UNIT NO. 5

WHAT'S NEW IN DIABETES CARE

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ABSTRACT

Diabetes mellitus is a chronic illness managed frequently by the family physician. Along with glycaemic control, consideration for other risk factor reduction for micro- and macrovascular complications of diabetes is important. With the introduction of newer pharmacological agents targeting the different pathophysiological aspects of diabetes, it is important for the family physician to make an informed decision, considering the risks and benefits, when choosing the most suitable therapeutic agent. A patient-centered approach is thus crucial in the management of diabetes. This review article focuses on the latest guidelines and new developments in diabetes management in the recent 1-2 years.

Keywords:
Diabetes mellitus; Hyperglycaemia; Blood Pressure; Lipid Management

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INTRODUCTION

The incidence of diabetes mellitus is rising worldwide. In Singapore, the proportion of people affected by diabetes has risen from 8.2 percent in 2004 to 11.3 percent in 2010. This is largely fuelled by an aging population and an increasingly sedentary lifestyle. The vast majority of cases are type 2 diabetes, and a much smaller proportion are type 1 diabetes and other forms of diabetes [gestational diabetes, maturity onset diabetes of the young (MODY), latent autoimmune diabetes of adults (LADA) and others]. The management of diabetes requires a multi-pronged approach to risk-factor reduction for the micro- and macrovascular complications associated with diabetes.

As part of chronic disease management, patient self-management education and support are crucial in preventing acute complications and reducing the risk of long-term complications. Diabetes education should ideally take place at the point of diagnosis and intermittently to address any knowledge gaps. Patients newly diagnosed with diabetes should receive education on lifestyle modification, including individualised diabetes medical nutritional therapy advice, weight reduction where appropriate and encouragement to lead an active lifestyle (150 min/week minimum of physical activity) to achieve treatment goals. An assessment of patient-support systems is also crucial in managing the patient holistically.

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GLYCAEMIC MANAGEMENT

Glycaemic control remains a fundamental component in the management of patients with diabetes. Improved glycaemic control is associated with decreased rates of microvascular complications of retinopathy, neuropathy and nephropathy, with persistence of these benefits in the long term. In terms of macrovascular disease, the benefits of optimal glycaemic control (achieving target glycated haemoglobin, HbA1c <7%) remains uncertain, and is likely seen only after many years of improved control.

Glycaemic targets have to be individualised for the patient, based on certain patient and disease factors (Table 1).1-4 A reasonable HbA1c goal for many non-pregnant adults is <7 percent, with more stringent goals (HbA1c <6.5%) for individuals who can achieve this goal without significant hypoglycaemia.[2,3] Less stringent goals (7–8.5%) may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetes complications or extensive comorbid conditions.[2,3]

Table 1: Patient and disease factors to determine optimal HbA1c targets[2,3]

Patient/ Disease factors		HbA1c targets		
		More stringent, HbA1c <7%	HbA1c 7%	Less stringent, HbA1c >7%
Usually not modifiable	Risks associated with hypoglycaemia and other adverse drug effects	Low risk		High risk
	Disease duration	Newly diagnosed		Long-standing
	Life expectancy	Long		Short
	Important comorbidities	Absent	Few/mild	Severe
	Established vascular complications	Absent	Few/mild	Severe
Potentially modifiable	Patient attitude and expected treatment efforts	Highly motivated, adherent, excellent self-care capability		Less motivated, non-adherent, poor self-care capability
	Resources and support system	Readily available		Limited

