Cohort studies with statistical adjustment for potential confounders.
    - Cohort studies without adjustment.
    - Case series with historical or literature controls.
    - Uncontrolled case series.
  - Statements in published articles or textbooks.
- **Level 3 (L3):**
  - Expert opinion.
  - Unpublished data, examples include:
    - Large database analyses.
    - Written protocols or outcomes reports from large practices.

In order to give additional insight into the reasoning underlying certain recommendations and the strength of recommendation, the following recommendation grading has been used, where recommendations are made:

- **Recommendation Grade A (RGA):** Evidence demonstrates at least moderate certainty of a net benefit from the recommendation.
- **Recommendation Grade B (RGB):** Evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended.
- **Recommendation Grade C (RGC):** Evidence demonstrates potential harm that outweighs benefit; additional research is recommended.
- **Recommendation of the GDG (R-GDG):** Recommended best practice on the basis of the clinical experience of the Guideline Development Group members.



## 1.6 Guideline Development Group Members

The following table lists members of the Guideline Development Group (GDG) nominated by their respective organisations and the National Clinical Guidelines & Pathways Committee. The GDG members have reviewed and provided their feedback and approval of the guideline document. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

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## 1.7 National Clinical Guidelines & Pathways Committee Members

The following table lists members of the National Clinical Guidelines & Pathways Committee (NCGPC), appointed by the MOPH. The NCGPC members have reviewed and provided their feedback and approval of the guideline document. Each member has completed a declaration of conflicts of interest, which has been reviewed and retained by the MOPH.

National Clinical Guidelines & Pathways Committee (NCGPC) Members		
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National Clinical Guidelines & Pathways Committee (NCGPC) Members		
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Dr Egon Toft	VP and Dean	College of Medicine, Qatar University

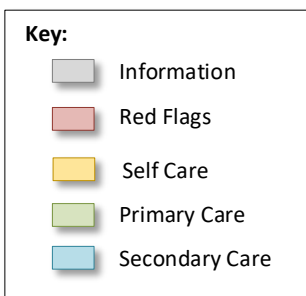
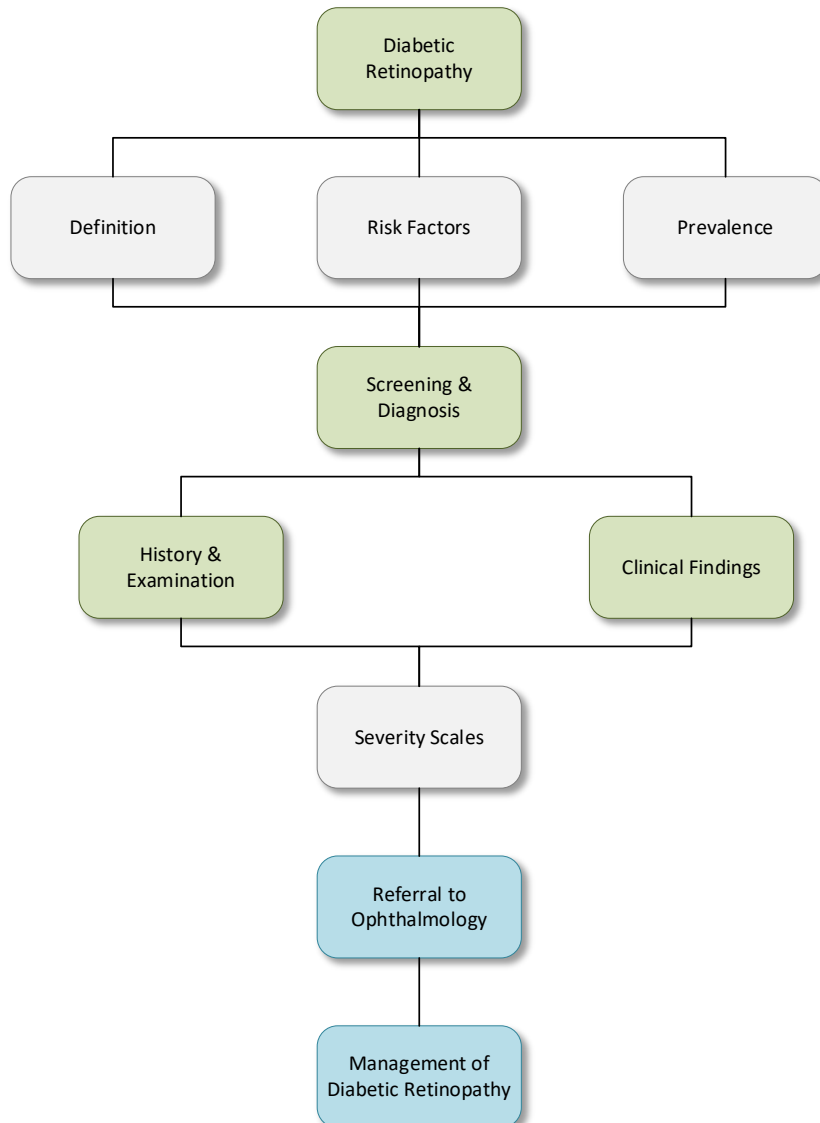
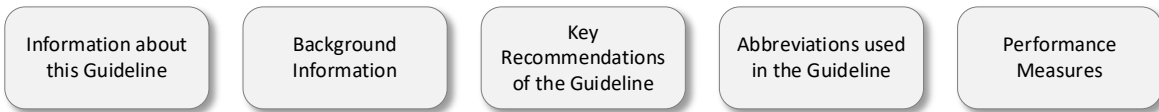
## 1.8 Responsibilities of Healthcare Professionals

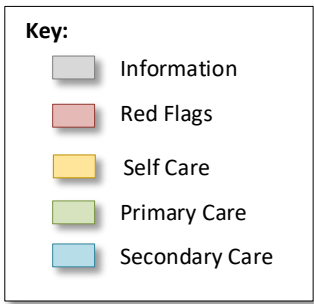
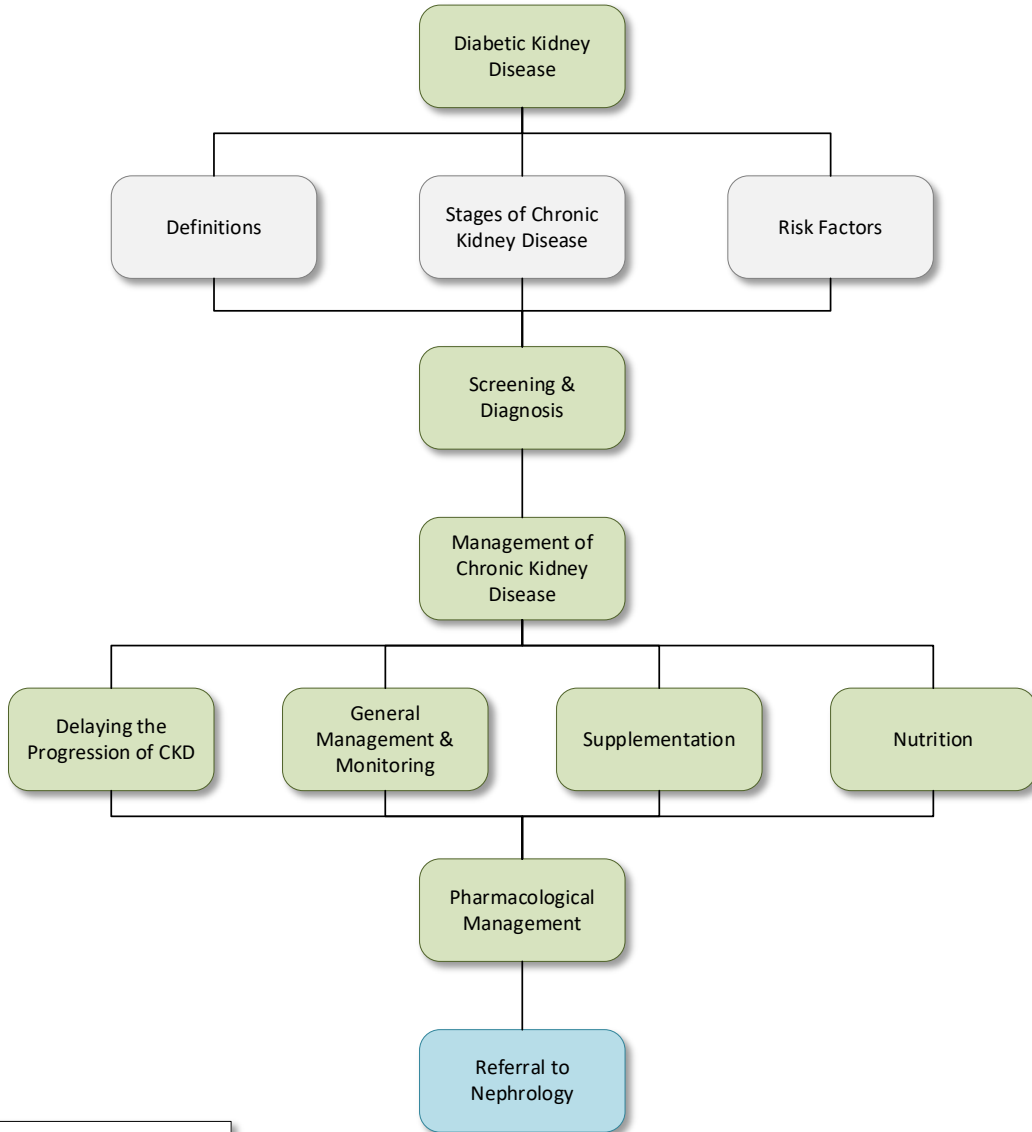
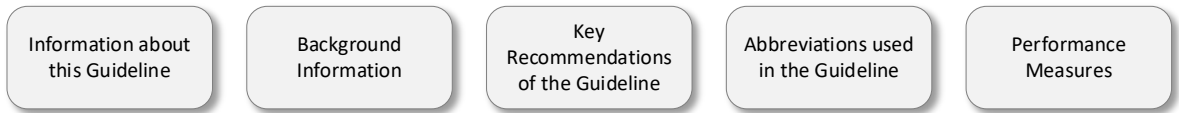
This guideline has been issued by the MOPH to define how care should be provided in Qatar. It is based upon a comprehensive assessment of the evidence as well as its applicability to the national context of Qatar. Healthcare professionals are expected to take this guidance into account when exercising their clinical judgement in the care of patients presenting to them.

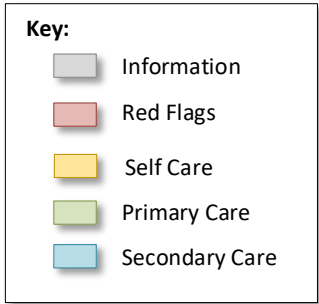
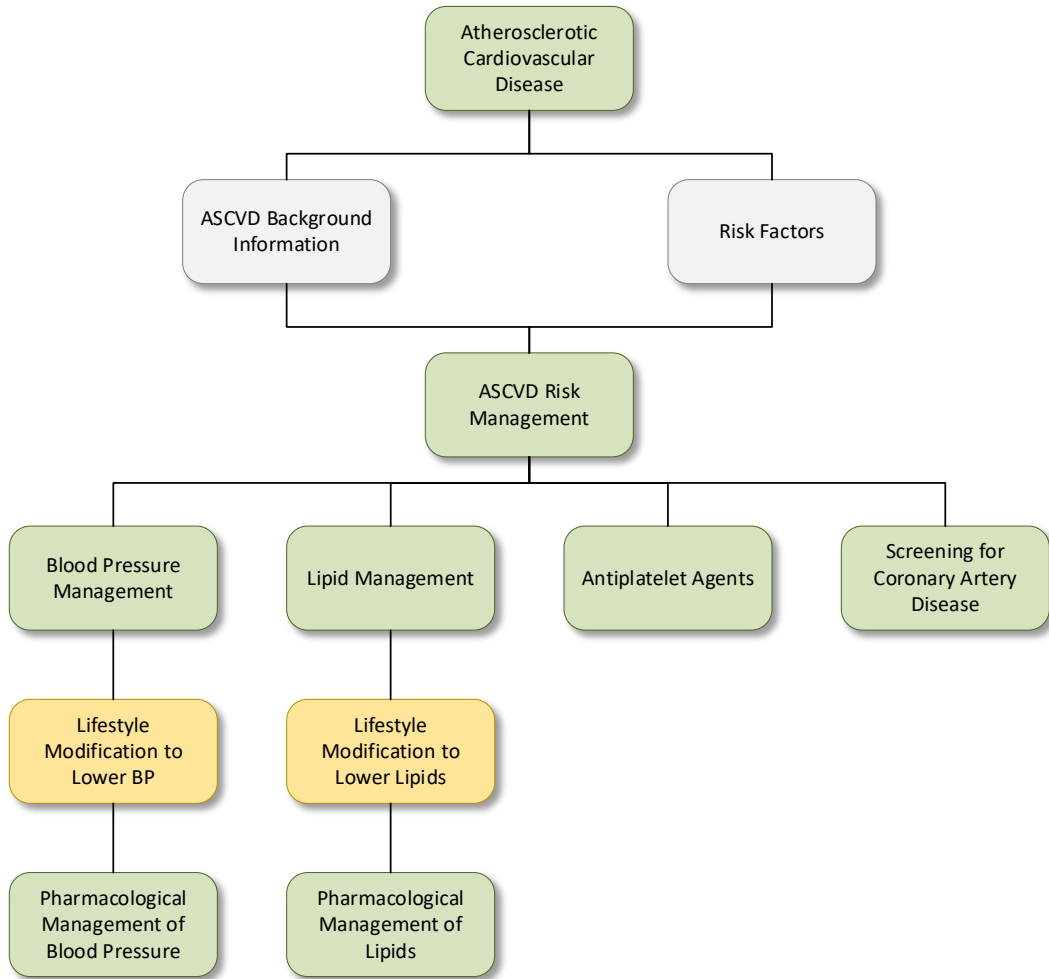
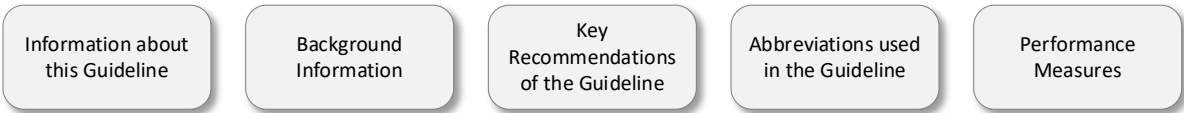
The guidance does not override individual professional responsibility to take decisions which are appropriate to the circumstances of the patient concerned. Such decisions should be made in consultation with the patient, their guardians, or caregivers and should consider the individual risks and benefits of any intervention that is contemplated in the patient's care.

