UNIT NO. 3

COMPLICATIONS OF DIABETES MELLITUS: PREVENTION IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Type 2 Diabetes Mellitus is a complex disorder which has many associated comorbidities besides hyperglycaemia. Micro- and macrovascular complications develop as a result of poor risk factor control and contribute to the disability, reduced quality of life and reduced life expectancy associated with the disease. Intensive glucose control and, more importantly, comprehensive care involving treatment of all modifiable cardiovascular risk factors over a sustained period decreases the risk of morbidity and mortality especially in people newly diagnosed with Type 2 Diabetes Mellitus. The need to recognise subgroups of people with diabetes with increased risk of complications and the importance of individualised treatment are also discussed. Early intensive treatment and control of risk factors provides the opportunity for greatest accrual of benefit over the longer term.

Type 2 Diabetes Mellitus; Prevention, Glycaemic Control; Microvascular Complications; Macrovascular Complications; Cardiovascular Disease; Young Onset Type 2 Diabetes; Multifactorial Intervention; SGLT2 inhibitors and GLP-1 agonists.

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ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
DKA	Diabetic ketoacidosis
ESRD	End-stage renal disease
GLP-1	Glucagon-like peptide-1
HHS	Hyperosmolar hyperglycaemic state
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results
SGLT2	Sodium–glucose cotransporter-2
SMBG	Self-monitoring of blood glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
YLD	Years lost to disability

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INTRODUCTION

The prevalence of diabetes in Singapore rose from 8.2 percent in 2004 to 11.3 percent in 2010 and has been projected to increase to 15 percent by 2050 if this issue is left unmanaged.[1–3]

T2DM is a complex disorder often featuring adiposity, hypertension, dyslipidaemia and increased blood platelet aggregation in addition to hyperglycaemia, giving rise to an increased risk of micro- and macrovascular damage, which includes nephropathy, retinopathy, neuropathy, ischaemic heart disease, stroke and peripheral arterial disease. These complications result in disability, reduced quality of life and reduced life expectancy.

In the 2010 Singapore Burden of Disease study, diabetes was found to be the second largest contributor to overall YLD and was the leading specific cause for DALY in persons between 15 to 64 years of age.[3] In 2013, The Institute for Health Metrics and Evaluation[4] showed that although the life expectancy for Singaporeans has increased over the years, DALY for people with diabetes has increased more than that for the general population and YLD was contributing to a greater proportion of the DALY. This implies that modern medical care could be helping diabetes patients live longer but with more years of complications and disability.

Diabetes places a large economic burden on our healthcare system with a cost of US$787 million in 2010. This has been projected to increase to US$1867 million in 2050.[5] In addition to the healthcare cost from a system perspective, the personal out-of-pocket spending for people living with diabetes is also significant. In America, more personal healthcare resources are estimated to be spent on diabetes than any other medical condition.[6]

The morbidity and mortality of T2DM is contributed to strongly by the presence of associated comorbidities such as obesity, hypertension, and dyslipidaemia. Other disorders, which may be present at diagnosis or may develop over time, include sleep apnoea, fatty liver disease, periodontal disease, cognitive impairment, depression, anxiety, fractures, and certain cancers possibly related to the coincident obesity.[7–10]

There are well-written international standards of care and local clinical practice guidelines on the management of diabetic complications.[11–13] The management of diabetes covers many

aspects of care, including prevention, screening, classification, glycaemic control, prevention of complications and the management of established complications. This article is focused on the important aspects of prevention of DM complications in people newly diagnosed with T2DM.

CLASSIFICATION OF DIABETES COMPLICATIONS

Diabetes complications can be classified broadly as acute metabolic or chronic microvascular and macrovascular (atherosclerosis) complications.

In people with diabetes, hyperglycaemia occurs when insulin levels are inadequate to maintain normal blood glucose concentrations. If severe hyperglycaemia is not identified and treated, either DKA or HHS may develop. DKA and HHS differ in magnitude of dehydration and degree of ketosis and acidosis. Although DKA is more common in patients with type 1 diabetes, it can also occur in patients with type 2 disease. The management of these acute metabolic crises will not be discussed further in this article.