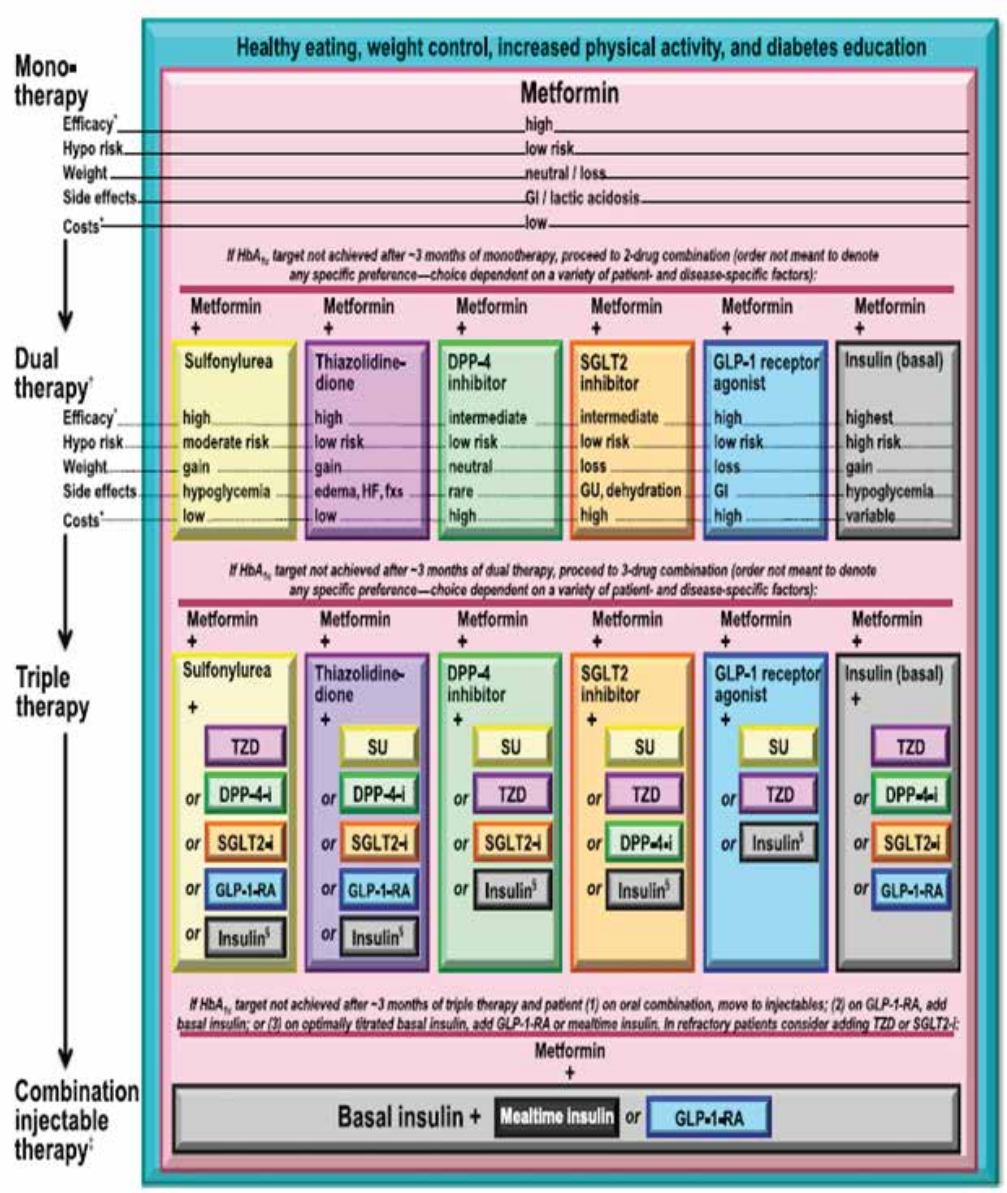
Self-monitoring of blood glucose (SMBG) should be advised to all patients with type 1 diabetes and selected patients with type 2 diabetes on insulin therapy, those with an evidence of hypoglycaemic episodes, patients on oral anti-diabetic agents that increase their risk of hypoglycaemia (e.g. sulphonylurea) while driving or operating machinery, if planning pregnancy or pregnant.[4]

Pharmacological Agents

In the recent decade, the therapeutic options available to treat diabetes have expanded, largely from a greater understanding of the pathophysiology of type 2 diabetes. There is now a large armamentarium of pharmacological agents and new drug classes available for the management of type 2 diabetes.

Several algorithms (Figure 1) are present to guide pharmacological choice of therapy.[2] Metformin remains the initial monotherapy of choice for patients with type 2 diabetes when initial lifestyle efforts alone do not achieve or maintain

Figure 1: Antihyperglycaemic therapy in type 2 diabetes[2,3]



glycaemic targets. Metformin is effective, weight- neutral, inexpensive and has a long safety record, with possible cardiovascular benefits. Due to its association with lactic acidosis, Metformin is contraindicated in the presence of severe renal (eGFR <30 ml/min/1.73m^2) or hepatic insufficiency. It is also used with caution in those with eGFR < 45 ml/min/1.73m^2 (whereby the dose of Metformin should be reviewed) or those with severe cardiac failure.

For the choice of a second or third-line agent, in addition to metformin, or in patients unable to tolerate Metformin, or in situations where Metformin is contraindicated, other oral agents are acceptable alternatives to metformin as initial therapy. The choice of the additional agent will need to be tailored to the individual, considering the following factors:

1) Drug factors — glucose-lowering effect and HbA1c reduction that can be achieved by the agent, hypoglycaemia risk, adverse effects profile including potential for weight gain and durability of glucose lowering.