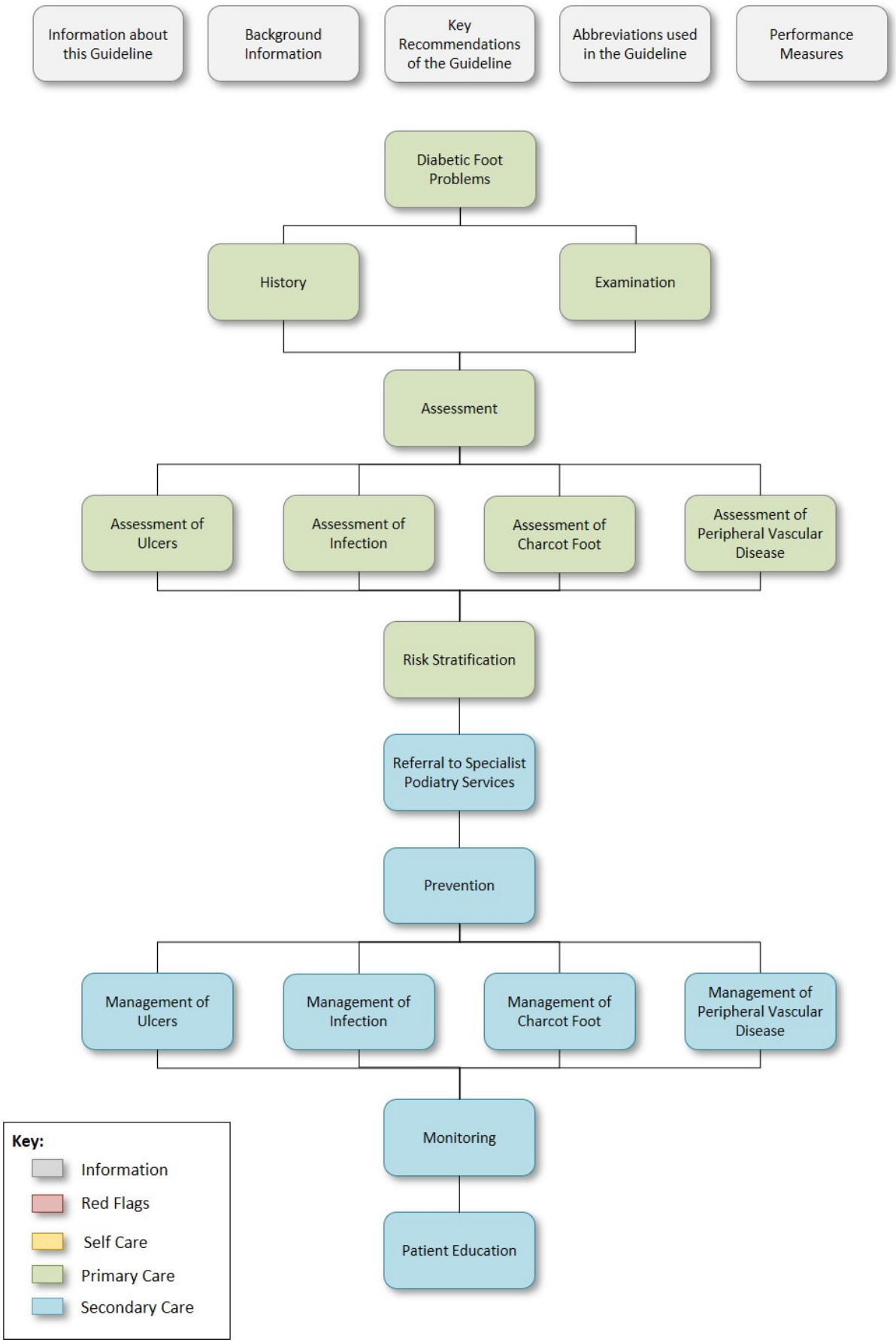
## 2 Chronic Complications of Diabetes Mellitus Pathway

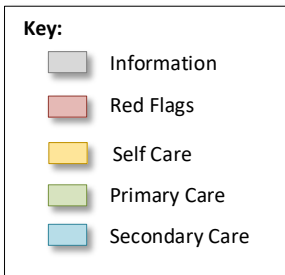
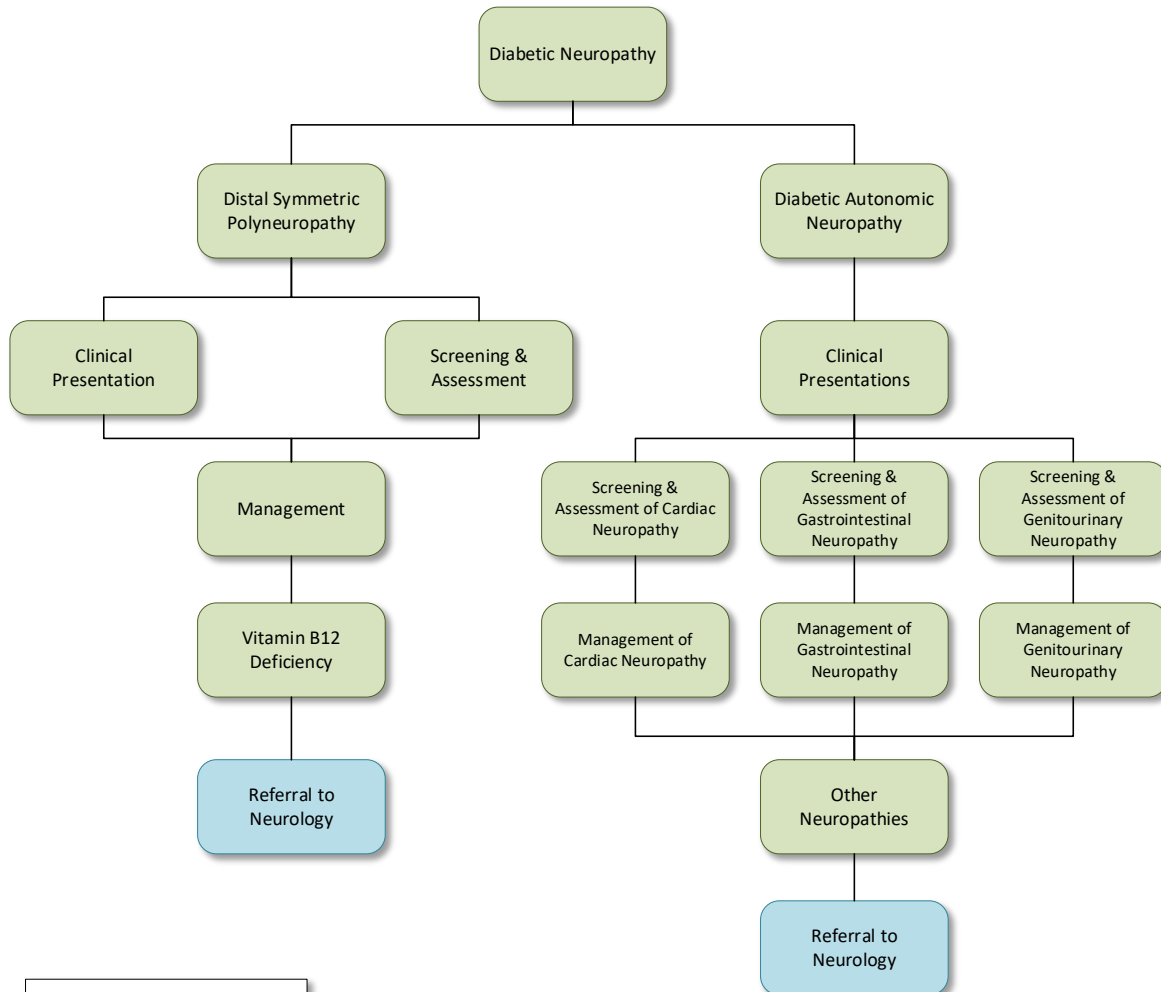
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### 3 Key Recommendations of the Guideline

The key recommendations of this guideline are:

#### Diabetic Retinopathy:

- Is the most common diabetic complication in Qatari patients attending a diabetic outpatient clinic (43.6% of patients) <sup>1</sup>.
- All patients with T2DM should undergo dilated or non-dilated retinal photography, which should be undertaken by a trained technician, optometrist or ophthalmologist [R-GDG].
- Screening should be undertaken at the time of diagnosis and annually thereafter, or at an alternative frequency as decided by the ophthalmologist <sup>2</sup>.
- All adult patients with T1DM should undergo retinal screening as above, within five years of the initial diagnosis <sup>2</sup>.
- Refer for an emergency review by an ophthalmologist in tertiary care hospital if the patient experiences any eye emergency and in particular, any of the following <sup>3,4</sup> [L2]:
  - Sudden loss of vision or deterioration in vision.
  - Rubeosis iridis.
  - Pre-retinal or vitreous haemorrhage.
  - Retinal detachment.

#### Management of Diabetic Retinopathy:

- To reduce the risk or slow the progression of diabetic retinopathy, optimise all of the following <sup>2</sup> [L1, RGA]:
  - Glycaemic control.
  - Blood pressure (BP).
  - Serum lipids, particularly triglycerides.
  - Smoking cessation.
- Decisions on ophthalmological treatments should be taken by an ophthalmologist (retinal specialist) <sup>2</sup> [L1, RGA].

#### Diabetic Kidney Disease:

- Screen for diabetic kidney disease in all adults with T2DM, at the time of diagnosis and all adults with T1DM patients, 5 years from initial diagnosis <sup>2</sup>.
- Screen for diabetic kidney disease at least annually using a spot urine sample for urinary ACR and eGFR <sup>2,5</sup>.
- Patients with urinary albumin ACR >30 and/or eGFR <60 mL/min/1.73 m<sup>2</sup> should be monitored twice annually to guide therapy.
- 2 of 3 ACR specimens collected within 3-6 months should be reported as abnormal, before a patient is considered as having albuminuria <sup>2,6</sup>.
- In order to delay the progression of diabetic kidney disease and prevent cardio-renal complications <sup>2,5,7</sup>:
  - Optimise glycaemic control to near normoglycaemic levels, where the risk and benefits allow <sup>2,7</sup> [L1].
  - Optimise BP control (<140/90 mmHg) <sup>2,7</sup> [L1]:
    - In patients with albuminuria, consider a BP target of <130/80 mmHg.
    - Use clinical judgement when aiming for systolic BP targets <130 mmHg to avoid diastolic BP levels <60-70 mmHg <sup>2</sup> [L2].
  - Achieve optimal lipid control.
  - Counsel on smoking cessation.
  - Avoid high protein intake (>1.3g/kg/day) in adults with CKD at risk of progression (see Section 6.6.5)



### Management of Diabetic Kidney Disease:

- In all non-pregnant patients with diabetes, an ACE inhibitor or ARB <sup>2,7,8</sup>:
  - Is recommended if there is modestly elevated urinary albumin excretion (30-299 mg/day) / ACR >3 mg/mmol <sup>2,9</sup> [L1, RGA].
  - Is strongly recommended if urinary albumin excretion is ≥300 mg/day and/or eGFR is <60 ml/min/1.73m<sup>2</sup> / ACR >30 mg/mmol <sup>2,9</sup> [L1, RGA].
  - Should be prescribed at the highest tolerated dose in patients with albuminuria <sup>7</sup> [L1].
  - Is not recommended for the primary prevention of diabetic kidney disease in patients with normal BP, normal urinary ACR (<3 mg/mmol), and normal eGFR (>60 ml/min/1.73m<sup>2</sup>).
  - Avoid using ACE inhibitors and ARBs together due to the increased risk of hyperkalaemia, hypotension and impairment of renal function <sup>8</sup>.
  - For patients with T2DM consider use of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) in patients with an eGFR ≥30 mL/min/1.73 m<sup>2</sup> and urinary albumin >30 mg/g creatinine, particularly in those with urinary albumin ACR >30 mg/mmol, to reduce risk of chronic kidney disease (CKD) progression, cardiovascular events, or both <sup>9</sup> [L1].
- Referral to a nephrologist should be arranged if any of the following apply <sup>2,5,10</sup>:
  - eGFR is 45 - 59 ml/min/1.73m<sup>2</sup>: for initial assessment to rule out other possible causes of CKD especially in the following clinical scenarios:
    - Absence of diabetic retinopathy.
    - Rapidly decreasing eGFR (i.e. an annual decline in eGFR of >5 ml/min/1.73 m<sup>2</sup>)
    - Rapidly increasing proteinuria or nephrotic syndrome.
    - Refractory hypertension.
    - Signs or symptoms of other systemic disease.
    - >30% reduction in eGFR within 2-3 months after initiation of an ACE inhibitor or ARB.
    - If significant microscopic or gross haematuria develops.
  - eGFR is 30 - 44 ml/min/1.73m<sup>2</sup>:
    - Refer to nephrologist for initial assessment, to rule out any other underlying renal disease.
  - eGFR is <30 ml/min/1.73m<sup>2</sup>:
    - For further management and follow up.

### Atherosclerotic Cardiovascular Disease and Risk Management:

- Atherosclerotic cardiovascular disease (ASCVD) is the primary cause of morbidity and mortality for patients diagnosed with diabetes and accounts for the greatest costs involved in diabetes care <sup>2</sup>.
- See *Table 7.2* for categorisation of ASCVD risk.

### Blood Pressure Management:

- Unless contraindicated, for diabetic patients with hypertension and renal impairment, an ACE inhibitor or ARB must be the first line drug <sup>2</sup>.
- Intensify therapy until BP is consistently within target range. Continue to reinforce lifestyle advice<sup>3</sup>.
- If BP is consistently attained at the target level, continue to monitor the patient's BP at every clinic visit [R-GDG] and check for adverse effects including hypotension <sup>2</sup>.
- Note that antihypertensive medications can increase the likelihood of side effects, e.g. orthostatic hypotension in a patient with autonomic neuropathy <sup>3</sup>.

### Lipid Management:

- T1DM in adults:

- Unless contraindicated, offer a high intensity statin for patients with T1DM who are at **high risk** or **very high risk** of ASCVD, irrespective of baseline LDL-C levels (see *Table 7.2*) <sup>11</sup> [**L2, RGA**].
- Consider offering statins to all patients with T1DM who are aged over 30 years <sup>11</sup> [**L2, RGA**].
- T2DM in adults:
  - Offer statin therapy for all patients aged over 40 years, irrespective of cholesterol value or risk categorisation (*Table 7.2*) <sup>11,12</sup> [**L1, RGA**].

