UNIT NO. 3

TARGET FOR CONTROL IN DIABETES MELLITUS

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ABSTRACT

Glycaemic control is fundamental to the management of diabetes. Prospective randomised controlled trials like the Diabetes Control and Complications Trial (DCCT), the Kumamoto study, and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that improved glycaemic control is associated with sustained decreased rates of retinopathy, nephropathy, and neuropathy[1-3]. Two primary techniques are available for health care providers and patients to assess the effectiveness of the management plan on glycaemic control: patient self-monitoring of blood glucose (SMBG) and glycated haemoglobin (HbA1c) measurement.

The author would like to acknowledge that this article is a close replication of the chapter on "Glycaemic Control" in the Clinical Practice Guidelines (CPG) on Diabetes Mellitus, Ministry of Health, Singapore[4]. Besides its relevance to our practice, the author was involved in drafting the original chapter on "Glycaemic Control" in the CPG.

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BLOOD GLUCOSE TESTING BY PATIENTS (SELF-MONITORING OF BLOOD GLUCOSE)

Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive glycaemic control on diabetes complications have included SMBG as part of multi-faceted interventions. SMBG is an integral component of effective diabetes management because the information obtained may be used to guide therapy, prevent hypoglycaemia, and assess the efficacy of treatment. It also serves as a useful educational tool to improve patient compliance and participation in diabetes self-care[5,6].

SMBG is indicated for the following types of patients:

1. All insulin-treated patients.
2. All pregnant patients with pre-existing diabetes or gestational diabetes.
3. Non insulin-treated patients who are at increased risk of developing hypoglycaemia and/or are vulnerable to permanent injury from hypoglycaemia.
4. All patients who have failed to achieve glycaemic goals.

The frequency of SMBG is as follows:

1. For patients with type 1 diabetes, daily monitoring is recommended. However, the frequency and timing of glucose monitoring should be determined by the needs and goals of each individual patient. For most patients with type 1 diabetes, SMBG is recommended 3 or 4 times daily. Some patients may need to perform SMBG at 2 am or 3 am if there are hypoglycaemic symptoms at night.
2. The optimal frequency of SMBG for non-insulin treated type 2 diabetic patients is not known, but it should be frequent enough to facilitate attaining glucose targets. For insulin-treated type 2 diabetic patients, testing 2 or 3 times a day on two to three days a week is deemed appropriate.
3. For patients with unstable metabolic control, changes in daily routine, alterations of treatment regimens, intercurrent illness or surgery, the frequency of SMBG should be increased.
4. Daily SMBG is superior to intermittent office monitoring of plasma glucose in pregnant patients with diabetes.

Based on evidence from well-conducted clinical trials, the American Diabetes Association (ADA) Clinical Practice Recommendations (2008) similarly recommend SMBG to be carried out three or more times daily for patients on multiple insulin injections or insulin pump therapy[7]. As a consensus opinion, the ADA recommends SMBG may be useful in achieving glycaemic goals for patients using less frequent insulin injections, non-insulin therapies, or medical nutrition therapy alone. It also shared the consensus opinion that continuous glucose monitoring may be a supplementary tool to SMBG for selected patients with type 1 diabetes, especially those with hypoglycaemic unawareness.

Glycated Haemoglobin

The measurement of glycated haemoglobin (HbA1c) quantifies average glycaemia over the previous 2-3 months, thereby complementing blood glucose testing which provides information on day-to-day glycaemic excursions. The glycated haemoglobin value has been shown to predict the risk for development of many of the chronic microvascular complications in diabetes[1-3]. As many different types of glycated haemoglobin assay methods are available in the routine clinical laboratory, physicians ordering the test should be aware of the assay methodology, the glycated components measured (HbA1 or HbA1c), the non-diabetic reference interval, and potential assay interference.