Table 1: Summary of the chronic diabetes complications which may develop with progressively worsening stages of dysglycaemia

<table>
<tr><th></th><th>Normal</th><th>At Risk</th><th>Early Disease</th><th>Late Disease</th><th>End Stage Disease</th></tr>
<tr><td>Glucose tolerance</td><td>Normal</td><td>Hyperinsulinaemia</td><td>Pre-diabetes</td><td>Diabetes mellitus</td><td>Complications and mortality from DM</td></tr>
<tr><td>Retinopathy</td><td rowspan="6">Normal</td><td rowspan="6">Endothelial injury induced by hyperglycaemia</td><td>Non proliferative diabetic retinopathy</td><td>Proliferative diabetic retinopathy</td><td>Blindness</td></tr>
<tr><td>Nephropathy</td><td>Increased GFR / Microalbuminuria</td><td>Reduced GFR / Proteinuria</td><td>End stage renal failure</td></tr>
<tr><td>Neuropathy</td><td>Axonal damage</td><td>Neuropathic ulcers</td><td>Amputation</td></tr>
<tr><td>Ischaemic heart disease</td><td rowspan="3">Asymptomatic fatty streaks and atherosclerosis in large vessels</td><td>Angina / Myocardial infarction</td><td>End stage heart failure</td></tr>
<tr><td>Cerebrovascular disease</td><td>Cerebrovascular accident</td><td>Severe functional disability</td></tr>
<tr><td>Peripheral vascular disease</td><td>Claudication / Arterial ulcers</td><td>Gangrene / Amputation</td></tr>
</table>

The pathologic processes that cause vascular disease include genetic susceptibility or expression, haemodynamic stressors such as salt/fluid imbalance and hypertension, and metabolic derangement such as dyslipidaemia and hyperglycaemia. A combination of these processes triggers end-organ cellular responses such as changes in energy use, protein expression and immune system responses; in particular, activation of cytokines, profibrotic elements and vascular growth factors. This cycle of events ultimately leads to cellular dysfunction and death.[14]

Microvascular Complications: Diabetic Nephropathy

Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy (peripheral and autonomic). Diabetic nephropathy is a progressive disorder of the microvasculature of the kidney. The earliest sign of diabetic nephropathy is moderately increased albuminuria, defined as persistent albumin excretion between 30 and 300 mg/day (20 to 200 mcg/min), and is the earliest stage of nephropathy. The earliest symptoms of diabetic nephropathy, however, occur late in the course of the disease, e.g. proteinuria with foamy urine, worsening hypertension or fluid retention. This disjoint in the presentation between the earliest signs of pathology and the earliest clinical symptoms of diabetes complications demonstrates the regular need to screen for early complications when managing diabetes. In fact, as the diagnosis of T2DM is often delayed, diabetic complications may be present at the time of diagnosis of diabetes. Therefore, screening for complications should begin at diagnosis in patients with type 2 diabetes.[15]

Singapore has one of the highest incidences of end-stage renal disease in the world, and diabetic nephropathy is associated with a high mortality rate. A study of patients with Stage 3–5 CKD (estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2) from the National Healthcare Group CKD Registry showed that over a median follow-up of 6.0 years, 985 out of 3008 patients (32.8%) died.[16] Among those who died, more than one-third died of cardiovascular causes and this is consistent with other studies that had confirmed chronic kidney disease as being an independent risk factor for the development of CVD and subsequent deaths from cardiac causes.[17] Thus, for these patients, it is even more important to optimise the control of their cardiovascular risk and to regard them as the "highest risk" group for CVD, irrespective of the levels of traditional CVD risk factors.[18]

Glycaemic Control, HbA1c and Microvascular Complications

The UKPDS showed that every 1 percent reduction in mean HbA1c levels was associated with a reduction of 37 percent in microvascular complications such as nephropathy, retinopathy and neuropathy.[19] Furthermore, long-term follow-up of the UKPDS cohorts showed enduring effects of early glycaemic control on most microvascular complications.[20] Analysis of the UKPDS results [21] demonstrates a curvilinear relationship between HbA1c and microvascular complications, and suggests that the greatest number of complications will be prevented by taking patients from very poor control to good control(e.g. from 10.0% to 7.5 or 7.0%). No lower threshold of risk was observed for any microvascular end point, which suggests that further lowering of HbA1c from, for example, 7.0 percent to 6.0 percent, is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycaemia with overly aggressive glycaemic control and polypharmacy in T2DM, the risks of lower glycaemic targets may outweigh the potential benefits on microvascular complications. (See section on "Not all T2DM benefit from intensive glycaemic control" below.)

Glycaemic Control, HbA1c and Macrovascular Complications

In T2DM, there is evidence that more intensive treatment of dysglycaemia in newly diagnosed patients may reduce long-term CVD rates.