#### Antiplatelet Therapy:

- Aspirin and other antiplatelet agents are not routinely recommended for patients with T1DM or T2DM in the absence of established ASCVD <sup>2,13–15</sup>.
- However, the *American Diabetes Association* recommends initiating low-dose aspirin for the primary prevention of ASCVD in adults aged 50-59 years who have a 10 year ASCVD risk of  $\geq 10\%$ , using the ACC/AHA Pooled Cohort Equations.
- Patients must not be at increased risk for bleeding, have a life expectancy of at least 10 years and be willing to take low-dose aspirin daily for at least 10 years <sup>2</sup>.

#### Diabetic Foot Problems:

- Diabetic foot problems include <sup>2,16</sup>:
  - Ulcers.
  - Soft tissue infections.
  - Charcot arthropathy.
  - Osteomyelitis.
  - Ischaemia.
- Comprehensive foot evaluation <sup>2</sup>:
  - Should be performed by either a person trained in diabetic foot examination, a podiatrist or a physician [**R-GDG**].
  - Perform a comprehensive foot evaluation at least annually.
- See *Sections 8.2.3 – 8.2.6* for detailed assessment of specific diabetic foot problems.
- Risk stratification of diabetic foot problems (see *Section 8.3*)

#### Referral to Specialist Podiatry:

- Refer patients to an HMC Podiatry Clinic at the Ambulatory Care Centre [**R-GDG**] for assessment and ongoing preventative care if the diabetic patient has any of the following <sup>2,16</sup> [**L2**]:
  - A history of previous lower extremity complications.
  - Loss of protective sensation.
  - Structural abnormalities of the feet.
  - Peripheral vascular disease.
  - Moderate or high risk of developing a diabetic foot problem (see *Section 8.3*).
  - Foot deformity due to a previous Charcot arthropathy, as they are at high risk of ulceration.
- NB: Assessment by the HMC Podiatry Clinic should be carried out within <sup>16</sup>:
  - 6-8 weeks for patients with moderate risk of a diabetic foot problem.
  - 2-4 weeks for patients with high risk of a diabetic foot problem.
- If a patient has a limb- or life-threatening diabetic foot problem <sup>16</sup>:
  - Refer the patient immediately to the Emergency Department <sup>17</sup> [**L3**].
  - Examples of limb- or life-threatening problems include:
    - Ulceration with fever or signs of sepsis.
    - Ulceration with acute limb ischaemia.

- Wet gangrene (with or without ulceration).
- See *Section 8.5.2* for a summary of the management of specific diabetic foot problems.

### **Diabetic Neuropathy:**

- Diabetic neuropathy is classified into the following types <sup>7</sup>:
  - Distal symmetric polyneuropathy (DSPN).
  - Autonomic neuropathy.
  - Radiculoplexus neuropathy (diabetic amyotrophy).
  - Mononeuropathy.
- Screening in patients with T2DM, should take place <sup>18</sup>:
  - At the time of initial diagnosis and annually thereafter.
- Screening in patients with T1DM, should take place <sup>18</sup>:
  - 5 years after initial diagnosis and annually thereafter.
- Assessment should include <sup>2,19</sup>:
  - A full history and a combination of at least two of the following:
    - 10 g monofilament testing (large fibre function and protective sensation).
    - At least one of the following tests:
      - Pinprick sensation (small fibre function).
      - Temperature discrimination (small fibre function).
      - Vibration sensation using a 128-Hz tuning fork (large fibre function).
  - Screening for dysfunction and assessment of future complication risk.
- Further specialist testing may include <sup>7</sup>:
  - Neurophysiological tests e.g.:
    - Nerve conduction studies.
    - Electromyography.
  - Corneal confocal microscopy may be used, if available, to detect small fibre neuropathy <sup>7</sup> [L2].

### **Management of Distal Symmetric Polyneuropathy:**

- Assess and treat patients with the aim of <sup>2</sup>:
  - Reducing the positive symptoms of pain related to painful distal symmetric polyneuropathy.
  - To improve quality of life <sup>2</sup> [L3].
- Although there are no disease modifying treatments to reverse diabetic neuropathy, it is speculated that the following treatment approaches may help <sup>2,7</sup>:
  - Improve glycaemic control:
    - Insulin sensitising agents are more effective than insulin-providing agents <sup>20</sup>.
  - Improve dyslipidaemia:
    - Particularly treatment of triglycerides with fibrates <sup>21</sup>.
  - Treat with an ACE inhibitor and/or CCB <sup>22,23</sup>.

### **Referral to Neurology:**

- Consider referral to a neurologist when there are atypical features or the diagnosis is unclear <sup>2</sup> [L2].
- Consider referral to a specialist pain service if <sup>24</sup>:
  - The patient has severe pain despite recommended therapies.
  - Their pain significantly limits their lifestyle, participation, or daily activities.
  - Their underlying health condition has deteriorated.

## 4 Background Information

### 4.1 Common Chronic Complications

The common chronic complications of diabetes include <sup>2,3,25</sup>:

- Microvascular complications, including:
  - Diabetic retinopathy.
  - Diabetic kidney disease.
  - Diabetic neuropathy including:
    - Distal symmetric polyneuropathy.
    - Autonomic neuropathy.
    - Radiculoplexus neuropathy (diabetic amyotrophy).
    - Mononeuropathy.
  - Diabetic foot problems, including:
    - Foot ulcers.
    - Foot soft tissue infection.
    - Osteomyelitis.
    - Charcot arthropathy.
    - Foot amputation.
  
- Macrovascular complications:
  - Atherosclerotic cardiovascular disease (ASCVD), including:
    - Coronary artery disease, including:
      - Acute coronary syndrome (ACS).
      - Myocardial infarction (MI).
      - Stable or unstable angina.
    - Cerebrovascular disease, including:
      - Stroke.
      - Transient ischaemic attack.
    - Peripheral vascular disease.

## 5 Diabetic Retinopathy

### 5.1 Definition

Diabetic retinopathy:

- Is a chronic, progressive, sight-threatening disease of the retinal microvasculature <sup>26</sup>.
- Is associated with prolonged hyperglycaemia, and other conditions associated with diabetes mellitus, e.g. hypertension and hyperlipidaemia etc <sup>26</sup>.
- Two mechanisms result in loss of vision <sup>26</sup>:
  - Retinopathy: Growth of new vessels leading to intraocular haemorrhage and possible retinal detachment with profound global sight loss.
  - Maculopathy: Localised damage to the macula or fovea of the eye resulting in loss of central visual acuity.

The lesions of diabetic retinopathy include <sup>7,27</sup>:

- Background or non-proliferative diabetic retinopathy (NPDR).
- Pre-proliferative diabetic retinopathy.
- Proliferative diabetic retinopathy (PDR).
- Macular oedema, defined as retinal thickening.

### 5.2 Prevalence

Diabetic retinopathy <sup>1,2,7,28-30</sup>:

- One of the most common microvascular complication of diabetes.
- Was found to be the most common diabetic complication in Qatari patients attending a diabetic outpatient clinic (43.6% of patients).
- Occurs in 25-45% of patients with type 2 diabetes mellitus (T2DM).
- May begin to develop as early as 7 years before a diagnosis of T2DM is confirmed.
- Is the most frequent cause of new cases of blindness among adults aged 20-74 years in developed countries.
- Prevalence is strongly related to the duration of diabetes and level of glycaemic control:
  - Rates are significantly higher in older patients with middle-age onset diabetes compared to old-age onset diabetes.
- Between 2-8% of patients with T2DM have proliferative retinopathy and/or macular oedema.

Disorders of the eye, glaucoma, and cataracts present earlier and more frequently in patients with diabetes<sup>2</sup>. When a person with diabetes complains of visual disturbance despite a visual acuity of 6/6, abnormalities of refraction, contrast sensitivity, straylight and amplitude of accommodation, should also be considered<sup>31</sup>.

### 5.3 Risk Factors

Risk factors <sup>2,26,32</sup>:

- Poor glycaemic control.
- Diabetic kidney disease.
- Hypertension.
- Dyslipidaemia.
- Longer duration of diabetes i.e. earlier age of onset.

- Smoking.
- Pregnancy.
- Carotid arterial disease.
- Elevated homocysteine levels.

#### 5.4 Screening and Diagnosis

All patients with T2DM should undergo dilated or non-dilated retinal photography, which should be undertaken by a trained technician, optometrist, or ophthalmologist [R-GDG]. Screening should be undertaken at the time of diagnosis and annually thereafter, or at an alternative frequency as decided by the ophthalmologist <sup>2</sup>.

All adult patients with T1DM should undergo retinal screening as above, within five years of the initial diagnosis <sup>2</sup>.

Explain to patients the reasons for, and success of, eye screening systems in order to prevent missed appointments due to fear of the outcome or lack of knowledge <sup>3,4</sup> [L2].

#### 5.5 History and Examination

Initial history should include the following <sup>27</sup>:

- Diabetes duration.
- Past glucose control (HbA<sub>1c</sub>).
- Current medications.
- Medical history including obesity, renal disease, systemic hypertension, serum lipid levels, pregnancy and neuropathy.
- Ocular history including trauma, other diseases of the eye, ocular injections, surgery (including retinal laser treatment and refractive surgery).

Initial examination should be conducted by (but not limited to) an ophthalmologist and should include <sup>27</sup>:

- Visual acuity.
- Slit lamp biomicroscopy.
- Intraocular pressure.
- Gonioscopy before dilatation, if indicated:
  - Neovascularization of the iris:
    - Is best seen before dilatation.
    - When present or suspected, or if intraocular pressure is elevated, undilated gonioscopy can be used to find neovascularization in the anterior chamber angle.
- Pupillary assessment for optic nerve dysfunction.
- Thorough funduscopy including stereoscopic examination of the posterior pole.
- Examination of the peripheral retina and vitreous.

Retinal photography <sup>2</sup>:

- Retinal photography may enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy [R-GDG].
- Should not be used as a substitute for a comprehensive eye exam <sup>2</sup>.
- Consider using mydriasis, if necessary, when photographing the retina <sup>3,4</sup> [L2].

### 5.5.1 Clinical Findings

Damage to the microvasculature in diabetic retinopathy leads to <sup>27</sup>:

- NPDR:
  - Loss of perfusion to the retinal capillaries.
  - Microaneurysms.
  - Venous abnormalities.
  - Haemorrhages.
  - Cotton wool spots (soft exudates).
  - Hard exudates.
- Pre-proliferative retinopathy <sup>3,4</sup>:
  - Cotton wool spots with any of the following <sup>3,4</sup> [L2]:
    - Venous beading.
    - Venous reduplication.
    - Multiple deep, round, or blot haemorrhages.
    - IRMA (intraretinal micro vascular anomalies).
- Proliferative retinopathy <sup>27</sup>:
  - Secondary proliferation of new vessels on the disc, retina, iris and in the filtration angle.
    - The new vessels can then lead to traction retinal detachments and neovascular glaucoma.
    - In this stage vision can be lost due to capillary non-perfusion or macular oedema, vitreous haemorrhage and distortion or traction retinal detachment.
- Diabetic macular oedema <sup>27</sup>:
  - Is seen as retinal thickening.
  - Requires a 3-dimensional assessment which is best done by dilated examination with slit-lamp biomicroscopy <sup>27</sup>, optical coherence tomography [R-GDG] and/or Fundus fluorescein angiography [R-GDG].
  - Clinically significant macular oedema [R-GDG]:
    - Any retinal oedema within 500 microns of the centre of the fovea.
    - Hard exudates within 500 microns of the centre of the fovea, if associated with adjacent areas of retinal thickening.
    - Retinal oedema more than one disc area in size within one disc diameter of the centre of the fovea.

## 5.6 Severity Scales

### 5.6.1 Diabetic Retinopathy Disease Severity Scale

Diabetic retinopathy disease severity scale (on dilated ophthalmoscopy)<sup>27</sup>:

Severity level	Dilated ophthalmoscopy findings
<b>No Apparent Retinopathy</b>	No abnormalities.
<b>Mild NPDR</b>	Microaneurysms only.
<b>Moderate NPDR</b>	More than just <u>microaneurysms</u> but less than severe NPDR.
<b>Severe NPDR</b>	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: <ul style="list-style-type: none"> <li>• Severe intraretinal haemorrhages and microaneurysms in each of 4 quadrants.</li> <li>• Definite venous beading in <math>\geq 2</math> quadrants.</li> <li>• Moderate IRMA in <math>\geq 1</math> quadrant.</li> </ul>
<b>Very Severe NPDR</b>	Any patient with $\geq 2$ characteristics of severe NPDR.
<b>Proliferative Diabetic Retinopathy</b>	One or both of the following: <ul style="list-style-type: none"> <li>• Neovascularization.</li> <li>• Vitreous/preretinal haemorrhage.</li> </ul> May be classified as high-risk and non-high-risk.

**Table 5.6.1:** Diabetic Retinopathy Disease Severity Based on Dilated Ophthalmoscopy Findings<sup>27</sup>.

### 5.6.2 Diabetic Macular Oedema Disease Severity Scale

International clinical diabetic macular oedema disease severity scale<sup>27</sup>:

- Diabetic macular oedema apparently absent:
  - No apparent retinal thickening or hard exudates in posterior pole.
- Diabetic macular oedema apparently present:
  - Some apparent retinal thickening or hard exudates in posterior pole.
- If diabetic macular oedema is present, categorise as follows:

Disease Severity	Clinical Findings
<b>Mild Diabetic Macular Oedema</b>	Some retinal thickening or hard exudates in posterior pole but distant from the centre of the macula.
<b>Moderate Diabetic Macular Oedema</b>	Retinal thickening or hard exudates approaching the centre of the macula but not involving the centre.
<b>Severe Diabetic Macular Oedema</b>	Retinal thickening or hard exudates involving the centre of the macula.

**Table 5.6.2:** International Clinical Diabetic Macular Oedema Disease Severity Scale<sup>27</sup>.



## 5.7 Referral to Ophthalmology

A competent ophthalmologist should perform the initial dilated and comprehensive eye examination <sup>2</sup>. All patients should thereafter be managed by an ophthalmologist (retinal specialist) if abnormalities are found on examination according to the approved HMC clinical practice guidelines for diabetic retinopathy, which is available in the hospital website [**R-GDG**].

