ABSTRACT

Diabetes patients are at high risk of developing cardiovascular and renal complications. These conditions increase cardiovascular mortality as well as the development of end-stage renal disease. In this article, we will discuss the mechanisms behind the development of heart and renal disease in diabetic patients and how to evaluate these patients to aid in the early detection of these conditions and identify high-risk patients who may benefit from treatment with new glucose-lowering therapies.

Keywords: Diabetes, cardiovascular complications, diabetic nephropathy

Diabetes, heart disease and renal disease are common conditions that are associated with adverse health outcomes and reduced survival. Diabetes patients are at high risk of developing cardiovascular complications and/or renal dysfunction. Two out of three people with diabetes die from heart disease or stroke, and diabetes patients have twice the incidence of heart disease as the general population. Two in three new kidney failure cases were due to diabetes.1

Diabetes Mellitus (DM) is one of the classical risk factors for the development of endothelial dysfunction. These factors initiate a chronic inflammatory process that is accompanied by a loss of vasodilator and anti-thrombotic factors and an increase in vasoconstrictor and pro-thrombotic products, resulting in atherosclerotic plaque formation and rupture, and eventually adverse cardiovascular events.2

Besides atherosclerotic cardiovascular disease (ASCVD), DM is also associated with a higher risk of heart failure (HF). Up to 68 percent of DM patients without overt cardiac disease can have asymptomatic LV systolic and/or diastolic dysfunction.3 In fact, the American Heart Association heart failure guidelines have identified patients with risk factors for heart failure, including DM, as Stage A Heart Failure.4 People with diabetes may have heart failure (HF) with preserved ejection fraction (HFP EF) or with reduced ejection fraction (HFrEF). The risk of incident HF hospitalisation was two-fold higher in patients with diabetes compared with those without.5 HF in patients with diabetes is associated with an increased risk of death compared to DM patients without HF.6

Many mechanisms have been postulated for the development of diabetic cardiomyopathy.7 Advanced glycation end products upregulate the hypertrophy-associated genes in cardiomyocytes via the activation of dendritic cells and may result in the hypertrophic and fibrotic phenotype in DM subjects.8 Diabetes-related alterations in the expressions of some calcium associated proteins may lead to progressive intracellular decay of calcium and in the development of diabetic cardiomyopathy.9 Hyperinsulinaemia also impairs phosphatidylinositol 3-kinases pathway and can precipitate myocardial dysfunction.10 Furthermore, accumulation of reactive oxygen species affects the coronary circulation and causes myocardial hypertrophy and fibrosis.11

Nephropathy is one of the most common microvascular complications of diabetes. Chronic kidney disease (CKD) typically develops after diabetes duration of ten years in type 1 diabetes, but as many as seven percent of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes.12 In the United Kingdom Prospective Diabetes Study (UKPDS), the incidence of microalbuminuria was two percent per year in patients with type 2 diabetes, and the ten-year prevalence after diagnosis was 25 percent.13 Nearly half of individuals with diabetes will develop CKD.14

Diabetic kidney disease is diagnosed based on the presence of albuminuria and/or reduced estimated glomerular filtration rate (eGFR) in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, albuminuria without gross haematuria, and gradually progressive loss of eGFR. However, reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes.15, 16 High albuminuria and low eGFR are independent risk factors for cardiovascular and renal events among patients with DM.17

It is important to assess the risk of acute and chronic diabetes complications and treatment during initial and follow-up visits.18 Amongst these include the risk of ASCVD and HF and CKD staging. Cardiovascular risk factors should be assessed at least once a year in all patients with DM. These risk factors include obesity/overweight, hypertension, dyslipidaemia, smoking, a family history of premature coronary disease, chronic kidney disease, and the presence of albuminuria. These risk factors should be treated as per respective guidelines. Assessment of patients for cardiovascular and renal complications include19, 20:

1. Cardiovascular risk assessment

   a. Patients should be risk-stratified according to their 10-year ASCVD risk. Decisions on whether to commence
treatment for each of the cardiovascular risk factor will be guided by the 10-year ASCVD risk.

2. Blood pressure assessment
   a. Blood pressure (BP) should be measured at every clinic visit. Home BP self-monitoring and 24 hours ambulatory BP monitoring may be useful to assess for white coat hypertension or masked hypertension.
   b. For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year ASCVD risk <15 percent), blood pressure target should be <140/80 mmHg.21
   c. The target blood pressure of <130/80 mmHg may be appropriate for individuals with diabetes and hypertension at higher cardiovascular risk (existing ASCVD or 10-year ASCVD risk ≥15 percent or diabetic CKD).

3. Lipid profile assessment
   a. Intensify lifestyle therapy and optimise glycaemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low high-density lipoprotein (HDL) cholesterol (<40 mg/dL [1.0 mmol/L]) for men, <50 mg/dL [1.3 mmol/L] for women).
   b. In adults not taking statins or other lipid-lowering therapy, a lipid profile should be assessed at the time of diabetes diagnosis, at initial medical evaluation, and every five years thereafter if under the age of 40 years, or more frequently if indicated.
   c. Obtain a lipid profile at the initiation of statins or other lipid-lowering therapy, 4 to 12 weeks after initiation or a change in dose, and annually thereafter.

4. Albuminuria and Estimated Glomerular Filtration Rate
   a. Urinary albumin-to-creatinine ratio (UACR) can be performed to assess for albuminuria. High urinary albumin excretion is defined as ≥30 mg/g Cr. Because of high biological variability of more than 20 percent between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have high or very high albuminuria.
   b. Estimated Glomerular Filtration Rate (eGFR) should be calculated from serum creatinine using a validated formula. An eGFR persistently less than 60 mL/min/1.73 m² is considered abnormal.
   c. Urinary albumin and eGFR should be assessed at least annually in patients with type 1 diabetes with a duration of ≥five years and in all patients with type 2 diabetes at the time of diagnosis. Patients with urinary albumin >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m² should be monitored twice annually to guide therapy.

5. Cardiac Testing
   a. The routine screening of asymptomatic patients with cardiac tests is not recommended.22 Previous randomised studies have not demonstrated improved cardiac outcomes with the routine screening of asymptomatic DM patients with routine screening, including coronary CT and myocardial perfusion scans.23, 24, 25 Therefore, indiscriminate screening is not considered cost-effective in DM patients.
   b. Measurement of coronary artery calcium may be considered for cardiovascular risk assessment to guide the decision on commencing aspirin or statin therapy.26
   c. DM patients who should be considered for advanced cardiac testing include those with 1) typical or atypical cardiac symptoms and/or 2) an abnormal resting electrocardiogram (ECG).

Identifying patients with cardiovascular and renal complications is an important first step in the risk stratification of DM patients not just in prompting early intervention for these conditions but also serves to guide the choice of DM therapy. Newer DM pharmacotherapies like SGLT-2 inhibitors or GLP-1 receptor agonists that have been shown to reduce adverse cardiovascular and renal outcomes in these high-risk patients are recommended as first-line DM treatment in international guidelines.27

In summary, there is a high incidence of cardiorenal complications in DM patients. Regular assessment and early detection of these conditions help identify high-risk patients who may be suitable for intervention with new glucose-lowering therapies.

REFERENCES


LEARNING POINTS

- Diabetes is associated with a high risk of cardiorenal complications which are associated with adverse cardiovascular and renal outcomes.
- Besides atherosclerotic cardiovascular disease, diabetes is also associated with heart failure from diabetic cardiomyopathy.
- Albuminuria and reduced glomerular filtration rate are independent risk factors for cardiovascular and renal events among patients with diabetes.