Unit No. 4

CAPTURING AND EVALUATING COMPLICATIONS IN TYPE 2 DIABETES

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ABSTRACT

The goal of Type 2 diabetes management is to prevent and delay diabetes-related micro- and macro-vascular complications. Unfortunately, Type 2 diabetes may remain undiagnosed for years before presentation, allowing the onset of diabetes-related complications to occur even before diabetes diagnosis. Then there is the heterogeneity of Type 2 diabetes – there are thought to be subtypes within Type 2 diabetes which have different disease progression rates and risk of complications. Additionally, there is the present-day concept that the concept of Type 2 diabetes as a coronary heart risk equivalent is overly simplistic as not all patients with diabetes are at the same cardiovascular risk. Instead, individual patients will need to be risk-stratified for appropriate interventions. Despite these conundrums, protocols should be in place for early and regular complication screening, together with proactive and holistic management of diabetes mellitus. This article seeks to remind readers of what is necessary.

INTRODUCTION

The goal of Type 2 diabetes management is to prevent and delay micro-vascular (retinopathy, nephropathy, and neuropathy) and macro-vascular complications (cardiovascular disease), which individually and collectively cause significant morbidity in the lives of persons living with diabetes and ultimately premature mortality. Achieving this is not easy. Holistic management for diabetes involves implementing lifestyle measures – medical nutrition therapy, physical activity and exercise, smoking cessation, and obesity management, which themselves are difficult to sustain; polypharmacy to achieve target-goal for blood glucose, lipid parameters, and blood pressure; counselling on self-management skills, which may include self-monitoring of

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blood glucose; employing technology like flash/continuous glucose monitoring and diabetes management apps; and home blood pressure monitoring. All these would best be achieved with access to a diabetes-care team comprising the doctor, nurse-educator, dietitian, and psychologist. Diabetes management would be otherwise simple if the complications could be predicted and effectively prevented, or their progression slowed with therapy. Unfortunately, this proves difficult in clinical practice.

Some of the reasons are as follows.

1. Type 2 diabetes may remain undiagnosed for years before presentation, leading to development in complications and their presence at diagnosis. In the United Kingdom Prospective Diabetes Study (UKPDS) consisting newly diagnosed Type 2 diabetes patients, which started recruiting in the 1970s, there was already a two percent prevalence of Nephropathy, 10 percent of Neuropathy, and 36 percent of Retinopathy at outset. The knowledge gleaned from the UKPDS and other studies translating into public health policies would have led to increased disease awareness and earlier diabetes diagnosis. However, in the more recent Verona Diabetes Study,[1] also of newly diagnosed Type 2 diabetes patients, 50 percent had microvascular and/or macrovascular complications on recruitment – 21 percent had Nephropathy, 21 percent had Neuropathy, and 4.9 percent had Retinopathy.

2. Dysglycaemia is a continuum and though the diagnosis of diabetes is predicated on certain glycaemic thresholds (fasting plasma glucose of 7 mmol/l or more, random or post-glucose challenge of 11.1 mmol/l or more, and Hba1c of seven percent or more), complications may already exist below these thresholds. For example, diabetes retinopathy was found in eight percent of pre-diabetic subjects in the Diabetes Prevention Programme[2] cohort. Cardiovascular risk increased in the pre-diabetes states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) such that one-third of patients presenting with an acute myocardial infarction were found to have new-onset diabetes.[3]

3. The complications themselves may exist as a continuum, and their diagnosis predicated on current diagnostic techniques. For example, the earliest detection of diabetic retinopathy on retinal photo screening or opthalmoscopy is the presence of micro-aneurysms. However, an even earlier diagnosis of fundal venous abnormalities detected by more sophisticated techniques can be made. Peripheral neuropathy can be elicited clinically by bedside methods, but earlier detection can be made with nerve conduction tests. Artherosclerotic Cardiovascular Disease (ASCVD) itself is a continuum

and some have dismissed the classification of primary and secondary prevention in the context of diabetes in favour of cardiovascular risk levels of moderate, high, and very high.

4. Type 2 diabetes is increasingly perceived as being a heterogenous condition. In a recent suggested reclassification of diabetes in a Swedish cohort,[4] five clusters or subsets could be defined, each with different disease progression and risk of complications. Excluding autoimmune Type 1 diabetes, the current Type 2 diabetes categorisation could be sub-divided into 1) Severe Insulin-deficient Diabetes (SIDD) with the greatest risk of retinopathy, 2) Severe Insulin-Resistant Diabetes (SIRD) with the greatest risk of nephropathy, 3) Mild obesity-related diabetes (MOD), and 4) Mild age-related diabetes. A similar reclassification was done for Type 2 diabetes in Asian-Indians[5]; four phenotypic clusters were identified: Severe Insulin-deficient Diabetes (SIDD); Insulin-Resistant Obese Diabetes (IROD); Combined Insulin Resistant and Deficient Diabetes (CIRDD); and Mild age-related Diabetes (MARD). Both the SIDD and CIRDD clusters had higher risks for retinopathy. There is also an Asian phenotype that distinguishes Type 2 diabetes in this part of the world from the west. Some of its features are obesity at a lower body mass index, lower pancreatic secretory reserve, younger disease onset, greater predilection for renal failure, and stroke complications.