Refer for an emergency review by an ophthalmologist in tertiary care hospital if the patient experiences any eye emergency and in particular, any of the following <sup>3,4</sup> [**L2**]:

- Sudden loss of vision or deterioration in vision.
- Rubeosis iridis.
- Pre-retinal or vitreous haemorrhage.
- Retinal detachment.

## 5.8 Management of Diabetic Retinopathy

To reduce the risk or slow the progression of diabetic retinopathy, optimise all of the following <sup>2</sup> [**L1, RGA**]:

- Glycaemic control.
- Blood pressure (BP).
- Serum lipids, particularly triglycerides:
  - Retinopathy progression may be slowed by the addition of Fenofibrate, particularly in those with very mild NPDR at baseline <sup>33</sup>.
- Smoking cessation.

Laser photocoagulation therapy may be used to reduce the risk of vision loss <sup>2</sup> [**L1, RGA**]:

- In patients with PDR.
- In some cases of severe NPDR.

Intravitreal injections of anti-vascular endothelial growth factor may be used in patients with centre-involved diabetic macular oedema that occurs beneath the foveal centre and threatens vision (e.g., clinically significant macular oedema). Decisions on treatment should be taken by an ophthalmologist (retinal specialist) <sup>2</sup> [**L1, RGA**].

## 6 Diabetic Kidney Disease

### 6.1 Definitions

Diabetic kidney disease <sup>6</sup>:

- Is disease of the kidneys that is directly related to diabetes <sup>2</sup>.
- Is usually identified by one of the following <sup>2,6</sup>:
  - Random spot urine sample for urinary albumin-to-creatinine ratio (ACR) >3mg/mmol:
    - 2 out of 3 samples should be abnormal over a 3-6 month period.
  - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m<sup>2</sup>.
- NB: People with diabetes may have other causes of CKD in addition to diabetes.

Chronic kidney disease (CKD) <sup>34</sup>:

- Abnormalities in kidney structure or function, present for more than 3 months.

### 6.2 Stages of Chronic Kidney Disease

Stages of CKD <sup>2,6</sup>:

- Stage 1 – Kidney damage with normal or increased eGFR:
  - eGFR –  $\geq 90$  ml/min/1.73m<sup>2</sup> with haematuria, albuminuria or abnormalities of kidney structure.
- Stage 2 – Kidney damage with mildly decreased eGFR:
  - 60-89 ml/min/1.73m<sup>2</sup> with haematuria, albuminuria or abnormalities of kidney structure.
- Stage 3 – Moderately decreased eGFR:
  - Stage 3a: mildly to moderately decreased eGFR: 45-59 ml/min/1.73m<sup>2</sup>.
  - Stage 3b: moderately to severely decreased eGFR: 30-44 ml/min/1.73m<sup>2</sup>.
- Stage 4 – Severely decreased eGFR:
  - 15-29 ml/min/1.73m<sup>2</sup>.
- Stage 5 – Kidney failure:
  - Less than 15 ml/min/1.73m<sup>2</sup>, or dialysis.

### 6.3 Prevalence

Diabetic kidney disease <sup>2,6</sup>:

- Occurs in 20-40% of patients with diabetes.
- Is the leading cause of end-stage renal disease (ESRD), attributed to approximately 50% of cases in developed regions.

### 6.4 Risk Factors for Diabetic Kidney Disease

Risk factors include <sup>35</sup>:

- Chronic hyperglycaemia.
- Longer duration of diabetes (earlier age of onset).
- Tobacco use.
- Dyslipidaemia.
- Hypertension.
- Obesity.

## 6.5 Screening and Diagnosis

Screen for diabetic kidney disease in all adults with T2DM, at the time of diagnosis and all adults with T1DM, 5 years from initial diagnosis <sup>2</sup>.

Screening tests <sup>2,5</sup>:

- Measurement of the urinary ACR in a random spot urine collection, taken at least annually:
  - Normal ACR is <3 mg/mmol.
  - Due to the variation in urine albumin excretion, 2 of 3 ACR specimens collected within 3-6 months should be reported as abnormal, before a patient is considered as having albuminuria.
  - Persistently elevated ACR is:
    - An early sign of diabetic kidney disease in T1DM.
    - A marker for development of diabetic kidney disease in T2DM.
    - A marker of increased ASCVD risk.
    - In the absence of retinopathy, an elevated ACR is suggestive of non-diabetic CKD.
  - Severely increased ACR  $\geq 30$  mg/mmol:
    - Is associated with increased likelihood of developing ESRD.
    - Is strongly suggestive of diabetic kidney disease, if retinopathy is present.
  - The following can elevate ACR without the presence of kidney damage:
    - Exercise within 24 hours.
    - Infection.
    - Fever.
    - Congestive heart failure.
    - Marked hyperglycaemia.
    - Menstruation.
    - Marked hypertension.
- Timed or 24-hour urine collections:
  - More tedious and do not significantly improve prediction.
- eGFR, measured at least annually <sup>5</sup>:
  - Use serum creatinine to estimate the GFR using the MDRD or CKD-EPI calculators.

Consider other causes of CKD in the presence of any of the following <sup>2,4,6</sup>:

- Absence of diabetic retinopathy
- Rapidly decreasing eGFR.
- Rapidly increasing proteinuria or nephrotic syndrome.
- Refractory hypertension.
- Signs or symptoms of other systemic disease.
- >30% reduction in eGFR within 2-3 months of initiating an ACE inhibitor or angiotensin receptor blocker (ARB).
- If significant microscopic or frank haematuria develops.

## 6.6 Management of Chronic Kidney Disease

### 6.6.1 Delaying the Progression of CKD

In order to delay the progression of diabetic kidney disease and prevent cardio-renal complications <sup>2,5,7,36</sup>:

- Optimise glycaemic control to near normoglycaemic levels, where the risk and benefits allow <sup>2,7</sup> [L1].
- Optimise BP control (<140/90 mmHg) <sup>2,7</sup> [L1]:
  - In patients with albuminuria, consider a BP target of <130/80 mmHg.

- Use clinical judgement when aiming for systolic BP targets <130 mmHg to avoid diastolic BP levels <60-70 mmHg <sup>2</sup> [L2].
- Achieve optimal lipid control.
- Counsel on smoking cessation.
- Weight reduction in obese patients.
- Avoid high protein intake (1.3 g/ kg/day) in adults with CKD at risk of progression (see *Section 6.6.5*)

## 6.6.2 General Management and Monitoring

Management and monitoring of CKD in patients with diabetes <sup>2,5,36</sup>:

- In all patients <sup>2,7</sup>:
  - Arrange annual creatinine, urinary ACR, potassium and lipid measurements.
  - Begin measurement in all adult patients with T2DM at the time of diagnosis and after 5 years of onset of T1DM.
- In patients with eGFR of 45-60 mL/min/1.73 m<sup>2</sup> <sup>2,4,7,10</sup>:
  - Monitor eGFR every 6 months.
  - Monitor calcium and phosphorous every 6-12 months.
  - Monitor PTH every 12 months.
  - Monitor electrolytes, bicarbonate, haemoglobin, vitamin D every 6-12 months.
  - Consider whether dose adjustment of medication is required.
  - Ensure sufficient vitamin D levels, using ergocalciferol or cholecalciferol [R-GDG].
  - Refer to a nephrologist for initial assessment to rule out other possible causes of CKD especially in the following clinical scenarios:
    - Absence of diabetic retinopathy.
    - Rapidly decreasing eGFR (i.e. an annual decline in eGFR >5 ml/min/1.73m<sup>2</sup>).
    - Rapidly increasing proteinuria or nephrotic syndrome.
    - Refractory hypertension.
    - Signs or symptoms of other systemic disease.
    - >30% reduction in eGFR within 2-3 months of initiating an ACE inhibitor or ARB.
    - If significant microscopic or frank haematuria develops.
- In patients with eGFR of 30-44 mL/min/1.73m<sup>2</sup> <sup>2,5,7,10</sup>:
  - Monitor eGFR every 3 months.
  - Monitor calcium and phosphorous every 6-12 months.
  - Monitor PTH every 12 months.
  - Monitor electrolytes, bicarbonate, vitamin D, albumin, and weight every 3-6 months.
  - Monitor haemoglobin at least annually.
  - Consider if dose adjustment of all medication is required (see *Section 6.6.3* below).
  - Refer to nephrologist for initial assessment, to rule out other possible primary kidney disease [R-GDG].
- In patients with an eGFR of <30 mL/min/1.73m<sup>2</sup>, arrange referral to a nephrologist for further management <sup>5</sup>.

When ACE inhibitors, diuretics, or ARBs are used <sup>2</sup>:

- Monitor serum creatinine and potassium levels within 7-10 days of dose changes <sup>5</sup>.
- It is reasonable to continue monitoring urinary ACR in patients with albuminuria treated with ACE inhibitors or ARBs to assess treatment response and the progression of diabetic kidney disease <sup>2</sup> [L3, RGA].

### 6.6.3 Pharmacological Management

For patients with T2DM consider use of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) in patients with an eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> and urinary albumin  $>30$  mg/g creatinine, particularly in those with urinary albumin ACR  $>30$  mg/mmol, to reduce risk of chronic kidney disease (CKD) progression, cardiovascular events, or both<sup>9</sup> [L1].

In all non-pregnant patients with diabetes, an ACE inhibitor or ARB<sup>2,7,8,36</sup>:

- Is recommended if there is modestly elevated urinary albumin excretion (30-299 mg/day) / ACR  $>3$  mg/mmol [R-GDG]<sup>2,9</sup> [L1, RGA].
- Is strongly recommended if urinary albumin excretion is  $\geq 300$  mg/day and/or eGFR is  $<60$  mL/min/1.73m<sup>2</sup> / ACR  $>30$  mg/mmol<sup>2,9</sup> [L1, RGA].
- Should be prescribed at the highest tolerated dose in patients with albuminuria<sup>7</sup> [L1].
- Is not recommended for the primary prevention of diabetic kidney disease in patients with normal BP, normal urinary ACR ( $<3$  mg/mmol), and normal eGFR ( $>60$  mL/min/1.73m<sup>2</sup>).
- Avoid using ACE inhibitors and ARBs together due to the increased risk of hyperkalaemia, hypotension, and impairment of renal function.

Dose adjustment of anti-diabetic drugs:

- Metformin<sup>2,37</sup>:
  - Use should be re-evaluated at an eGFR  $<45$  mL/min/1.73 m<sup>2</sup> with a reduction in maximum dose to 1,000 mg/day.
  - Discontinue if eGFR is  $<30$  mL/min/1.73 m<sup>2</sup>.
- Sulfonylureas<sup>37</sup>:
  - Use glipizide and glimepiride with caution in patients with an eGFR of  $<60$  mL/min/1.73m<sup>2</sup>.
  - Avoid the use of glimepiride if eGFR is  $<30$  mL/min/1.73m<sup>2</sup>.
  - Avoid the use of glyburide/glibenclamide if eGFR is  $<60$  mL/min/1.73m<sup>2</sup>.
  - No dose adjustment is required for gliclazide<sup>38</sup> but use with caution due to the increased risk of hypoglycaemia<sup>12</sup>.
- Meglitinides (glinides)<sup>8,37</sup>:
  - Use repaglinide with caution in patients with an eGFR of  $<30$  mL/min/1.73m<sup>2</sup>.
  - Avoid the use of nateglinide if the eGFR is  $<60$  mL/min/1.73m<sup>2</sup>.
- Thiazolidinedione<sup>37</sup>:
  - No dose adjustment is required.
- DPP-4 inhibitors<sup>36,37</sup>:
  - Sitagliptin:
    - If eGFR is  $\geq 50$  mL/min/1.73m<sup>2</sup> use 100 mg daily.
    - If eGFR is 30-49 mL/min/1.73m<sup>2</sup> use 50 mg daily.
    - If eGFR is  $<30$  mL/min/1.73m<sup>2</sup> use 25 mg daily.
  - Saxagliptin:
    - If eGFR is  $\geq 50$  mL/min/1.73m<sup>2</sup> use 2.5 mg or 5 mg daily.
    - If eGFR is  $<50$  mL/min/1.73m<sup>2</sup> use 2.5 mg daily.
  - Vildagliptin<sup>12</sup>:
    - If eGFR is  $<50$  mL/min/1.73m<sup>2</sup> use 50 mg daily.
  - Linagliptin:
    - No dose adjustment is required.
- SGLT2 inhibitors:
  - We recommend treating patients with T2DM, CKD, and an eGFR 30 mL/min per 1.73 m<sup>2</sup> or above with an SGLT2i<sup>9</sup> [L1].
- GLP-1 receptor agonists<sup>8,37</sup>:
  - Exenatide:
    - Use with caution if the eGFR is 30-50 mL/min/1.73m<sup>2</sup>.
    - Avoid use if the eGFR is  $<30$  mL/min/1.73m<sup>2</sup>.

- Liraglutide:
  - No dose adjustment is required but use with caution when starting or titrating the dose.
- Lixisenatide <sup>8</sup>:
  - Use with caution if the eGFR is 30-50 ml/min/1.73m<sup>2</sup>.
  - Avoid use if the eGFR is <30 ml/min/1.73m<sup>2</sup>.
- Dulaglutide:
  - No dose adjustment is required.
- Insulins <sup>37</sup>:
  - Adjust dose based on patient response.

#### 6.6.4 Supplementation

Calcium and vitamin D <sup>7</sup>:

- Adequate calcium intake and attaining 25-hydroxyvitamin D (25(OH)D) levels of >30 ng/mL in all patients is recommended.
- Supplementation with vitamin D2 or D3 may reduce parathyroid hormone (PTH) levels without causing harm:
- Active vitamin D preparations may be needed even after adequate levels of 25(OH)D have been achieved, in order to keep PTH levels from increasing as kidney function declines.

Anaemia <sup>7</sup>:

- Any deficiencies in iron, vitamin B12, or folate causing anaemia should be replaced.
- A transferrin saturation target of 30-50% is recommended to be achieved, regardless of the ferritin level.

Hyperphosphataemia <sup>7</sup> [L2]:

- Correct to normal range using dietary modification and careful use of phosphate binders.