2) Patient factors — tolerability, cost, patient preferences, and other practical aspects of diabetes care such as dosing schedule and requirement for glucose monitoring.

These other pharmacological agents are detailed in Table 2, which details the advantages, disadvantages and primary actions.

SGLT2 inhibitors

A new class of glucose-lowering agents, the sodium-glucose cotransporter 2 (SGLT2) inhibitors was introduced in recent years. This class of agents provides insulin-independent glucose lowering by blocking renal glucose reabsorption by the inhibition of SGLT2 in the proximal renal tubules. Other than the glucose-lowering effect (with HbA1c reduction of 0.6-0.8%), SGLT2 inhibitors have the ability to aid blood pressure lowering of 4-10mmHg reduction in systolic blood pressure, without a compensatory increase in heart rate. In addition to this, SGLT2 inhibitors also provide modest weight loss, something of benefit to overweight type 2 diabetes

Table 2: Glucose-lowering agents used commonly to treat type 2 diabetes (adapted)[2,15]

Drug Classes and Compound(s)	Primary physiological action	HbA1c lowering (%)	Advantages	Disadvantages	Cost
Biguanide • Metformin	• Reduce hepatic glucose production	~1.0-1.5	• Extensive experience • No hypoglycaemia • Decrease CVD events (UKPDS)	• GI side effects • Lactic acidosis (rare) • Vitamin B12 deficiency	Low
Sulphonylureas • Glipizide • Gliclazide • Glibenclamide • Glimepiride • Tolbutamide	• Increase insulin secretion	~1.0-1.5	• Extensive experience • Decrease microvascular risk (UKPDS)	• Hypoglycaemia • Weight gain • Low durability	Low
Meglitinides • Repaglinide • Nateglinide	• Increase insulin secretion	~1.0	• Decrease postprandial glucose excursions • Dosing flexibility	• Hypoglycaemia • Weight gain • Frequent dosing schedule	Moderate
Thiazolinediones • Pioglitazone • Rosiglitazone	• Increase insulin sensitivity	~1.0	• No hypoglycaemia • Durability • Increased HDL, lowers triglycerides	• Weight gain • Oedema/ heart failure • Bone fractures • Increased myocardial infarction (rosiglitazone, meta-analyses)	Moderate
α-Glucosidase Inhibitors • Acarbose	• Slows intestinal carbohydrate digestion/ absorption	~0.5-0.8	• No hypoglycaemia • Decrease postprandial glucose excursions • Non systemic	• GI side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 Inhibitors • Sitagliptin • Linagliptin • Vildagliptin • Saxagliptin • Alogliptin	• Increase insulin secretion (glucose dependent) • Decrease glucagon secretion (glucose dependent)	~0.6-0.8	• No hypoglycaemia • Well-tolerated • Weight neutral	• Angioedema/ urticarial and other immune-mediated dermatological effects • ?Acute pancreatitis • ?Increase heart failure	High
SLT2 Inhibitors • Canaglifozin • Dapaglifozin • Empaglifozin	• Blocks glucose reabsorption by the kidney, increasing glucosuria	~0.6-0.8	• No hypoglycaemia • Weight loss • Decrease blood pressure • Decrease CVD events and mortality in patients with CVD (EMPA-REG)	• Genitourinary and urinary tract infections • Polyuria • Volume depletion/ hypotension/ dizziness • Risk of euglycaemic DKA	High
GLP-1 receptor agonists • Exenatide • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	• Increase insulin secretion (glucose-dependent) • Reduce glucagon secretion (glucose-dependent) • Slows gastric emptying • Increase satiety	~1.0	• No hypoglyccaemia • Weight loss • Decrease postprandial glucose excursions •	• GI side effects (nausea/ vomiting/diarrhea) • Injectable • ?Acute pancreatitis	High
Insulins • Rapid-acting insulin analogues - Aspart, Lispro Glulisine • Short-acting - Human Regular • Intermediate-acting - Human NPH • Basal insulin analogues - Glargine, Detemir • Premixed (several types)	• Increase glucose disposal • Decrease hepatic glucose production • Suppresses ketogenesis	>1.5%	• Most potent, nearly universal response • Theoretically unlimited efficacy • Decrease microvascular risk (UKPDS)	• Hypoglycaemia • Weight gain • Injectable • Patient reluctance	Low to high (cost is variable and dependent on type/ brand/ dosage)

patients who are struggling with further weight gain.