5. Microvascular and macro-vascular complications are inter-related. The presence of one micro-vascular complication, e.g., neuropathy can predict CV disease, nephropathy, and retinopathy as well. The presence of microalbuminuria is an indicator of widespread endothelial damage and confers an increased cardiovascular risk when present. Severe retinopathy predicts cardiovascular mortality.

6. There are multiple determinants for each complication. For retinopathy, though hyperglycaemia is the strongest predictor, duration of diabetes, hypertension, dyslipidaemia, insulin deficiency, and genetic factors also contribute to its presence, which would explain why a person with long-standing, poorly controlled diabetes could avoid retinopathy, while a person with better control and shorter diabetes duration could develop retinopathy earlier.

SCREENING FOR COMPLICATIONS

Despite these issues, it is still important to have protocols in place for early detection and surveillance on diabetes-related complications.

Upon diagnosis of Type 2 diabetes, history and physical examination should additionally elucidate the presence of diabetes-related complications.

RETINOPATHY

The retina is the most glucose-sensitive target tissue. The earliest clinical sign of retinopathy on direct ophthalmoscopy is the presence of micro-aneurysms, which can serve as biomarkers of retinopathy progression. Direct ophthalmoscopy and retinal photography remain the screening methods for the primary-care physician. If dilatation of the pupils is required, care should be made to exclude glaucoma. Subsequently, this should be done annually. Retinal photography is preferred and available by community providers, for example, Diabetes Singapore. Direct ophthalmoscopy by an inexperienced physician has a limited field of view in poorly dilating pupils and in the presence of cataracts; it also lacks a hard/softcopy documentation. Referral to the opthalmologist should occur when there is macular edema, moderate non-proliferative retinopathy and more severe grades, an unexplained drop in visual acuity, or other unexplained eye findings.

NEPHROPATHY

The classical phenotype of diabetic kidney disease (DKD) goes through the stages of progressively worsening albuminuria (from micro- to macro-), then deteriorating eGFR, and finally to End Stage Renal Failure. However, there are alternative DKD phenotypes characterised by:

i.   albuminuria regression;

ii. a rapid decline in eGFR; and

iii. non-proteinuric and non-albuminuric DKD7.

Measurement of serum creatinine as part of a renal profile should be done and estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPA) formula. Additionally, urine should be checked for proteinuria and/or albuminuria with a urine FEME and urine albumin-creatinine ratio (ACR). With these parameters, chronic kidney disease if present can be staged and stratified for increased risk of progression, morbidity, and mortality (Table 1).[6] Low- and moderate-risk patients can be renally monitored annually, high-risk patients twice yearly, and very high-risk patients 3-4 times a year.

Table 1: Chronic Kidney Disease Risk Categories – for progression, morbidity, and mortality.

			Persistent albuminuria categories		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
GFR categories (ml/min/1.73m²)			<30 mg/g <3 mg/mmol	30-300 mg/g 3-40 g/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90	**LOW**	**MODERATE**	**HIGH**
G2	Mildly decreased	60-89	**LOW**	**MODERATE**	**HIGH**
G3a	Mildly to moderately decreased	45-59	**MODERATE**	**HIGH**	**VERY HIGH**
G3b	Moderately to severely decreased	39-44	**HIGH**	**VERY HIGH**	**VERY HIGH**
G4	Severely decreased	15-29	**VERY HIGH**	**VERY HIGH**	**VERY HIGH**
G5	Kidney failure	<15	**VERY HIGH**	**VERY HIGH**	**VERY HIGH**

Referral to a nephrologist can be made when there is uncertainty about the aetiology of kidney disease, when there is difficulty in management, when it is beyond the capability of the managing physician, when there is rapid decline of eGFR (>5 ml/min/1.73 m² per year), or when there is advanced kidney disease.

PERIPHERAL NEUROPATHY AND PERIPHERAL VASCULAR DISEASE – THE AT-RISK FOOT

The diabetic foot is the most neglected aspect of diabetes complication screening despite the fact that no sophisticated instruments or tools are required. However, time and patience are required as this entails a complete foot examination elucidating colour and the health of skin and nails, foot deformities, calluses, pulses, capillary return, testing for pain, vibration and proprioception, tendon reflexes, and 10 gram monofilament testing. Alternatively, patients can be sent to community podiatry services run by trained nurses or podiatrists, e.g., Diabetes Singapore. The at-risk foot should firstly be identified, then managed with good metabolic control, patient education, and advice on footwear with access to a multi-disciplinary foot-care team.

Feet examination should be performed at least annually, with more frequent attention paid to feet at high risk for ulceration and amputation.

AUTONOMIC NEUROPATHY

In the presence of peripheral neuropathy, autonomic neuropathy should not be forgotten. Presentation could be subtle and diverse – gastrointestinal disturbance (bloating, diarrhoea), erectile dysfunction, postural giddiness, palpitations, hypoglycaemic unawareness. Signs of resting tachycardia (more than 100 bpm) and orthostatic hypotension may suggest autonomic neuropathy but other causes should be first excluded. Cardiac autonomic neuropathy (CAN) predicts cardiovascular disease, cardiac failure, and sudden death.