#### 6.6.5 Nutrition

Dietary protein <sup>2,4</sup>:

- Avoid high protein intake (>1.3 g/kg/day) in patients with CKD at risk of progression.
- In patients on dialysis consider higher levels of dietary protein to that recommended for non-dialysis-dependent patients <sup>2</sup> [L1].
- Excessive protein consumption (>1.3 g/kg/day) is associated with increased albuminuria, more rapid loss in kidney function, and increased ASCVD mortality. Very low protein diets can lead to protein malnutrition <sup>6</sup> [L2]:
  - Incorporate vegan protein sources into the meal plan.
  - Reduce intake of fatty animal protein sources.

NB: Depending on CKD risk level and stage, advise avoidance of excessive salt, phosphate, and potassium [20] [L2].

### 6.7 Referral to Nephrology

Referral to a nephrologist should be arranged if any of the following apply <sup>2,5,10</sup>:

- eGFR is 45 - 59 ml/min/1.73m<sup>2</sup>: for initial assessment to rule out other possible causes of CKD especially in the following clinical scenarios:

- Absence of diabetic retinopathy.
- Rapidly decreasing eGFR (i.e. an annual decline in eGFR of  $>5$  ml/min/1.73 m<sup>2</sup>)
- Rapidly increasing proteinuria or nephrotic syndrome.
- Refractory hypertension.
- Signs or symptoms of other systemic disease.
- $>30\%$  reduction in eGFR within 2-3 months of initiating an ACE inhibitor or ARB.
- If significant microscopic or gross haematuria develops.
- eGFR is 30 - 44 ml/min/1.73m<sup>2</sup>:
  - Refer to nephrologist for initial assessment, to rule out any other underlying renal disease.
- eGFR is  $<30$  ml/min/1.73m<sup>2</sup>:
  - For further management and follow up.

## 7 Atherosclerotic Cardiovascular Disease

### 7.1 Background Information

Atherosclerotic cardiovascular disease (ASCVD) is the primary cause of morbidity and mortality for patients diagnosed with diabetes and accounts for the greatest costs involved in diabetes care <sup>2</sup>. ASCVD includes <sup>2</sup>:

- Coronary artery disease, including:
  - Acute coronary syndrome (ACS).
  - Myocardial infarction (MI).
  - Stable or unstable angina.
- Cerebrovascular disease, including:
  - Stroke.
  - Transient ischemic attack.
- Peripheral vascular disease.

### 7.2 Risk Factors

Major risk factors for ASCVD in patients with T2DM include <sup>2,4,11</sup>:

- Age.
- Hypertension.
- Dyslipidaemia:
  - Low density lipoprotein-cholesterol (LDL-C)  $\geq 100$  mg/dL (2.6 mmol/L).
- Smoking.
- Obesity.

Additional risk factors include:

- Overweight.
- Family history of premature ASCVD.
- Albuminuria.
- Abdominal adiposity.

Table 7.2 below indicates the categorisation of ASCVD risk <sup>11</sup>:

Risk Level	Risk Factors
<b>Very High Risk</b>	<ul style="list-style-type: none"><li>• Patients with DM and established cardiovascular disease,</li><li>• Patients with DM and either:<ul style="list-style-type: none"><li>○ Other target end organ damage.</li><li>○ <math>\geq 3</math> major risk factors (see above).</li><li>○ Patients with early onset T1DM and duration of <math>\geq 20</math> years.</li></ul></li></ul>
<b>High Risk</b>	<ul style="list-style-type: none"><li>• Patients with DM duration of <math>\geq 10</math> years without end organ damage or other risk factors.</li></ul>
<b>Moderate Risk</b>	<ul style="list-style-type: none"><li>• Patients with T1DM aged <math>&lt; 35</math> years and no other risk factors.</li><li>• Patients aged <math>&lt; 50</math> years with T2DM duration of <math>&lt; 10</math> years, with no other risk factors.</li></ul>

**Table 7.2:** Categorisation of ASCVD Risk <sup>11</sup>.



## 7.3 Blood Pressure Management

For patients with either T1DM or T2DM without known hypertension, review BP at every visit or at least annually<sup>4</sup>. Provide and emphasise lifestyle advice to all diabetic patients<sup>3</sup>.

### 7.3.1 Blood Pressure Goals

Aim to achieve a clinic BP of<sup>2</sup>:

- <140/90 mmHg; or
- <130/80 mmHg, if the target can be achieved without undue treatment burden, in:
  - Younger patients; or
  - Those with albuminuria; or
  - Those with hypertension and one or more additional ASCVD risk factors

If BP remains above target levels following lifestyle improvement, add medication to reduce BP to target levels<sup>2,3</sup>.

### 7.3.2 Lifestyle Modification

Lifestyle modification in adults:

- Advise the patient on lifestyle modifications if their BP is more than 120/80 mmHg<sup>2</sup>:
  - Consider recommending the Dietary Approaches to Stop Hypertension (DASH) diet<sup>39</sup> [**L1, RGA**]:
    - Low in sodium and high in potassium.
    - Contraindicated in patients with renal insufficiency.
  - Weight loss if overweight or obese<sup>2</sup> [**L1, RGA**].
  - Moderation of alcohol intake, in those who drink<sup>2</sup>.
  - Increasing physical activity<sup>2</sup> [**L1, RGA**].
  - Salt intake<sup>7</sup> [**L2**]:
    - Should be limited to 2 g per day in all patients who require antihypertensive medications.

### 7.3.3 Pharmacological Management of Blood Pressure

#### 7.3.3.1 First-Line Medication

First-line BP lowering therapy should be<sup>3</sup>:

- A once daily ACE inhibitor; or
- For people of African or Caribbean descent:
  - An ACE inhibitor; plus
  - Either a diuretic or CCB.
- For women who may become pregnant, start with a CCB:
  - Avoid the use of ACE inhibitors and angiotensin II-receptor antagonists.
- If there is ongoing intolerance to an ACE inhibitor, other than renal deterioration or hyperkalaemia, an angiotensin II-receptor antagonist may be used instead.

NB: Unless contraindicated, for diabetic patients with hypertension and renal impairment, an ACE inhibitor or ARB must be the first line drug<sup>2</sup>.

Intensify therapy until BP is consistently within target range. Continue to reinforce lifestyle advice<sup>3</sup>. If BP is consistently attained at the target level, continue to monitor the patient's BP at every clinic visit [R-GDG] and check for adverse effects including hypotension<sup>2</sup>. Note that antihypertensive medications can increase the likelihood of side effects, e.g. orthostatic hypotension in a patient with autonomic neuropathy<sup>3</sup>.

### 7.3.3.2 Inadequate Control with First-Line Medication

If BP is not adequately controlled to the agreed target level<sup>3</sup>:

- With first-line therapy, add a:
  - CCB; or
  - Diuretic (usually thiazide or thiazide-like diuretic).
- With dual therapy, add the other drug – i.e., a:
  - CCB; or
  - Diuretic.
- With triple therapy, add:
  - An alpha-blocker; or
  - A beta-blocker; or
  - A potassium-sparing diuretic.

Note the following key points<sup>3</sup>:

- Use potassium-sparing diuretics with caution if the patient is already taking an ACE inhibitor or an angiotensin II-receptor antagonist.
- Do not combine an ACE inhibitor with an angiotensin II-receptor antagonist.
- Refer to Specialist Care if BP remains above target levels following triple therapy including a diuretic [R-GDG].

## 7.4 Lipid Management

### 7.4.1 Lifestyle Modification

Consider lifestyle modification<sup>2</sup>:

- Focusing on weight loss, if indicated<sup>2</sup> [L1].
- Reduce consumption of saturated fat, trans fat, and cholesterol<sup>2</sup> [L1].
- Increase consumption of omega-3 fatty acids, viscous fibre, and plant stanols and sterols<sup>2</sup> [L1].
- Intensify lifestyle therapy and optimise glycaemic control in patients with<sup>6</sup> [L2]:
  - Elevated triglyceride levels:
    - $\geq 150$  mg/dL (1.7 mmol/L).
  - Low high-density lipoprotein (HDL) cholesterol:
    - $< 40$  mg/dL (1.0 mmol/L) for men.
    - $< 50$  mg/dL (1.3 mmol/L) for women.

### 7.4.2 Pharmacological Management of Lipids

T1DM in adults:

- Unless contraindicated, offer a statin therapy for patients with T1DM who are at **high risk** or **very high risk** of ASCVD, irrespective of baseline LDL-C levels (see *Table 7.2*)<sup>11</sup> [L2, RGA].
- Consider offering statins to all patients with T1DM who are aged over 30 years<sup>11</sup> [L2, RGA].

T2DM in adults:

- Offer statin therapy for all patients aged over 40 years, irrespective of cholesterol value or risk categorisation (*Table 7.2*)<sup>11,12</sup> [**L1, RGA**].

In patients aged over 75 years with diabetes mellitus<sup>12</sup>:

- Evaluate the potential benefit of reducing ASCVD risk.
  - The risk of adverse effects and drug-drug interactions
  - Consider also patient preferences when deciding whether to initiate, continue, or intensify statin therapy.

### 7.4.3 Treatment Targets

Patients with T2DM at **very high risk** of ASCVD<sup>11</sup>:

- LDL-C target of <1.4 mmol/L and reduction by ≥50% of baseline level.
- Non-HDL-C target of <2.2 mmol/L.

Patients with T2DM at **high risk** of ASCVD<sup>11</sup>:

- LDL-C target of <1.8 mmol/L and reduction by ≥50% of baseline level.
- Non-HDL-C target of <2.6 mmol/L.

Patients with T2DM at **moderate risk** of ASCVD<sup>11</sup>:

- LDL-C target of <2.6 mmol/L.

Patients with T1DM<sup>11</sup>:

- No specific treatment target set.
- Lower cholesterol as much as possible, considering the patient's tolerance of the drug.

### 7.4.4 Combination Therapy

Non-statin therapies may also be needed in combination with statin therapy.

- Ezetimibe is a recommended option for hypercholesterolaemia in adults, under the following conditions<sup>12,40</sup>:
  - In conjunction with initial statin treatment when:
    - Serum total cholesterol or LDL-C levels are not appropriately controlled after titration of the statin treatment; or dosing is limited by intolerance to the statin.
  - As monotherapy if there is:
    - A contraindication to initial statin treatment.
    - Intolerance to statin treatment
- Do not routinely offer fibrates for ASCVD prevention in patients with diabetes that have been started on statins<sup>41</sup>:
  - Only use if the patient is intolerant of statins.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may also be considered in patients with very high-risk ASCVD or with severe primary hypercholesterolemia<sup>12</sup> [**L1, RGB**]:
  - Consider evolocumab or alirocumab.
  - The long-term safety (>3 years) is uncertain.

NB: Intensify treatment with statins before introducing combination therapy<sup>11</sup>.

## 7.5 Antiplatelet Agents

Aspirin and other antiplatelet agents are not routinely recommended for patients with T1DM or T2DM in the absence of established ASCVD <sup>2,13-15</sup>. However, the *American Diabetes Association* recommends initiating low-dose aspirin use for the primary prevention of ASCVD in adults aged  $\geq 50$  years who have a 10 year ASCVD risk of  $\geq 10\%$ , using the ACC/AHA Pooled Cohort Equations. Patients must not be at increased risk for bleeding, have a life expectancy of at least 10 years and be willing to take low-dose aspirin daily for at least 10 years <sup>14</sup>.

Aspirin may therefore be considered for primary prevention, in diabetic patients with a high risk of ASCVD, but the decision to use antiplatelets must be balanced against the risk of bleeding [R-GDG].

Note: Retinopathy is not a contraindication for the use of aspirin for cardioprotection<sup>2</sup>. Aspirin does not increase the risks of retinal haemorrhage<sup>2</sup>.

## 7.6 Screening for Coronary Artery Disease

Screening <sup>2</sup>:

- Routine screening is not recommended in asymptomatic diabetic patients <sup>2</sup> [L1, RGA].
- Consider screening when there are <sup>2</sup> [L3, RGA]:
  - Atypical cardiac symptoms, e.g. unexplained dyspnoea or chest discomfort.
  - Signs and symptoms of associated vascular disease, e.g.:
    - Carotid bruits.
    - Claudication.
    - Transient ischaemic attack.
    - Stroke.
    - Peripheral vascular disease.
  - ECG abnormalities, e.g. Q waves.
  - Abnormal coronary calcium score on coronary imaging <sup>7</sup>.

NB: Refer to cardiology for assessment and further management, as indicated [R-GDG].

## 8 Diabetic Foot Problems

### 8.1 Background Information

Foot problems are common in patients with diabetes due to associated neuropathy and peripheral vascular disease <sup>16</sup>. A study found that foot ulcer(s) affected 4% of Qatari nationals attending a diabetic outpatient clinic over a one-year period <sup>1</sup>.

Diabetic foot problems are also associated with high mortality rates. 42% of patients that develop a diabetic foot ulcer die within 5 years, and if amputation is required up to 70% of patients die within 5 years of an amputation <sup>16</sup>.

Diabetic foot problems include <sup>2,16</sup>:

- Ulcers.
- Soft tissue infections.
- Charcot arthropathy.
- Osteomyelitis.
- Ischaemia.

Risk factors include <sup>2,16</sup>:

- History of foot ulcer.
- Pre-ulcerative callus or corn.
- Previous amputation.
- Foot deformities.
- Onychomycosis.
- Improper footwear.
- Improper hygiene [**R-GDG**].
- Visual impairment.
- Poor glycaemic control.
- Distal symmetric polyneuropathy with loss of protective sensation.
- Peripheral vascular disease.
- Diabetic kidney disease, particularly in patients on dialysis.
- Hypertension.
- Smoking.

### 8.2 Assessment

Comprehensive foot evaluation <sup>2</sup>:

- Should be performed by either a person trained in diabetic foot examination, a podiatrist or a physician [**R-GDG**].
- Perform a comprehensive foot evaluation at least annually.
- May be used to identify risk factors for ulcers and amputations.

#### 8.2.1 History

Obtain a history, including history of <sup>2</sup> [**L2**]:

- History of diabetes, including type, onset, control and complications.
- History of foot problems and current symptoms including:
  - Skin and nail deformities.

- Neuropathy.
    - Pain.
    - Burning.
    - Numbness.
  - Vascular disease:
    - Leg fatigue.
    - Claudication.
    - Rest pain.
  - Ulceration.
  - Amputation.
  - Charcot foot.
  - Previous foot surgery.
  - Angioplasty.
  - Vascular surgery.
- Smoking.
  - Foot care and footwear.