Glycated haemoglobin result will be affected by conditions that affect erythrocyte turnover (e.g. haemolysis, blood loss, recent blood transfusion) and haemoglobin variants. This limitation must be considered, particularly when the HbA1c result does not correlate with the patient's clinical situation. Notably, HbA1c does not provide a measure of day-to-day glycaemic excursions or glycaemic variability. For patients prone to marked glycaemic variability and hypoglycaemia, glycaemic control is best judged with concomitant SMBG evaluation.

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FREQUENCY OF TESTING

The following schedule is recommended for glycated haemoglobin testing:

1. 3- to 4-monthly in patients with unstable glycaemic control, failure to meet treatment goals, recent adjustment in therapy, or intensive insulin therapy.
2. 6-monthly in patients who have stable glycaemic control and who are meeting treatment goals.

TARGETS OF GLYCAEMIC CONTROL

Results from large scale clinical trials in both patients with type 1 and type 2 diabetes mellitus have consistency shown strong correlation between prevailing glycaemia and microvascular complications[1-3]. Although its findings were released in 1993, the Diabetes Control and Complications Trial (DCCT) remains the landmark trial that provided conclusive evidence of the relationship between elevated blood glucose levels and microvascular complications in patients with type 1 diabetes[1]. Continued follow-up of DCCT subjects revealed tight glucose control also lowered the risk of macrovascular events, including heart attack or stroke, by 58%[8]. In type 2 diabetes, both the Kumamoto study[2] and the UK Prospective Diabetes Study[3] demonstrated significant reduction in microvascular and neuropathic complications with intensive therapy. Based on the UKPDS, a 1% decrease in absolute HbA1c value translates to a 35-60% reduction in risk for microvascular complications[3]. The potential of intensive glycaemic control to reduce cardiovascular disease in type 2 diabetes is supported by epidemiologic studies[9-10].

Patients striving to achieve near-normal or normal glycaemia may encounter an increased risk of hypoglycaemic reactions. This has been clearly demonstrated in clinical studies especially in patients with type 1 diabetes who are put on "intensive" treatment to aim for near-normal glycaemic control[1]. Although the risk of severe hypoglycaemia in patients with type 2 diabetes is generally lower, this may still occur in susceptible patients like the elderly subjects, those with impaired liver or renal function, and patients treated with potent and long-acting sulfonylurea drugs. It is therefore important to individualise the glycaemic targets to ensure that patients do not incur an undue risk of hypoglycaemia or other hazards associated with tight control.

Defining targets of glycaemic control

"Ideal" 4.5-6.4%: this refers to HbA1c levels within the normal range. This level of glucose control may not always be safely attainable by the majority of patients with diabetes, with the exception of patients with early diabetes or those who can be adequately managed with lifestyle modification or the use of oral non-insulin secretagogue agents like metformin, thiazolidinediones, or acarbose. However, this is the desired target for pregnant women with pre-existing diabetes or gestational diabetes. It is likely that the ideal target for pregnant women with diabetes might be redefined because emerging evidence suggests a lower reference interval for normal HbA1c value in pregnancy[11].

"Optimal" 6.5-7.0%: this refers to HbA1c levels that approach the normal range and it is the desirable target of control for the majority of patients with diabetes. This is because it is associated with a significantly reduced risk of developing chronic microvascular complications, as shown by DCCT and UKPDS results.

"Suboptimal" 7.1-8.0%: this refers to HbA1c levels that are attainable in the majority of patients with diabetes. However, patients with HbA1c results in this category should be encouraged to lower their glucose levels further towards optimal levels. In special subset of patients however, this suboptimal level of glucose control may be the best that is safely attainable.

"Unacceptable" > 8.0%: this refers to glucose levels that may be associated with acute metabolic decompensation and/or complications of hyperglycaemia. Patients with glucose levels within this range require reassessment and readjustment of therapy. Referral to the diabetes care team is necessary if no improvement occurs.