SGLT2 inhibitors have received considerable attention due to the EMPA-REG study data showing for the first time, the ability of an anti-diabetic agent in reducing cardiovascular events and all-cause mortality. The majority of the 7082 patients with type 2 diabetes and established cardiovascular disease (CVD) were taking metformin, antihypertensives, and lipid-lowering agents with approximately half of the patients also on insulin therapy. In this trial, the primary outcome (a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) was lower in patients assigned to Empaglifozin than in the placebo group, mainly driven by a significant reduction in the risk of death

from CVD causes.[5] The minimal difference in glycaemia between the groups (7.8% vs 8.2%) suggests that factors other than glycaemia were responsible for the CVD outcome. Whether this is a class effect representing all other SGLT2 inhibitors is unknown and further trials are awaited.

A warning about the risk of developing diabetic ketoacidosis (DKA) with mild to moderate glucose elevations (euglycaemic DKA) was issued by international health regulatory authorities, including the Singapore Health Sciences Authority recently. Risk factors for DKA include patients with low beta-cell function reserve (such as in type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin-dose reduction, reduced caloric intake or increased insulin requirements from sepsis, illness or surgery, and alcohol abuse.[6] To ameliorate the risk of DKA, physicians should exercise caution in the use of these agents in the presence of these risk factors and assess for ketoacidosis in patients on SGLT2 inhibitors presenting with signs and symptoms suggestive of metabolic acidosis.

OBESITY AND DIABETES MANAGEMENT AND OPTIONS FOR SURGERY

For adults with type 2 diabetes who are overweight, an initial body weight loss target of 5-10 percent is desired.[4] Bariatric surgery for the treatment of obesity in patients with diabetes can result in sustained weight loss (20-30% weight loss at 1-2 years), and in accordance with weight loss, large improvement in glycaemic control. Remission of diabetes is generally defined as HbA1c <6.5 percent without the use of anti-diabetic medications. According to the International Diabetes Federation (IDF) position statement on bariatric surgery, this is an accepted option in people with type 2 diabetes and a BMI ≥ 35 kg/m^2; and considered as an alternative treatment option in patients with BMI 30-35 kg/m^2 when diabetes cannot be controlled by optimal medical therapy, especially in the presence of other major cardiovascular disease risk factors.[7] It is also recognised that in Asian and other ethnicities of increased risk, BMI action points may be reduced by 2.5 kg/m^2.[7]

In the follow-up study of 53 diabetic patients with obesity who underwent bariatric surgery, only approximately 50 percent of patients in the surgical group maintained diabetes remission at 5 years, with a larger proportion of patients in the biliopancreatic diversion group in remission compared to the gastric bypass group.[8] Although weight changes did not predict diabetes remission or relapse after surgery, surgical patients lost more weight than medically treated patients, and had lower plasma lipids, cardiovascular risk, and medication use.

The Future in Glucose Monitoring and Insulin Delivery

Advancements in diabetes technologies have enabled more precise insulin delivery and more convenient methods of glucose monitoring. Several studies have been published in recent years evaluating the efficacy of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM), particularly in patients with type 1 diabetes. With a sensor-augmented pump (CSII combined with continuous glucose sensing), information from a CGM device enables manual adjustment to insulin dosing delivered via CSII. In an automated closed-loop insulin pump, the delivery of insulin is automated based upon continuous glucose sensing via inbuilt algorithms. The safety and efficacy of these closed-loop insulin delivery systems have now been tested out in the home setting. In a study of 32 adults with type 1 diabetes, the closed-loop system was used for a 12-week period, and compared against sensor-augmented pump therapy.[9] Compared with the sensor-augmented pump, the closed-loop system resulted in a greater proportion of time spent within the target blood glucose range of 3.9 – 10 mmol/l), with lower mean glucose level (8.7 vs 9.3 mmol/l), and mean HbA1c level (7.3 vs 7.6%), with reduced time spent in the hypoglycaemic range.[9]

Blood Pressure (BP) Management

Early treatment of hypertension is important in patients with diabetes to prevent cardiovascular disease and to minimise progression of renal disease and diabetic retinopathy. Several new guidelines, reviews and new trials have emerged in the last 1–2 years on the target blood pressure and antihypertensive agent of choice in patients with diabetes.