### 8.2.2 Examination

Examination should include at least the following <sup>2</sup> [L2]:

- Inspection of skin integrity.
- Assessment of musculoskeletal deformities.
- Assessment of foot deformities.
- Neurological assessment:
  - 10g monofilament sensation.
  - Pain and temperature sensation.
  - Vibration-sense (128Hz tuning fork).
  - Deep tendon reflexes.
  - Proprioception.
- Gait evaluation.
- Vascular assessment, including:
  - Pulses in the legs and feet by palpation.
  - If pulses are not palpable use a hand-held Doppler to assess the ankle-brachial pressure index <sup>2</sup>.

NB: When a patient presents with a diabetic foot problem consider that they may also have an undiagnosed increased risk of cardiovascular disease. Consider further investigation <sup>16</sup> [L3].

### 8.2.3 Assessment of Ulcers

If a patient presents with a diabetic foot ulcer, refer to a multi-disciplinary foot care service for the following<sup>16</sup>:

- Identification of the cause of the ulcer.
- Duration of ulceration.
- Previous treatments including antibiotics and surgery.
- Document the size, depth, and position of the ulcer.
- Use a standardised system to document the severity of the foot ulcer <sup>42</sup> e.g. The *University of Texas* classification system which classifies the ulcer based on grade and stage of infection <sup>43</sup>:
  - Grade of ulcer:
    - Grade 0: Pre-ulcerative or post-ulcerative lesion(s) that is/are completely epithelialized.

- Grade 1: Superficial wound that does not involve the tendon, capsule or bone.
- Grade 2: Wound penetrating to the tendon or capsule.
- Grade 3: Wound penetrating to the bone or joint.
- Stage of infection:
  - Stage A: No infection or ischaemia.
  - Stage B: Infection.
  - Stage C: Ischaemia.
  - Stage D: Infection and ischaemia.

#### 8.2.4 Assessment of Infection

Symptoms and signs indicative of wound infection in patients with diabetes <sup>44</sup>:

- Inflammation e.g.:
  - Erythema
  - Warmth
  - Tenderness or pain
  - Swelling or induration
- Purulent secretions.
- Systemic features (indicates severe infection) e.g.:
  - Temperature >38°C or <36°C
  - Tachycardia
  - Raised respiratory rate
  - Raised white blood cell count
  - Raised CRP.

To confirm the diagnosis of a diabetic foot infection, the following should be undertaken by a podiatrist:

- A soft tissue or bone sample from the base of the debrided wound for microbiological examination <sup>16</sup> [L2].
- Deep swab, if a soft tissue or bone sample cannot be obtained <sup>16</sup> [L3].
- A radiographic assessment of the affected foot to assess for osteomyelitis <sup>16</sup> [L3].

Osteomyelitis <sup>7,44</sup>:

- Should be considered if a patient has any of the following <sup>44</sup>:
  - Chronic non-healing ulcer over a bony prominence for >6 weeks of appropriate wound care and off-loading.
  - Wound that extends to the bone or joint.
  - Presence of exposed bone and ulcerated area of >2 cm<sup>2</sup>.
  - Ulcer depth of >3mm.
  - ESR >60 mm/hr.
  - CRP >3.2 mg/dL.
- If osteomyelitis is suspected, immediate plain x-ray and urgent referral to podiatric surgery is indicated.
- Osteomyelitis may be present in a patient with diabetes even when there are normal inflammatory markers, radiographs, or probe-to-bone testing.

### 8.2.5 Assessment of Charcot Foot

Charcot neuropathic osteoarthropathy (Charcot foot) <sup>17</sup>:

- A typically unilateral, acute localised inflammatory condition which may result in bone destruction, subluxation, deformity, and dislocation.
- Results from a combination of diabetes, trauma, previous surgery, previous ulcers, autonomic neuropathy, and sensory-motor neuropathy.
- Characterised by midfoot collapse.
- The diagnosis of active Charcot foot is primarily based on history and clinical findings, but should be confirmed by radiographic and MRI imaging.
- Clinical findings include <sup>17</sup>:
  - Swollen, warm, and often erythematous foot. There may be a temperature difference between the patient's feet by  $>2^{\circ}\text{C}$ .
  - Mild to moderate pain and discomfort.
  - Acute inflammation may be the first sign of bone and joint injury.
  - Pedal pulses are typically bounding, unless oedema is also present.
  - The presence of acute foot/ankle fractures or dislocations may be considered signs of active Charcot foot.
  - The initial clinical picture may resemble cellulitis, deep vein thrombosis, or acute gout.
  - Rocker-bottom foot, with or without plantar ulceration.
- A personal history concerning antecedent trauma is often unreliable due to the presence of insensitivity.
- To confirm the diagnosis of Charcot arthropathy refer the patient within 1 working day to the HMC Podiatry Clinic at the Ambulatory Care Center **[R-GDG]**:
  - Non-weight bearing treatment can be provided until definitive treatment can be given by the Podiatry team (see *Management* section).
- The initial imaging test should be a weight-bearing radiograph of the affected foot and ankle <sup>16,17</sup> **[L2]**:
  - Look for fractures or subluxations, but early Charcot arthropathy may only show focal demineralisation or Lisfranc joint disruption **[R-GDG]**
- MRI or nuclear imaging can be used to confirm the diagnosis when radiographs appear normal, but Charcot arthropathy is still suspected <sup>16,17</sup> **[L2]**.

### 8.2.6 Assessment of Peripheral Vascular Disease

Consider assessing for the presence of peripheral vascular disease in patients with any of the following<sup>45</sup>**[L2]**:

- Symptoms suggestive of peripheral vascular disease e.g. intermittent claudication or rest pain.
- Diabetes, leg or foot ulcers, or unexplained leg pain.
- When considering compression hosiery.

Measuring the Ankle-Brachial Pressure Index <sup>45</sup> **[L3]**:

- With the patient in a resting supine position, if possible.
- Record systolic BP in:
  - Both arms.
  - The posterior tibialis arteries.
  - Dorsalis pedis arteries.
  - Peroneal arteries.
- Use a validated Doppler probe/machine to assess pulses.
- Divide the highest ankle pressure by the highest arm pressure to calculate the index.



If the Ankle Brachial Pressure Index is normal, further investigations should be carried to rule out peripheral arterial disease <sup>45</sup>.

Pulse oximetry cannot be used for the diagnosis of peripheral arterial disease in diabetic patients <sup>45</sup>.

Refer to vascular surgery if any of the following are present <sup>45</sup>:

- Non-palpable peripheral pulses.
- Monophasic Doppler sounds.
- ABPI is  $\leq 0.8$ , indicating arterial stenosis.
- ABPI is  $\geq 1.05$ , indicating arterial calcification.

### 8.3 Risk Stratification

Assess the patient’s current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification <sup>16</sup> [L2]:

Risk level	Definition
<b>Low Risk</b>	<ul style="list-style-type: none"> <li>• No risk factors present except callus alone.</li> </ul>
<b>Moderate Risk</b>	<ul style="list-style-type: none"> <li>• Deformity; or</li> <li>• Neuropathy; or</li> <li>• Non-critical limb ischaemia.</li> </ul>
<b>High Risk</b>	<ul style="list-style-type: none"> <li>• Previous ulceration; or</li> <li>• Previous amputation; or</li> <li>• On renal replacement therapy; or</li> <li>• Neuropathy and non-critical limb ischaemia together; or</li> <li>• Neuropathy in combination with callus and/or deformity; or</li> <li>• Non-critical limb ischaemia in combination with callus and/or deformity.</li> </ul>
<b>Active Diabetic Foot Problem</b>	<ul style="list-style-type: none"> <li>• Ulceration; or</li> <li>• Spreading infection; or</li> <li>• Critical limb ischaemia; or</li> <li>• Gangrene; or</li> <li>• Suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.</li> </ul>

**Table 8.3:** Stratification of Current Risk of Developing a Diabetic Foot Problem or Needing an Amputation <sup>16</sup>.

According to risk stratification, refer or review as follows <sup>16</sup>:

- Low risk – continue annual foot assessments.
- Moderate or high risk – refer to the HMC Podiatry Clinic at the Ambulatory Care Centre (See Section 8.4).

NB: Consider more frequent assessments for patients who are not able to carry out assessments of their own feet <sup>16</sup>.

NB: Patients with a history of ulcers or amputations, foot deformities, peripheral vascular disease, or insensate feet should have their feet examined at every visit to the diabetologist or family physician <sup>2</sup> and should be followed up every 1-2 months by the podiatry clinic [R-GDG].

## 8.4 Referral to Specialist Podiatry

Refer patients to an HMC Podiatry Clinic [R-GDG] for assessment and ongoing preventative care if the diabetic patient has any of the following <sup>2,16</sup> [L2]:

- A history of previous lower extremity complications.
- Loss of protective sensation.
- Structural abnormalities of the feet.
- Peripheral vascular disease.
- Moderate or high risk of developing a diabetic foot problem (see *Section 8.3*).
- Foot deformity due to a previous Charcot arthropathy, as they are at high risk of ulceration.

NB: Assessment by the HMC Podiatry Clinic should be carried out within <sup>16</sup>:

- 6-8 weeks for patients with moderate risk of a diabetic foot problem.
- 2-4 weeks for patients with high risk of a diabetic foot problem.

If a patient has a limb- or life-threatening diabetic foot problem <sup>16</sup>:

- Refer the patient immediately to the Emergency Department <sup>17</sup> [L3].
- Examples of limb- or life-threatening problems include:
  - Ulceration with fever or signs of sepsis.
  - Ulceration with acute limb ischaemia.
  - Wet gangrene (with or without ulceration).

Patients that have been admitted to hospital and have diabetic foot problems should be referred to the HMC Podiatry Clinic at the Ambulatory Care Centre within 24 hours of the initial foot examination [R-GDG]. If the diabetic foot problem is the main reason for inpatient admission, responsibility of care should lie with the consultant in the foot care service team <sup>16</sup>.

## 8.5 Prevention and Management

### 8.5.1 Prevention

#### 8.5.1.1 Monitoring

Assess a patient's risk of developing a diabetic foot problem at the following times <sup>16</sup> [L3]:

- At diagnosis of diabetes and at least annually thereafter:
  - If at moderate risk of developing a foot problem, reassessment should be carried out frequently by the HMC Podiatry Clinic, e.g. 3-6 monthly.
  - If at high risk of developing a foot problem, reassessment should be carried out by the HMC Podiatry Clinic:
    - More frequently e.g. 1-2 monthly, provided there is no immediate concern
    - Very frequently, e.g. every 1-2 weeks, if there is immediate concern
- If any foot problems arise.
- On admission to hospital, and when there is a change in their status while they are in hospital.

### 8.5.1.2 Patient Education

Patient information and education should be provided verbally and in writing, including <sup>16</sup> [L3]:

- A clear explanation of the patient's foot problem.
- Pictures of diabetic foot problems.
- Description of a foot emergency and relevant contact details for further assistance.
- Advice on appropriate footwear <sup>2</sup>:
  - Patients with neuropathy or evidence of increased plantar pressures require well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure.
  - Patients with bony deformities may need extra-wide or -deep shoes.
  - If diabetic-therapeutic shoes are not suitable, custom-moulded shoes may be needed.
- Wound care.
- Information on diabetes including the importance of glycaemic control.
- General foot care education should be given to all patients with diabetes, including <sup>2</sup> [L2]:
  - Nail and skin care.
  - The importance of daily foot inspection.
- Patients should understand risk factors for the development of diabetic foot problems <sup>2</sup> [L2].
- Patients with loss of protective sensation should be educated on methods of assessment using <sup>2</sup> [L2]:
  - Palpation.
  - Visual inspection using a mirror for the sole of the foot.

## 8.5.2 Management of Diabetic Foot Disease

### 8.5.2.1 Management Foot Ulcers

Management of patients with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot, prior ulcers, or amputation) should be carried out by the HMC Podiatry Clinic at the Ambulatory Care Centre [R-GDG].

Consider one or more of the following, as part of standard of care for treating diabetic foot ulcers <sup>16</sup> [L1]:

- Ulcer debridement.
- Ulcer dressings.
- Control of ischaemia.
- Control of foot infection.
- Offloading.

Offloading <sup>16</sup> [L1]:

- To offload plantar neuropathic diabetic ulcers - non-removable casting, or an alternative offloading device may be offered.
- When patients at moderate to high risk of diabetic foot problems are in hospital use a pressure redistribution device in order to off load heel pressure <sup>7</sup> [L2].

Ulcer debridement [R-GDG]:

- Should only be performed by the HMC Podiatry service.
- Advanced wound care including negative pressure wound therapy, should be considered after surgical debridement of the wound(s).

### 8.5.2.2 Management of Foot Infections

#### Antibiotic Therapy:

- Do not offer antibiotic therapy to prevent diabetic foot infections <sup>16</sup> [L2].
- Antibiotic treatment for a diabetic foot infection should be initiated as soon as possible with antibiotic choice based on the <sup>16</sup> [L2]:
  - Severity of the infection.
  - Care setting.
  - Clinical situation.
  - Patient's medical history.
  - Risk of complications.
  - Patient's preference.
- Collect cultures and samples of the infection before, or as close as possible to, the start of antibiotic therapy [L2].
- Consider the clinical response to antibiotics and the results of the microbiological examination when deciding on the targeted antibiotic regimen [L2].
- For mild diabetic foot infections [L2]:
  - Start oral antibiotics with activity against gram-positive organisms.
  - Prolonged antibiotic treatment (>14 days) is not recommended for mild soft tissue infections.
- For moderate and severe diabetic foot infections <sup>16</sup> [L2]:
  - Start antibiotics with activity against gram-positive and gram-negative organisms.
  - Moderate infections: choose the route of administration based on the clinical situation and antibiotic choice.
  - Severe infections: begin treatment with intravenous antibiotics and then reassess based on the clinical situation <sup>16</sup> [L2].
- IDSA recommend that both primarily medical or surgical strategies can be considered for patients with diabetes and osteomyelitis but careful selection is required <sup>44</sup>:
  - Following radical resection:
    - If there is no infected tissue remaining, consider prescribing antibiotic therapy for a short duration only e.g. 2-5 days.
    - If there is persistent infected bone or necrosis, prolonged antibiotics are recommended e.g. 6 weeks.
- NICE recommend that patients with diabetes and osteomyelitis should be given prolonged antibiotic treatment (usually 6 weeks), taking into account local protocols <sup>16</sup> [L3].

### 8.5.2.3 Management of Charcot Arthropathy

#### Management of Charcot Arthropathy aims to <sup>17</sup>:

- Offload the foot.
- Treat bone disease.
- Prevent further foot fractures.

