Unit No. I

### ASSESSMENT OF THE TYPE 2 DIABETES PATIENT AT RISK OF CARDIO-RENAL COMPLICATIONS

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#### 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.<sup>1</sup>

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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup> People with diabetes may have heart failure (HF) with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). The risk of incident HF hospitalisation was two-fold higher in patients with diabetes

LIM CHOON PIN Cardiologist Mount Elizabeth Hospitals compared with those without.  $^5~{\rm HF}$  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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> Hyperinsulinaemia also impairs phosphatidylinositol 3-kinases pathway and can precipitate myocardial dysfunction.<sup>10</sup> Furthermore, accumulation of reactive oxygen species affects the coronary circulation and causes myocardial hypertrophy and fibrosis.<sup>11</sup>

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.<sup>12</sup> 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.<sup>13</sup> Nearly half of individuals with diabetes will develop CKD.<sup>14</sup>

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.<sup>15, 16</sup> High albuminuria and low eGFR are independent risk factors for cardiovascular and renal events among patients with DM. <sup>17</sup>

It is important to assess the risk of acute and chronic diabetes complications and treatment during initial and follow-up visits.<sup>18</sup> 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 include<sup>19, 20</sup>:

#### 1. Cardiovascular risk assessment

a. Patients should be risk-stratified according to their 10year 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.<sup>21</sup>
- 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.
- 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 m<sup>2</sup> 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</p>

mL/min/1.73 m<sup>2</sup> should be monitored twice annually to guide therapy.

# 5. Cardiac Testing

- a. The routine screening of asymptomatic patients with cardiac tests is not recommended.<sup>22</sup> 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.<sup>23, 24, 25</sup> 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.<sup>26</sup>
- 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 and are recommended as first-line DM treatment in international guidelines.<sup>27</sup>

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

- National Registry of Diseases Office. Information Paper on Diabetes in Singapore [Internet]. Singapore: National Registry of Diseases Office; 2016 [updated 2016 Nov 14; cited 2020 July 14]. Available from: https:// www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/ diabetes-info-paper-v6.pdf?sfvrsn=0.
- Widlansky ME, Gokce N, Keaney JF, Vita JA. The clinical implications of endothelial dysfunction. Journal of the American College of Cardiology. 2003 Oct 1;42(7):1149-60.
- Faden G, Faganello G, De Feo S, Berlinghieri N, Tarantini L, Di Lenarda A, Faggiano P, Cioffi G. The increasing detection of asymptomatic left ventricular dysfunction in patients with type 2 diabetes mellitus without overt cardiac disease: data from the SHORTWAVE study. Diabetes research and clinical practice. 2013 Sep 1;101(3):309-16.
- 4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Oct 15;62(16):e147-239.
- McAllister DA, Read SH, Kerssens J, Livingstone S, McGurnaghan S, Jhund P, Petrie J, Sattar N, Fischbacher C, Kristensen SL, McMurray J. Incidence of hospitalization for heart failure and case-fatality among

3.25 million people with and without diabetes mellitus. Circulation. 2018 Dec 11;138(24):2774-86.

- Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes care. 2004 Mar 1;27(3):699-703.
- 7. Tousoulis D, Oikonomou E, Siasos G, Stefanadis C. Diabetes mellitus and heart failure. European Cardiology Review. 2014 Jul;9(1):37.
- Cao W, Chen J, Chen Y, Chen X, Liu P.Advanced glycation end products promote heart failure through inducing the immune maturation of dendritic cells. Applied biochemistry and biotechnology. 2014 Apr 1;172(8):4062-77.
- Zhao SM, Wang YL, Guo CY, Chen JL, Wu YQ. Progressive decay of Ca 2+ homeostasis in the development of diabetic cardiomyopathy. Cardiovascular diabetology. 2014 Dec 1;13(1):75.
- Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. Circulation research. 2006 Mar 17;98(5):596-605.
- 11.Clark RJ, McDonough PM, Swanson E, Trost SU, Suzuki M, Fukuda M, Dillmann WH. Diabetes and the accompanying hyperglycemia impairs cardiomyocyte calcium cycling through increased nuclear O-GlcNAcylation. Journal of biological chemistry. 2003 Nov 7;278(45):44230-7.
- 12. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clinical diabetes. 2008 Apr 1;26(2):77-82.
- 13.Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes care. 2005 Jan 1;28(1):164-76.
- 14. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, De Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ. Diabetic kidney disease: a report from an ADA Consensus Conference. American journal of kidney diseases. 2014 Oct 1;64(4):510-33.
- I5.Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. Jama. 2003 Jun 25;289(24):3273-7.
- 16. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, De Boer IH, Zinman B, Lachin J. Development and progression of renal insufficiency with and without albuminuria in adults with type I diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes care. 2010 Jul 1;33(7):1536-43.
- 17. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M. Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with

and without diabetes: A meta-analysis. Lancet. 2012;380(9854):1662-73. 18. American Diabetes Association. 16. Diabetes Advocacy: Standards

- of Medical Care in Diabetes—2019. Diabetes Care. 2020 Jan 1;43(Supplement 1):S203-4.
- 19. American Diabetes Association. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019 Jan 1;42(Supplement 1):S103-23.
- 20. American Diabetes Association. Microvascular complications and foot care: standards of medical care in diabetes—2019. Diabetes Care. 2019 Jan 1;42(Supplement 1):S124-38.
- 21. Ministry of Health Singapore. MOH Clinical Practice Guidelines 1/2017 on Hypertension [Internet]. Singapore: Ministry of Health; 2017 [updated 2017 Nov; cited 2020 July 14] Available from: https:// www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg\_hypertensionbooklet---nov-2017.pdf
- 22. Bax JJ,Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. Diabetes care. 2007 Oct 1;30(10):2729-36.
- 23. Muhlestein JB, Lappé DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL, Vavere AL. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. Jama. 2014 Dec 3;312(21):2234-43.
- 24. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR. Optimal medical therapy with or without PCI for stable coronary disease. New England Journal of Medicine. 2007 Apr 12;356(15):1503-16.
- 25. Wackers FJ, Chyun DA, Young LH, et al. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care*. 2007;30(11):2892-2898. doi:10.2337/dc07-1250.
- 26. Elkeles RS, Godsland IF, Feher MD, Rubens MB, Roughton M, Nugara F, Humphries SE, RichmondW, Flather MD. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. European heart journal. 2008 Sep 1;29(18):2244-51.
- 27. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). European heart journal. 2020 Jan 7;41(2):255-323.

#### 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.