The JNC8 (Joint National Committee) guidelines relaxed the threshold for the initiation of BP-lowering treatment from systolic BP 130 mmHg to 140 mmHg in patients with diabetes, with goal BP of <140/90 mmHg.[10] The recommended antihypertensive treatment in those with chronic kidney disease and hypertension, regardless of diabetes status, is an ACE-inhibitor or angiotensin-receptor blockers (ARB) to improve kidney outcomes.

In a large meta-analysis of 40 trials (with 100,354 diabetic participants), antihypertensive therapy reduced mortality rates, total cardiovascular disease and stroke, and with the exception of stroke, the benefit of antihypertensive therapy was limited to those with initial systolic BP ≥140 mmHg.[11] In those with lower initial systolic BP <140mmHg, antihypertensive therapy reduced the risk of stroke, retinopathy and progression of albuminuria. In terms of the achieved systolic BP, treatment was associated with lower risks for stroke and albuminuria in those who achieved systolic BP <130 mmHg. When comparing against antihypertensive classes of medications, there was no significant difference between classes except in heart failure (favouring diuretics and ARB) and stroke (favouring calcium channel blockers).[11]

Taking these new guidelines and meta-analysis evidence, pharmacological agents should be initiated in patients with diabetes who develop hypertension (blood pressure ≥140/90 mmHg). In those at high risk of stroke, retinopathy or nephropathy, treatment below an initial systolic BP level of 140 mmHg can be considered. Antihypertensive medications should be targeted to a BP goal of <140/90 mmHg. Lower BP targets <130/80 mmHg may be considered for those with albuminuria, and/or one or more additional cardiovascular

disease risk factor(s), if they can be achieved without undue treatment burden. The antihypertensive agent of choice is an ACE inhibitor or ARB as initial therapy in a hypertensive diabetic patient who has albuminuria in an attempt to slow renal disease progression. Multiple-drug therapy with other antihypertensive agents is required in patients who do not achieve target BP and the choice of second of third antihypertensive agent should then consider the other comorbidities present (e.g. heart failure, cardiovascular disease).

Lipid Management

Patients with type 2 diabetes have an increased risk of lipid abnormalities, contributing to the overall risk of atherosclerotic cardiovascular disease. Since the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on lipid-lowering therapy, the focus of management has shifted from an LDL-C or non-HDL-C target to using the intensity of statin therapy as the goal of treatment.[12] Moderate-intensity statin therapy lowers LDL-C by 30–50 percent (Atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg or other equivalent statins), while high-intensity statin lowers LDL-C by ≥50 percent (e.g. Atorvastatin 40-80 mg or Rosuvastatin 20-40 mg). Based on the CVD risk-factor profile and age (<40 years, 40-75 years and >75 years), patients can then be recommended for moderate or high intensity statin use. Those aged 40 years and above with presence of CVD risk factors (diabetes conferring an increased risk for CVD) would qualify for high-intensity statin use. The Singapore Clinical Practice Guidelines maintains LDL-C goals for patients with diabetes, with the majority of patients with type 2 diabetes having an LDL-C goal <2.6 mmol/l, and those with overt CVD and/or chronic kidney disease having a more stringent LDL-C goal of <2.1 mmol/l.[1]

Older adults with diabetes

The American Diabetes Association recently published a position statement for the management of diabetes in long-term care and skilled-nursing facilities.[13] It recognises that hypoglycaemia is the major limiting factor in determining glycaemic goals and that simplified treatment regimens are preferred and better tolerated in this patient population. Choice of therapy should also take into consideration the need to reduce polypharmacy and complexity of treatment.[13,14]

CONCLUSION

As physicians committed to caring for patients with diabetes, we recognise that diabetes is a complex chronic illness. Patients with diabetes are a heterogeneous population presenting with unique challenges (physical, social and psychological) to diabetes management. It is thus essential that clinicians try as best as possible to individualise treatment goals to each patient based on patient preferences and comorbidities, and to stay current with new developments. Along with glycaemic control, the care of the patient with diabetes should include comprehensive risk-factor reduction, including smoking cessation, healthy lifestyle habits, blood pressure control, lipid management and, in some circumstances, the addition of antiplatelet therapy.

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LEARNING POINTS

- **Individualise treatment (glycaemia, BP, lipid) goals according to each patient's unique characteristics.**
- **Consider the various pharmacological agents and their advantages/disadvantages along with cost of treatment when choosing the anti-diabetic agent of choice.**
- **Initiate antihypertensive treatment for patients with diabetes with BP 140/90 mmHg. The choice of antihypertensive agent will depend on additional comorbidities and the presence of albuminuria.**
- **Patients at high CVD risk should be on high-intensity statin therapy.**