#### Offloading <sup>17</sup>:

- Can prevent further destruction.
- Is the most effective management strategy.
- The foot should be immobilised in an appropriate cast or similar device [L2].
- Where a cast is used:
  - The cast should be replaced after 3 days and checked once a week.
  - The cast should be changed frequently as the oedema subsides.
  - The patient should avoid weight-bearing on the affected foot.

- Remove the cast when the swelling has resolved, and the temperature of the affected foot is within 2°C of the contralateral foot.

Protective Weight Bearing <sup>17</sup> [L2]:

- Should be carried out after an active episode.
- Involves the use of weight-bearing devices, e.g.:
  - Prescription shoes, boots, or braces.

The evidence surrounding the use of pharmacological therapy for Charcot arthropathy is limited <sup>17</sup> , but bisphosphonates should be considered.

Surgery <sup>17</sup> [L2]:

- Surgery may be beneficial when the patient does not respond to offloading and immobilisation, and in the case of recalcitrant ulcers.
- There should be no difference between the initial management of acute neuropathic fractures and dislocations, and the management of other fractures.
- Exostectomy may be useful to relieve bony pressure that cannot be managed with orthotic and prosthetic means.
- Consider lengthening of the Achilles tendon or gastrocnemius tendon, in order to reduce forefoot pressure and improve the alignment of the ankle and hindfoot; or the midfoot and forefoot.
- Arthrodesis may be considered in patients with instability, pain, or recurrent ulcerations that fail non-operative treatment.
- In cases of severe Charcot foot of the ankle, consider surgical management as the primary treatment.

Monitor the effect of treatment Using Clinical Assessment <sup>16</sup>:

- Measure foot-skin temperature difference. Charcot arthropathy is likely to resolve when there is a sustained temperature difference of less than 2°C between both feet <sup>16</sup> [L2].
- Take serial radiographs. Charcot arthropathy is likely to resolve when radiographic changes show no further progression <sup>16</sup> [L3].

#### 8.5.2.4 Management of Peripheral Vascular Disease

Provide patients oral and written information about the condition including <sup>45</sup> [L2]:

- Disease severity and progression.
- Causes of symptoms.
- Risk of limb loss and cardiovascular events.
- Pain management.
- The key elements of risk factor management include:
  - Smoking cessation.
  - Diet and body weight optimisation.
  - Dyslipidaemia management.
  - Antiplatelet therapy.
  - Glycaemic control.
  - BP control.
- All appropriate treatment options, including the benefits and risks of each.
- Options available to them to support depression and anxiety.

Tailor information to the individual patient and ensure it is available at the time of diagnosis [R-GDG].

Patients should be under the care of a vascular surgical team for management of peripheral vascular disease [R-GDG].

## 9 Diabetic Neuropathy

### 9.1 Background

Diabetic neuropathy <sup>7</sup>:

- Is a set of clinical syndromes with distinct patterns of neurological signs and symptoms:
  - Disorders may affect proximal, distal, somatic and autonomic nerves.
- Is classified into the following types:
  - Distal symmetric polyneuropathy (DSPN).
  - Autonomic neuropathy.
  - Radiculoplexus neuropathy (diabetic amyotrophy).
  - Mononeuropathy.

Diabetic neuropathy affects around half of all patients with diabetes mellitus <sup>7</sup>. It is responsible for 50-75% of non-traumatic amputations and is the most common form of neuropathy in developed countries <sup>7</sup>. Neuropathic pain occurs in an estimated ~3-25% of patients with diabetes <sup>7,20</sup>. The aetiology of painful diabetic neuropathy is unclear but there is evidence suggesting that vitamin D deficiency and insufficiency may be associated with it (see details in *Section 9.2.5*) <sup>46</sup>.

The prevalence of diabetic peripheral neuropathy (DPN) and painful DPN among patients with T2DM is lower in Primary than in Secondary Healthcare (14.8% vs 23.9% and 18.1% vs 37.5%, respectively) in Qatar <sup>47,48</sup>. The prevalence of undiagnosed DPN is comparably high (79.5% in Primary and 82.3% in Secondary Healthcare). Undiagnosed pDPN is lower in Primary Healthcare compared with Secondary Healthcare (24.1% vs 71.5%).

DPN occurs more often in <sup>47</sup>:

- Older patients.
- Patients with extended diabetes duration.
- Patients with poor glycemic control.
- Patients with hyperlipidemia.
- Patients with hypertension.

Painful DPN occurs more often in <sup>47</sup>:

- Older patients.
- Patients with extended diabetes duration.
- Obese patients.
- Patients with reduced physical activity.

Risk factors for diabetic neuropathy <sup>7</sup>:

- Metabolic syndrome.
- Impaired fasting glucose.
- Impaired glucose tolerance.
- Chronic hyperglycaemia.
- The presence of ASCVD risk factors.
- Microalbuminuria.

## 9.2 Distal Symmetric Polyneuropathy

### 9.2.1 Clinical Presentation

Distal Neuropathies:

- Are characteristically symmetrical, with a glove and stocking distribution, including:
  - Numbness or decreased sensation.
  - Weakness.
  - Absent deep tendon reflexes.
- Length-dependent sensorimotor polyneuropathies.
- Develop alongside longstanding chronic hyperglycaemia and ASCVD risk factors.

Symptoms vary according to the class of sensory neurones involved <sup>2,7</sup>:

- Symptoms involving small fibres include:
  - Pain.
  - Dysesthesias (unpleasant burning and tingling sensations).
  - Usually occurs early and often without objective signs or electrophysiological evidence of nerve damage.
- Symptoms involving large fibres include:
  - Numbness.
  - Loss of protective sensation:
    - Indicates distal sensorimotor polyneuropathy.
    - Is a risk factor for diabetic foot ulceration.

### 9.2.2 Screening and Assessment

Screening in patients with T2DM, should take place <sup>18</sup>:

- At the time of initial diagnosis and annually thereafter.

Screening in patients with T1DM, should take place <sup>18</sup>:

- 5 years after initial diagnosis and annually thereafter.

Assessment should include <sup>2,19</sup>:

- A full history and a combination of at least two of the following:
  - 10 g monofilament testing (large fibre function and protective sensation).
  - At least one of the following tests:
    - Pinprick sensation (small fibre function).
    - Temperature discrimination (small fibre function).
    - Vibration sensation using a 128-Hz tuning fork (large fibre function).
- Screening for dysfunction and assessment of future complication risk.

Further specialist evaluation or referral to a neurologist is rarely needed except in situations where the clinical features are atypical, the diagnosis is unclear, or a different aetiology is suspected. Atypical features include motor greater than sensory neuropathy, rapid onset or an asymmetrical presentation.

Further specialist testing may include <sup>7</sup>:

- Neurophysiological tests e.g.:
  - Nerve conduction studies.
  - Electromyography.
- Corneal confocal microscopy may be used, if available, to detect small fibre neuropathy <sup>7</sup> [L2].

The differential diagnosis of distal symmetric polyneuropathy, may include <sup>2,7,18</sup>:

- Metabolic disease:
  - Thyroid disease.
  - Renal disease.
- Systemic disease:
  - Systemic or non-systemic vasculitis.
  - Paraproteinaemia
  - Amyloidosis.
- Infectious disease:
  - HIV.
  - Hepatitis B.
  - Lyme disease
- Chronic inflammatory demyelinating polyradiculoneuropathy.
- Toxins, e.g. alcohol.
- Neurotoxic medications, e.g. chemotherapy.
- Vitamin B12 deficiency.
  - Metformin-associated vitamin B12 deficiency may lead to neuropathy-like symptoms <sup>7</sup>.
- Malignancies:
  - Multiple myeloma.
  - Bronchogenic carcinoma.
- Inherited neuropathies.

### 9.2.3 Management of Diabetic Neuropathy

Assess and treat patients with the aim of <sup>2</sup>:

- Reducing the positive symptoms of pain related to painful distal symmetric polyneuropathy.
- To improve quality of life <sup>2</sup> [L3].

Although there are no disease modifying treatments to reverse diabetic neuropathy, it is speculated that the following treatment approaches may help <sup>2,7</sup>:

- Improve glycaemic control:
  - Insulin sensitising agents are more effective than insulin-providing agents <sup>20</sup>.
- Improve dyslipidaemia:
  - Particularly treatment of triglycerides with fibrates <sup>21</sup>.
- Treat with an ACE inhibitor and/or CCB <sup>22,23</sup>.

#### 9.2.3.1 Pain Management

Pain management:

- Consider one of the following drugs to control painful neuropathic symptoms <sup>18,24</sup>:
  - First-Line:
    - Pregabalin.
    - Duloxetine.
  - Second-Line:
    - Tricyclic antidepressants.
    - Gabapentin.
    - Venlafaxine.
    - Tramadol.
- Treatment considerations should include <sup>18,24</sup> [L1]:
  - If the initial choice is not tolerated, or is not effective, offer one of the other options.



- Review dosage titration, tolerability, and adverse effects when initiating or changing treatment.
- On treatment withdrawal or change, taper the withdrawal regimen to take into account any dosage and discontinuation symptoms.
- Combination therapy.
- When agreeing a pain management plan with the patient consider and discuss <sup>24</sup>:
  - Pain severity and impact on lifestyle and daily activities.
  - The underlying cause and deterioration of the condition.
  - Information on pharmacological therapy including:
    - Reasons for offering each therapy.
    - The benefits and risks of each treatment, including potential adverse effects.
    - Consideration of any physical or psychological problems.
    - Concurrent medications.
    - The importance of dosage titration and how it is done.
  - Coping strategies for pain.
- Perform regular reviews to assess and monitor the effectiveness of the treatment, including <sup>24</sup> [L2]:
  - Pain control:
    - Assess and record a pain score on a scale of 0-10 at each review.
  - Impact on lifestyle, participation, and daily living.
  - Physical and psychological wellbeing.
  - Adverse effects of medications and the continued need for treatment.

### 9.2.3.2 Non-Pharmacological Treatments

Management of peripheral neuropathies may also include <sup>7</sup>:

- Strength, gait, and balance training <sup>7</sup> [L2].
- Low-impact activities that emphasise muscular strength and coordination <sup>7</sup> [L2].
- Orthotics to treat and prevent foot deformities <sup>7</sup> [L2].
- Foot protection.
- Regular foot and shoe inspection.
- Prevention of heat injury.
- The use of emollient creams to moisturise dry skin to prevent cracking and infection.

### 9.2.4 Vitamin B12 Deficiency

Metformin-associated vitamin B12 deficiency <sup>7</sup> [L1]:

- May lead to neuropathy-like symptoms.
- Symptoms may be reversed using hydroxocobalamin supplementation.

### 9.2.5 Vitamin D Deficiency

Vitamin D deficiency and insufficiency may be associated with painful diabetic neuropathy <sup>46</sup>.

If vitamin D deficiency is suspected:

- Further evaluation should be carried out in accordance with the NCG on The Diagnosis and Management of Vitamin D Deficiency by MOPH <sup>49</sup>.
- Consider treatment with a single intramuscular dose of 600 000 IU of vitamin D <sup>50</sup> [L2, RGA] to improve patient's quality of life <sup>51</sup> [L2, RGA].

### 9.2.6 Referral to Neurology

Consider referral to a neurologist when there are atypical features or the diagnosis is unclear <sup>2</sup> [L2].

Consider referral to a Specialist Pain Service if <sup>24</sup>:

- The patient has severe pain despite recommended therapies.
- Their pain significantly limits their lifestyle, participation, or daily activities.
- Their underlying health condition has deteriorated.

## 9.3 Diabetic Autonomic Neuropathy

### 9.3.1 Clinical Presentations

Neuropathy	Symptoms
<b>Cardiac</b>	<p>Cardiac autonomic neuropathy <sup>2,7</sup>:</p> <ul style="list-style-type: none"> <li>• Is associated with mortality independent of other ASCVD risk factors.</li> <li>• May be used to predict cardiovascular risk.</li> <li>• May be completely asymptomatic to begin with, only presenting as decreased heart rate variability with deep breathing.</li> <li>• Symptoms include:               <ul style="list-style-type: none"> <li>○ Postural hypotension.</li> <li>○ Dizziness</li> <li>○ Fatigue.</li> <li>○ Exercise intolerance and bradycardia.</li> </ul> </li> <li>• Advanced disease may be associated with:               <ul style="list-style-type: none"> <li>○ Resting tachycardia (more than 100 bpm).</li> <li>○ Orthostatic hypotension:                   <ul style="list-style-type: none"> <li>▪ A fall in systolic BP by &gt;20 mmHg.</li> <li>▪ A fall in diastolic BP by &gt;10 mmHg.</li> <li>▪ Without an appropriate increase in heart rate.</li> </ul> </li> </ul> </li> </ul>
<b>Gastrointestinal</b>	<p>Gastrointestinal neuropathies <sup>2</sup>:</p> <ul style="list-style-type: none"> <li>• May involve any portion of the gastrointestinal tract.</li> <li>• May manifest as <sup>2,7</sup>:               <ul style="list-style-type: none"> <li>○ Oesophageal dysmotility.</li> <li>○ Gastroparesis.</li> <li>○ Early satiety.</li> <li>○ Nausea or vomiting.</li> <li>○ Bloating.</li> <li>○ Belching.</li> <li>○ Erratic glucose control</li> <li>○ Constipation or diarrhoea.</li> <li>○ Faecal incontinence.</li> <li>○ Abdominal pain.</li> </ul> </li> </ul>

Neuropathy	Symptoms
<b>Genitourinary</b>	Sexual dysfunction <sup>2,7</sup> : <ul style="list-style-type: none"> <li>• Men:               <ul style="list-style-type: none"> <li>○ Genitourinary disturbances in men may include erectile dysfunction, retrograde ejaculation.</li> </ul> </li> <li>• Women:               <ul style="list-style-type: none"> <li>○ Symptoms may include vaginal dryness.</li> </ul> </li> </ul> Bladder dysfunction <sup>7</sup> : <ul style="list-style-type: none"> <li>• Frequency and urgency.</li> <li>• Nocturia, urinary retention, incontinence.</li> </ul>
<b>Other Diabetic Autonomic Neuropathies</b>	Sudomotor dysfunction <sup>7</sup> : <ul style="list-style-type: none"> <li>• Anhidrosis or hyperhidrosis.</li> <li>• Heat intolerance.</li> <li>• Dry skin.</li> </ul> Pupillary dysfunction <sup>7</sup> : <ul style="list-style-type: none"> <li>• Visual blurring, impaired light adaption to ambient light, Argyll-Robertson pupil.</li> </ul> Visceral dysfunction <sup>7</sup> : <ul style="list-style-type: none"> <li>• Impaired visceral sensation, including silent MI and hypoglycaemia unawareness</li> </ul>

**Table 9.3.1:** Clinical Presentations of Diabetic Autonomic Neuropathy <sup>2,7</sup>.

### 9.3.2 Assessment and Screening

Assess for the signs and symptoms of autonomic neuropathy in patients with microvascular and neuropathic complications <sup>2</sup>:

- Screening for diabetic autonomic neuropathy in patients with T2DM <sup>2,18</sup>:
  - Should take place at the time of diagnosis.
  - Should take place at least annually thereafter.
- Screening for diabetic autonomic neuropathy in patients with T1DM <sup>2,18</sup>:
  - Should take place 5 years after initial diagnosis in all adults.