The UKPDS is relevant to this discussion as the study subjects have newly diagnosed T2DM without known CVD, as compared to later landmark studies of intensive treatment which studied older subjects with established diabetes and a higher risk of CVD.[19,22–24]

The research question of the UKPDS was: In newly diagnosed people with T2DM, will intensive use of pharmacological therapy to lower blood glucose levels result in clinical benefits of reduced cardiovascular and microvascular complications?

At the end of the study, the difference in the HbA1c achieved between the intensive glycaemic control arm and the control arm was 7.0 percent and 7.9 percent. There was a 16 percent reduction in CVD events (combined fatal or nonfatal myocardial infarction and sudden death) in the intensive glycaemic control arm that did not reach statistical significance (P = 0.052). However, in the post-trial monitoring, which consisted of 10 years of observational follow-up, those originally randomised to intensive glycaemic control had significant long-term reductions in myocardial infarction and in all-cause mortality (13% and 27%, respectively).[20] Long-term beneficial effects in the UKPDS-Post Trial Monitoring have been termed "metabolic memory" or the "legacy effect".

Not All Patients Benefit from Intensive Glycaemic Control

The ACCORD, ADVANCE, and VADT studies which had more advanced T2DM than UKPDS participants, showed no significant reduction in CVD outcomes with intensive glycaemic control in participants followed for 3.5–5.6 years. All 3 trials were conducted in relatively older participants with a longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors.

In fact, the glycaemic control comparison in ACCORD was stopped early due to an increased mortality rate due to cardiovascular deaths in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]).[22]

Although analysis of the ACCORD study did not identify a clear explanation for the excess mortality in the intensive treatment arm,[25] certain worrisome characteristics were observed. In trying to reach a target HbA1c of <6 percent in the intensive glycaemic control arm, the ACCORD study had an aggressive protocol to titrate therapy based on monthly HbA1c and self-monitoring of capillary glucose values. Treatment was only reduced in the presence of significant hypoglycaemia or when >25 percent of capillary glucose readings were <3.9 mmol/L. Despite the aggressive protocol, the study did not achieve the target HbA1c. The mean achieved HbA1c was 6.4 percent in the intensive arm versus 7.5 percent in the control arm. However, there was significantly greater use of multiple oral medications and greater use of insulin in the intensive arm. Patients in the intensive arm had a greater amount of weight gain as compared to the control arm (3.5 kg vs 0.4 kg in 3 years). Severe hypoglycaemia was 3 times more likely in participants who were assigned to the intensive arm.

Therefore, the mortality findings in ACCORD suggest that the potential risks of intensive glycaemic control may outweigh its benefits in higher-risk patients with long duration of diabetes, a known history of hypoglycaemia, advanced atherosclerosis, or advanced age/frailty. These patients should not be burdened by polypharmacy and high medication doses. Clinicians should be vigilant in avoiding hypoglycaemia and should not attempt to achieve HbA1c levels in patients in whom such targets cannot be safely and reasonably achieved. Severe or frequent hypoglycaemia is an absolute indication for the modification of treatment regimens, including setting less aggressive glycaemic targets.

In our effort to achieve good glycaemic control for the purpose of preventing diabetes complications, we need to consider many patient factors, including patient preferences and develop individualised goals for our patients.[26] While glycaemic goals for most patients should remain unchanged, i.e. targeting HbA1c <7 percent, higher HbA1c targets may be acceptable for patients at risk of severe hypoglycaemia, with established CVD, and in older frail patients. Lower HbA1c targets are appropriate in patients with a shorter duration of diabetes and those without established CVD.

Comprehensive Care Involves Treatment of All Modifiable CVD Risk Factors Over a Sustained Period

Steno-2 showed that a targeted, long-term, intensified multifactorial intervention reduced the risk of cardiovascular events among patients with T2DM and microalbuminuria. Subsequently, the 21-year follow-up of the Steno-2 trial showed long-term survival benefit of early intervention intensification in patients at lower absolute risk for late diabetic complications compared to intensification in later stages of the disease.[27,28]

The Steno-2 study was an open trial designed to compare the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for CVD in patients with T2DM and microalbuminuria. Patients were allocated standard treatment (n=80) which followed Danish national guidelines or intensive treatment (n=80). Intensive treatment consisted of a stepwise implementation of behaviour modification, pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria, along with secondary prevention of CVD with aspirin.