CARDIOVASCULAR RISK ASSESSMENT

Screening for asymptomatic coronary artery disease in diabetes remains controversial as benefit for this has not been shown. However, a variety of risk assessment tools are available – resting ECG, carotid or femoral ultrasound for plaque detection, coronary calcium score, ankle-brachial index, CT coronary angiography, or functional imaging.

There has been renewed interest in heart failure in diabetes as it gains dominance even as we are now better able to reduce death from ASCVD and stroke, as well as with the trial-evidence of "heart failure" benefits from using SGLT-2 inhibitors within and outside the realm of diabetes. Heart failure may be sub-clinical and unrecognised in diabetes patients, and again may antedate Type 2 diabetes diagnosis. Heart failure screening for high and very high cardiovascular risk diabetes patients may soon be in guidelines as data emerge on the use of clinical risk scores (incorporating a past history of heart failure, atrial fibrillation, coronary artery disease eGFR and urine albuminuria),[8] or a panel of biomarkers (troponin-T, N-Terminal (NT)-proB-type Natriuretic Peptide (BNP), highly-sensitive C-reactive protein (hsCRP), and Left Ventricular Hypertrophy on ECG)[9] to predict those at risk for developing heart failure so as to guide choice of therapy with SGLT-2 inhibitors.

Type 2 diabetes had previously been regarded as a cardiovascular-risk equivalent, meaning that a person with Type 2 diabetes, even without known cardiovascular disease, had the same cardiovascular risk of events and mortality as compared to a non-diabetic individual with a previous cardiovascular event. Together with this were the concepts of primary prevention (to prevent a first cardiovascular event) and secondary prevention (to reduce the future impact after having the event). This dichotomy is now found to not be entirely true – there is heterogeneity of cardiovascular risk in Type 2 diabetes, cardiovascular disease is a continuum, and there is no single point of intervention.

This has led to the concept of cardiovascular risk categories in diabetes (Table 2). For example, in the European Society of Cardiology guidelines,[10] the lowest category of young diabetes patients (age <50 for Type 2 and age <35 for Type 1) with diabetes duration of <10 years, with no target organ damage and no other cardiovascular risk factors, are already regarded as being of MODERATE cardiovascular risk (i.e., 10-year risk of cardiovascular death is <5 percent). Those with diabetes duration of 10 years or more with an additional cardiovascular risk factor (age, hypertension, dyslipidaemia, smoking, or obesity) are regarded as HIGH risk (10-year risk of cardiovascular death between 5 and 10 percent) and diabetes with either established cardiovascular disease OR other target organ damage (retinopathy, proteinuria, renal impairment with eGFR <30 ml/min/1.73 m^2, left ventricular hypertrophy) OR three or more major risk factors OR long duration Type 1 of more than 20 years are regarded as VERY HIGH risk (10-year risk of cardiovascular death is >10 percent).

Table 2: Cardiovascular Risk Categories in Diabetes patients

VERY HIGH RISK	Patients with Diabetes and established Cardiovascular Disease or other target organ damage or ≥3 major risk factors or early onset Type 1 diabetes of >20 years
HIGH RISK	Patients with Diabetes ≥10 years and 1 other risk factor without target organ damage
MODERATE RISK	Young Diabetes patients (Type 1 age <35, Type 2 age <50) with diabetes duration <10 years without target organ damage

The American Association of Clinical Endocrinologists (AACE)[11] has counterpart categories classifying as HIGH, VERY HIGH, and EXTREME risk respectively. Patients at initial diagnosis should be cardiovascular-risk stratified and this should be reviewed regularly during follow-up. The cardiovascular-risk stratification has implications in initiation of pharmaco-therapy with Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors and Glucagon-like Peptide-1 (GLP-1) receptor agonists, as well as treatment goals for lipid parameters.

In a recent multi-national, non-interventional, cross-sectional study with the acronym CAPTURE,[12] it was found that one in three persons with Type 2 diabetes had cardiovascular disease but less than one in four were on glucose-lowering agents with proven cardiovascular benefit (SGLT-2 inhibitors and GLP-1 receptor agonists), and this proportion was similar to those without cardiovascular disease. In comparison, almost 90 percent of those with cardiovascular disease were taking cardiovascular medication. In a separate exploratory analysis of high cardiovascular risk diabetes patients, again less than one in four were on glucose-lowering agents with proven cardiovascular benefit.

The authors concluded that there remains potential for reducing the excess cardiovascular risk by further evidence-based interventions.

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LEARNING POINTS

- **Effective management of Type 2 diabetes aims not only to relieve symptoms of hyperglycaemia but also to prevent and treat early micro- and macro-vascular complications so as to reduce the morbidity and early mortality associated with this condition.**

- **A surveillance programme to screen and early detect diabetes-related complications should be in place for all diabetes patients in the outpatient setting.**

- **By effectively detecting the onset of complications early and/or identifying at-risk patients, therapies and measures can be put in place to prevent or slow down the progression of these complications.**