#### 9.3.2.1 Cardiac Neuropathy

Assessment should include <sup>2</sup>:

- Resting pulse assessment for tachycardia (heart rate >100bpm).
- Heart rate variability assessment with deep inspiration or Valsalva manoeuvre.
  - Do not perform Valsalva manoeuvre in patients with proliferative retinopathy <sup>7</sup> [L2].
- BP change from lying to standing position (orthostatic hypotension).

#### 9.3.2.2 Gastrointestinal Neuropathy

Gastrointestinal investigations may include <sup>7</sup> [L2]:

- Gastric emptying study.
- Barium study.
- Endoscopy.
- Manometry.
- Electrogastrogram.

### 9.3.2.3 Genitourinary Neuropathy

Evaluation of bladder function in diabetic patients may include <sup>2</sup> [L2]:

- Recurrent urinary tract infections.
- Pyelonephritis.
- Incontinence.
- Palpable bladder.
- Unexplained bladder-emptying problems <sup>3</sup>.

Consider referral to Urology (andrology) for specialist assessment of neurogenic bladder or erectile dysfunction and appropriate specialist investigation [R-GDG].

### 9.3.3 Management of Diabetic Neuropathy

Assess and treat patients with the aim of <sup>2,7</sup>:

- Reducing the symptoms of autonomic neuropathy (see following sections).
- To improve quality of life.
- Glycaemic control is important in preventing progression of diabetic neuropathy.

#### 9.3.3.1 Cardiac Autonomic Symptom Management

Orthostatic hypotension:

- The therapeutic goal when managing orthostatic hypotension is to minimise postural symptoms, not to restore normotension <sup>2</sup>.
- Non-pharmacological management <sup>2,3</sup>:
  - Maintaining adequate salt intake.
  - Avoiding the use of medications that may aggravate hypotension, e.g. tricyclic drugs and hypertensive drug treatments.
  - The use of compressive garments over the legs and abdomen.
- Pharmacological management may include <sup>7,52</sup>:
  - Midodrine.
  - Fludrocortisone <sup>52</sup>.

Resting tachycardia and exercise intolerance <sup>7</sup> [L2]:

- Graded supervised exercise.
- ACE inhibitors.
- Beta blockers.

Exercise bradycardia and exercise intolerance <sup>7</sup> [L2]:

- Graded supervised exercise.
- Dopaminergic agonists.

#### 9.3.3.2 Gastrointestinal Symptom Management

Consider stopping drugs with effects on gastrointestinal motility, such as opioids, anticholinergics, tricyclic antidepressants, GLP-1 receptor agonists and possibly DPP-4 inhibitors <sup>2</sup>.

Antiemetic/prokinetic treatments for vomiting caused by gastroparesis include <sup>2,3</sup> [L2]:

- Erythromycin:
  - Consider alternating use of erythromycin and metoclopramide.

- Metoclopramide <sup>2,3</sup> [L2]:
  - Chronic use should be avoided due to the risk of developing irreversible tardive dyskinesia.
  - Should only be used in patients with severe symptoms who are unresponsive to other therapies.
  - Should be used at the lowest dose and for the shortest duration possible.
  - Generally, should not be used for longer than 3 months.
  - Side effects should be closely monitored.
- Domperidone [1,4]:
  - Domperidone may be used at low doses of no more than 10mg three times a day.

Consider the following dietary modifications:

- A low-fibre diet <sup>2,7</sup> [L2].
- Frequent, small meals <sup>7</sup> [L2].

Constipation may be managed with the following <sup>7</sup> [L2]:

- High fibre diet.
- Bulking agents.
- Osmotic laxatives.
- Lubricating agents.

### 9.3.3.3 Genitourinary Symptom Management

Erectile dysfunction treatments include <sup>2,3,7</sup> [L2]:

- Phosphodiesterase-5 inhibitors.
- Intracorporeal or intraurethral prostaglandins.
- Vacuum devices.
- Penile prostheses.
- Psychological counselling.
- Education and support on contributory factors, e.g. cardiovascular disease and treatment options.
- At each annual review, offer patients the opportunity to discuss erectile dysfunction.

Consider using vaginal lubricants in patients with vaginal dryness <sup>7</sup> [L2].

Consider the following for the management of bladder dysfunction <sup>7</sup> [L2]:

- Bethanechol.
- Intermittent catheterisation.

## 9.4 Other Diabetic Neuropathies

Other diabetic neuropathy presentations include:

- Diabetic radiculoplexus neuropathy (diabetic amyotrophy) <sup>38,53,54</sup>:
  - Occurs in around 1% of patients with diabetes.
  - Classically presents with asymmetric (although may be symmetrical) proximal muscle weakness and pain of the lower limbs, with minimal or no sensory involvement. May also occur in the upper limb.
  - Important differentials include demyelinating neuropathy, spinal stenosis and pelvic malignancy.

- Refer patients with suspected diabetic radiculoplexus neuropathy to a neurologist for confirmation of diagnosis and further management as timely immunotherapy may be beneficial [R-GDG].
- Mononeuropathies:
  - The nerves most commonly affected are the median, ulnar, radial and common peroneal nerves <sup>38,53</sup>.
  - Usually due to compression/entrapment, but may also be due to intrinsic changes in the nerve <sup>55,56</sup>.
  - In general, management is the same as for non-diabetic patients <sup>38</sup>.

## 9.5 Referral to Specialist Clinics

Refer patients from primary care to the relevant speciality according to the nature of symptoms including [R-GDG]:

- Gastroenterology.
- Cardiology.
- Urology (andrology).

## 10 Key Considerations for Patient Preferences

Patient preferences refer to patient perspectives, beliefs, expectations, and goals for health and life, and to the steps employed by individuals in assessing the potential benefits, harms, costs, and limitations of the management options in relation to one another. Patients may have preferences when it comes to defining their problems, identifying the range of management options and selecting or ranking the outcomes used to compare these options.

It is important for healthcare professionals to develop an understanding of the patient as an individual and the unique way in which each person experiences a condition and its impact on their life.

The following recommendations are therefore made for physicians and other healthcare professionals regarding general principles of patient care in Qatar:

- **Respect Patients:** Treat patients with respect, kindness, dignity, courtesy and honesty. Ensure that the environment is conducive to discussion and that the patient's privacy is respected, particularly when discussing sensitive, personal issues. Ask the patient how they wish to be addressed and ensure that their choice is respected and used.
- **Maintain Confidentiality:** Respect the patient's right to confidentiality and avoid disclosing or sharing patients' information without their informed consent. In this context, students and anyone not directly involved in the delivery of care should first be introduced to the patient before starting consultations or meetings, and let the patient decide if they want them to stay.
- **Clarify Third-Party Involvement:** Clarify with the patient at the first point of contact whether and how they like their partner, family members or carers to be involved in key decisions about their care or management and review this regularly. If the patient agrees, share information with their partner, family members or carers.
- **Obtain Informed Consent:** Obtain and document informed consent from patients, in accordance with MOPH policy and guidance.
- **Encourage Shared Decision Making:** Ensure that patients are involved in decision making about their own care, or their dependent's care, and that factors that could impact the patient's participation in their own consultation and care including physical or learning disabilities, sight, speech or hearing impairments and problems with understanding, reading or speaking English are addressed.
- **Disclose Medical Errors:** Disclose errors when they occur and show empathy to patients.
- **Ensure Effective Communication:** Explore ways to improve communication including using pictures, symbols or involving an interpreter or family members. Avoid using medical jargon. Use words the patient will understand and confirm understanding by asking questions.
- **Ensure Continuity of Care:** Provide clear and timely sharing of patient information between healthcare professionals especially at the point of any transitions in care.

## 11 Performance Measures

A performance measure is given in the table below. Healthcare organisations are encouraged to monitor service performance using the indicator definition below <sup>57</sup>.

Ref	Numerator	Denominator
DCC01	The number in the denominator with a record of testing foot sensation using a 10g monofilament within the preceding 12 months.	Total number of adult diabetes patients seen at least twice in the last 12 months.

**Table 11.1:** Performance measure <sup>57</sup>.



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## Appendix: Detailed Description of the Literature Search

A systematic search for existing literature on chronic complications of diabetes was performed in the period July 10<sup>th</sup> – August 24<sup>th</sup>, 2020.

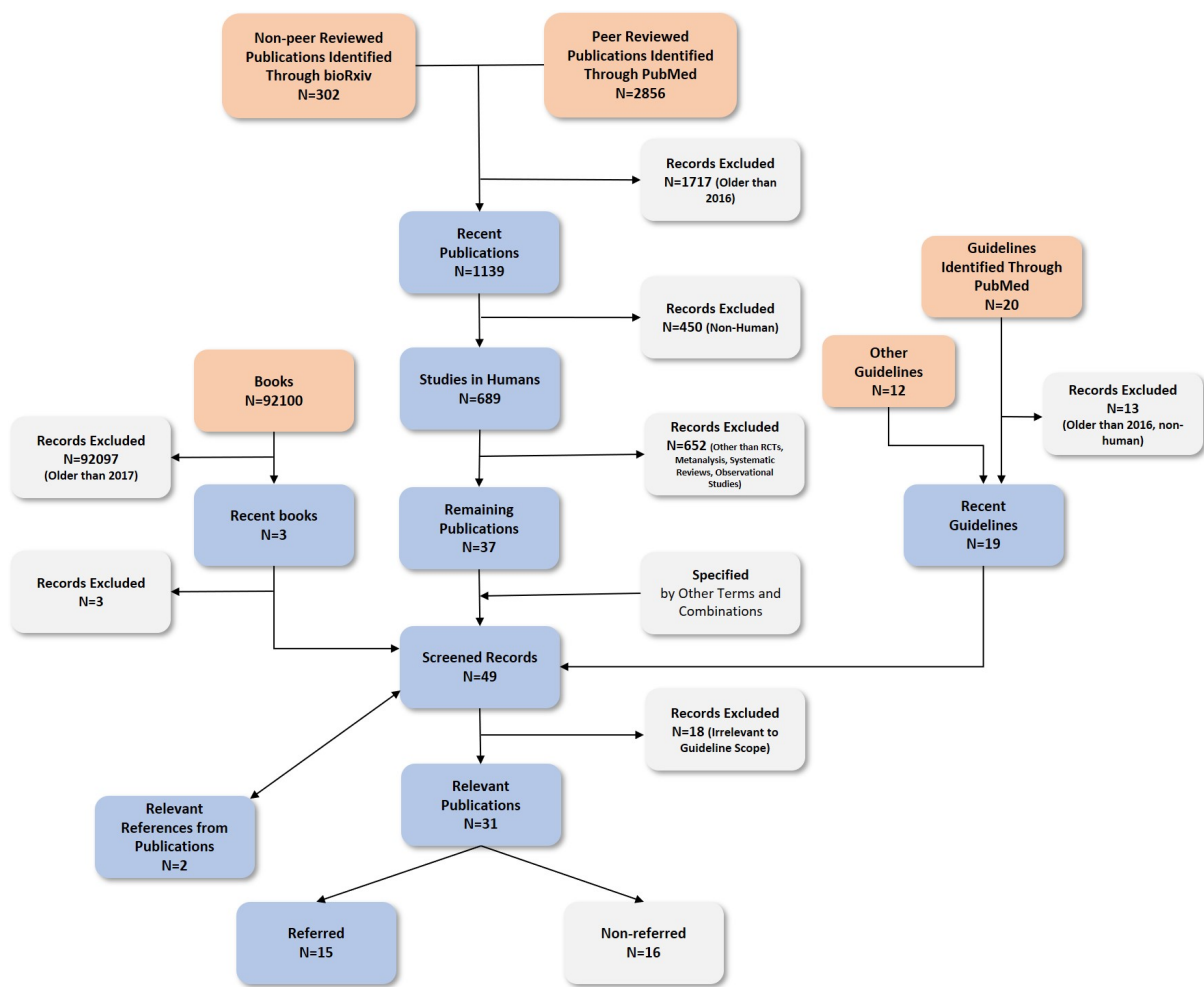
All existing references were evaluated and where necessary and applicable, the latest version of the specific manuscript was used to update the guideline and replace the older reference. The search for clinical practice guidelines on the management of the complications of diabetes was performed in the *PubMed* database and websites of relevant organisations and societies including the *UK NICE*, the *Royal College of Ophthalmologists*, the *Supreme Council of Health (Qatar)*, the *Scottish Intercollegiate Guidelines Network* and the *KIDGO*. The present guideline is primarily based on *UK NICE*, the *American Academy of Ophthalmology*, the *American Diabetes Association* and the *American Association for Clinical Endocrinologists* guidelines and is supplemented with other relevant studies.

Peer-reviewed scientific publications were found in *PubMed* and via *Google Scholar* Internet search engine. Non-peer reviewed studies were identified in *bioRxiv*. Books were checked on *Amazon* and via *Google* and *Google Scholar* search engines.

The included publications were identified using the terms “*diabetes complications*” and specified with the following terms in combinations:

*Guideline, complication, chronic, retinopathy, glucose, type 1, type 2, kidney disease, cardiovascular disease, diabetic foot, neuropathy, classification, prevalence, epidemiology, risk, presentation, examination, complication, investigation, diagnosis, management, referral, specialist, self-management, nutrition, smoking, exercise, immunization, psychology, glycaemic target, therapy, pharmacological, insulin, metformin, antiplatelet, hypoglycaemia, follow-up.*

*Figure A.1* on the next page demonstrates graphically the results of the search and application of exclusion criteria.



**Key:**

Orange box: Type of Publication

Blue box: Process

Grey box: Notes

**Fig A.1:** Literature search results and application of exclusion criteria.

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