After a mean follow-up of 7.8 years, the patients in the intensive-therapy group had a significantly greater decline in

mean HbA1c values (-0.5 ± 0.2 vs 0.2 ± 0.3), systolic and diastolic blood pressure, fasting serum cholesterol and triglyceride levels, and urinary albumin excretion as compared to the conventional-therapy group. Patients receiving intensive therapy also had a significantly lower risk of CVD (hazard ratio, 0.47; 95% CI, 0.24 to 0.73), nephropathy (hazard ratio, 0.39; 95% CI, 0.17 to 0.87), retinopathy (hazard ratio, 0.42; 95% CI, 0.21 to 0.86), and autonomic neuropathy (hazard ratio, 0.37; 95% CI, 0.18 to 0.79).

The original cohort of 160 patients were then followed-up to study the potential long-term impact of the intensified multifactorial intervention in terms of gained years of life and years free from incident cardiovascular disease. After the initial 7.8 years, the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group. Thus, from year 7.8 onwards all patients in both treatment arms in the Steno-2 study received identical intensive treatment in both groups.

After 21.2 years of follow-up, the patients in the intensive-therapy group survived for a median of 7.9 years longer than those in the conventional-therapy group. The increase in lifespan was matched by time free from incident cardiovascular disease. The median time before the first cardiovascular event after randomisation was 8.1 years longer in the intensive-therapy group (p=0.001). The hazard for all microvascular complications continued to be decreased in the intensive-therapy group in the range of 0.52 to 0.67, except for peripheral neuropathy (HR 1.12).

Specific Medications—SGLT2 Inhibitors and GLP-1 Agonists

CVD remains the leading cause of morbidity and mortality in individuals with type 2 diabetes. Yet, randomised clinical trials using conventional anti-hyperglycaemic medications seem to show minimal effect on lowering CVD risk despite achieving reductions in HbA1c and associated reductions in microvascular risk. This shortfall in beneficial effect might reflect the adverse consequences of increased hypoglycaemia, the adverse effects of many anti-diabetic agents on weight gain, or both. As mentioned above, there is a paradigm shift in T2DM management, moving from a primary objective of glycaemic control to that of CVD and renal protection. SGLT2 inhibitors have emerged as noteworthy anti-hyperglycaemic agents with concomitant CVD and renal protection in T2DM patients when added to standard care.

A meta-analysis which included 3 large randomised, placebo-controlled SGLT2 inhibitor trials, studied the cardiovascular outcome in patients with T2DM.[33] SGLT2 inhibitors reduced the risk of hospitalisation for heart failure by 30 percent with a similar benefit in patients with and without known atherosclerotic CVD and a history of heart failure. SGLT2 inhibitors also reduced the risk of progression of renal disease by 45 percent, with a similar benefit in those with and without atherosclerotic CVD. However, the reduction of risk reduction of 11 percent in myocardial infarction, stroke, or cardiovascular death was present only in patients with established atherosclerotic CVD and not in those with multiple risk factors.

To date, the exact mechanisms of the beneficial cardiac and renal effects of SGLT2 inhibitors remain unclear.[34] The addition of SGLT2 inhibitors to standard care results in a reduction in HbA1c of only approximately 0.5–0.6 percent, suggesting that glucose control itself is not the reason for the reduction in macrovascular complications.[35,36]

In summary, the efficacy of this class of diabetes medications in reducing the risk of hospitalisation for heart failure and progression of renal disease in patients without established CVD shows promise for their use in primary prevention. The data also suggests that SGLT2 inhibitors should be considered in patients with T2DM with established atherosclerotic CVD given the reductions in major adverse cardiovascular events.

GLP-1 receptor agonists are the other pharmacological class that have proven their efficacy to reduce cardiovascular events in patients with T2DM and established CVD in large prospective cardiovascular outcome trials.

In the LEADER trial, which studied patients with T2DM and high cardiovascular risk, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was lower with liraglutide than with placebo. Fewer patients died from cardiovascular causes in the liraglutide group (hazard ratio, 0.78. P = 0.007).[37]

Subgroups of People with T2DM Who Have Increased Risks of Complications

T2DM is a very heterogenous disease with possibly many different subgroups we presently do not recognise well. One subgroup of early onset T2DM appears to be a more aggressive disease compared to older onset T2DM and confers a higher risk of cardiovascular disease relative to age-matched control subjects.[29]

In a population-based study of 7,844 patients with newly diagnosed T2DM (consisting of approximately 90% non-Hispanic whites) were followed up for an average of 3.9 years for the medications they required and incident complications. Patients were classified as early onset if they were diagnosed at < 45 years of age and were considered usual-onset if diagnosed at > 45 years of age.

The study showed that a higher proportion of early-onset T2DM required insulin treatment compared with adults with usual onset T2DM (18 vs. 11%, P < 0.001). Adults with early-onset T2DM had a higher average HbA1c and were 20 percent more likely to develop microalbuminuria than those with usual-onset T2DM.