FACTORS MODIFYING GLYCAEMIC TARGETS

Although adult patients with diabetes should aim for at least an "optimal" level of glucose control, "suboptimal" control may be adequate in the following situations:

1. Older patients with significant atherosclerosis burden who may be vulnerable to permanent injury from hypoglycaemia.
2. Patients with severe diabetes-related complications or co-morbidities (e.g. severe coronary artery disease, cerebrovascular disease, renal failure, proliferative retinopathy, advanced autonomic neuropathy) who may be at increased risk for hypoglycaemia and/or vulnerable to permanent injury from hypoglycaemia.
3. Preadolescent children (because of their unpredictable eating habits, variable physical activity, and difficulty in adherence to treatment schedules) who may be at increased risk for hypoglycaemia.

Based on clear evidence from well-conducted clinical studies, the ADA Clinical Practice Recommendations proposed a similar HbA1c goal for non-pregnant adults in general to be <7%[7]. Because of supportive data from epidemiologic studies suggesting an incremental (albeit small in absolute terms) benefit to lowering HbA1c from 7% into the normal range, the ADA further recommended the HbA1c goal for selected individuals to be as close to normal (< 6%) as possible without significant hypoglycaemia. Nevertheless, the ADA shared a similar consensus opinion of less stringent HbA1c goals for patients with a history of severe hypoglycaemia, patients with limited life expectancies, children, individuals with comorbid conditions, and those with longstanding diabetes and minimal or stable microvascular complications. Based on consensus opinion, it also recommended the use of point-of-care testing for HbA1c, when necessary, for timely decision on therapy adjustments.

The targets for glycaemic control are summarised in Table 1. As patients with diabetes often have underlying metabolic syndrome with concomitant hypertension and dyslipidaemia, Table 2 provides a brief summary of the respective goals based on our CPG *vis a vis* the ADA recommendations.

Key References:
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Table 1. Targets of Glycaemic Control (adapted from CPG on Diabetes Mellitus 2006; MOH)

	Assessment of Glucose Control			
	Ideal (non-diabetic levels)	**Optimal** (target goal for majority of patients)	**Suboptimal** (adequate goal for some patients)	**Unacceptable** (action needed in all patients)
HbA1c (%)	4.5 – 6.4	6.5 – 7.0	7.1 – 8.0	> 8.0
Preprandial capillary blood glucose (mmol/L)	4.0 – 6.0	6.1 – 8.0	8.1 – 10.0	> 10.0
2-h postprandial capillary blood glucose (mmol/L)	5.0 – 7.0	7.1 – 10.0	10.1 – 13.0	> 13.0

Table 2. Targets for Blood Pressure and Lipids: Comparison of CPG on Diabetes Mellitus (2006) MOH and the ADA Clinical Practice Recommendations (2008)

		CPG (2006)	ADA (2008)
1.	**Blood pressure goal**		
	Systolic blood pressure:	< 130 mmHg	< 130 mmHg
	Diastolic blood pressure:	< 80 mmHg	< 80 mmHg
2.	**Lipids goal**		
	A. LDL-cholesterol level:		
	Individuals without overt CVD:	< 2.6 mmol/L (< 100 mg/dL)	< 2.6 mmol/L (< 100 mg/dL)
	Individuals with overt CVD:	< 2.1 mmol/L (< 70 mg/dL)	< 1.8 mmol/L (< 80 mg/dL)
	B. Triglycerides level:	< 2.3 mmol/L (< 200 mg/dL)	< 1.7 mmol/L (< 150 mg/dL)
	C. HDL-cholesterol level:	> 1.0 mmol/L (> 40 mg/dL)	Men: > 1.0 mmol/L (> 40 mg/dL) Women: > 1.3 mmol/L (> 50 mg/dL)

LEARNING POINTS

- **Self-monitoring of blood glucose (SMBG) contributes to effective diabetes mellitus management; the frequency of monitoring depends on the type of diabetes and stability of diabetes control.**
- **Targets of glycaemic control into ideal, optimal, suboptimal and unacceptable control help both doctor and patient in setting up individual goals of control.**
- **Targets for blood pressure control and lipid control are also recommended in view of the fact that patients with diabetes often have underlying metabolic syndrome with concomitant hypertension and dyslipidaemia.**