Importantly, although the absolute risk of CVD was naturally higher in older adults with and without diabetes, young adults with early-onset T2DM had an eightfold higher overall hazard

of developing any macrovascular disease relative to control subjects (HR 7.9, 95% CI 4.8 –13.0) compared with only a fourfold increased hazard in the usual-onset type 2 diabetic group (HR 3.8, 95% CI 3.4–4.2).

In addition to the increased risk of microalbuminuria in adults with early-onset T2DM, the study found a high rate of the metabolic syndrome components of hypertension and dyslipidaemia among the early-onset group at the time of diagnosis.

Studies comparing young-onset T2DM versus T1DM patients have been used to show that the excess risk of developing cardiovascular and renal complications is driven primarily by accompanying metabolic risk factors. A study on Chinese patients from a Hong Kong Diabetes Registry showed that young patients with T2DM had greater risks of developing cardiovascular renal complications compared with patients with T1DM.[30] In this prospective study, young-onset diabetes was defined by diagnosis age <40 years. Patients with T1DM and normal-weight (BMI <23 kg/m^2) and overweight (BMI >23 kg) patients with T2DM were compared for incident cardiovascular disease.

Over a median follow-up of 9.3 years, the study showed that overweight patients with T2DM had the worst metabolic profile and highest prevalence of microvascular complications. Compared with patients with T1DM, overweight patients with T2DM had 15- and 5-fold greater hazards of developing CVD and ESRD, respectively, when adjusted for age, sex, and time from diagnosis. The association remained robust when adjustment was made for HbA1c but became nonsignificant upon additional adjustment for BMI, blood pressure, and lipids.

Another study, conducted in Australia, which looked at the long-term clinical outcomes and survival in young-onset T2DM patients compared with T1DM patients with similar age of onset, showed that young-onset T2DM is the more lethal phenotype of diabetes and is associated with a greater mortality, more diabetic complications, and unfavourable CVD risk factors.[31]

These studies support the conclusion that early-onset T2DM appears to be a more aggressive disease compared to older-onset T2DM and confers a higher risk of cardiovascular disease relative to age-matched control subjects. Intensive intervention should not only target glycaemic control but also optimise the associated unfavourable CVD risk factors, as per the findings of the Steno-2 trial.

FUTURE STRATEGIES TO STRATIFY RISK

Apart from our traditional methods of classifying the forms of diabetes and risk-scoring for CVD, new methods of classification have been proposed. Emma Ahlquist et al used six laboratory and clinical variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance) measured at diagnosis in adult patients, to identify 5 replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications.[32] Amongst the patients with non-autoimmune diabetes, there was a cluster of very insulin-resistant individuals with significantly higher risk of diabetic kidney disease than the other clusters; a cluster of relatively young insulin-deficient individuals with high HbA1c; and a large group of elderly patients with the most benign disease course. Such new methods of substratification could change the way we think about T2DM and help to tailor and target early intensive treatment to patients who would benefit.

PERSPECTIVE

Although the ultimate aim of managing diabetes is the prevention or total avoidance of all diabetic complications, any effort to delay the onset of major complications is of great clinical and socioeconomic significance. The morbidity of major diabetic complications, e.g. ESRF and the need for dialysis, is of the greatest impact if it happens to a person with diabetes at the prime of his life when he could be the breadwinner of a dependent family. Delaying the onset of such complications by 5 or 10 years, beyond retirement age if possible, will lessen the economic impact to the individual and his family. This scenario of a person developing complications in the prime of his life is especially likely for people with young-onset diabetes, e.g. at the age of 38 years, with suboptimal control of diabetes and its comorbidities for numerous years.

The benefits arising from intensive and multifactorial interventions cited in this article were achieved in the context of clinical trials. In the real world, there are many challenges to achieving ideal glycaemic control. It is well recognised that young people with diabetes are more difficult to manage owing to a greater level of diabetes-related distress, competing social demands, poor drug compliance, and high appointment default rates. Clinicians and their care teams should establish a good long-term relationship-based practice with their patients and have timely initiation of impactful treatment. Early intensive treatment and control of risk factors provides the opportunity for greatest accrual of benefit over the longer term.

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LEARNING POINTS

- **Understand the burden of diabetes complications.**
- **Understand the factors which contribute to the development of diabetic complications.**
- **Strategies in the prevention of diabetic complications— what landmark trials teach us.**
- **Recognise specific subgroups of patients who are at a greater risk of developing complications.**