

## The clinical biochemistry of diabetes mellitus in Singapore

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### INTRODUCTION

Diabetes mellitus is a common and growing health problem worldwide. In Singapore, the prevalence of diabetes mellitus among adults has risen from 1.9% in 1975 and 4.7% in 1984 to 8.6% in 1992 (1). In the 1998 National Health Survey (NHS), the crude prevalence of diabetes was 8.5% in males and 9.6% in females (2). Among the ethnic groups, the prevalence was highest among the Indians (15.8%), followed by the Malays (11.3%) and Chinese (8.0%). It was also noted that type 2 diabetes mellitus is increasing in the youth and in children. The survey found that 62.1% of Singapore residents who had diabetes mellitus (through screening) had not been previously diagnosed.

Diabetes mellitus is generally managed by the Ministry of Health outpatient polyclinics, with almost 1-in-10 visits (approximately 350,000) per year attributable to diabetes mellitus (3). In 1998, about 240,000 bed-days, accounting for 8% of the total, were utilised for diabetes mellitus management, with an average length of stay per episode of 8.8 days. Diabetes mellitus-related deaths are the sixth commonest cause the death in Singapore, contributing to 9.3% of mortality statistics (4).

Diabetes mellitus is a chronic and complex disease, requiring continued life-long management aimed at reducing the high morbidity and premature mortality caused by chronic complications associated with the disease. Many people with diabetes mellitus receive sub-optimal care. In a recent DiabCare Asia Study conducted to assess the status of diabetes mellitus control and chronic complications, about 50% of almost 1700 Singapore patients surveyed at hospital and government outpatient clinics had glycated haemoglobin levels in the sub-optimal or unacceptable levels (5).

### SCREENING OF ASYMPTOMATIC INDIVIDUALS

The 1998 National Health Survey showed that 62.1% of Singaporeans detected to have diabetes were previously unaware of the diagnosis. This is consistent with reports that type 2 diabetes mellitus generally manifests 4-7 years prior to clinical diagnosis (6). Fingerprick capillary blood glucose measured by a portable glucometer is not considered to have sufficient accuracy for initial diagnosis of diabetes, but can be used for screening purpo-

ses. Individuals screened to have fasting capillary blood glucose  $>6.0$  mmol/L or casual capillary blood glucose  $\geq 7.8$  mmol/L using a glucometer should have venous blood taken and sent for estimation of venous plasma glucose by a standardised laboratory based determination.

The local recommended guidelines for the screening of asymptomatic individuals for diabetes mellitus are:

- All individuals aged 40 and above, at 3 yearly intervals.
- At a younger age if the following are present:
- Obesity (BMI  $>27$  kg/m<sup>2</sup>)
- Hypertension (BP  $>140/90$  mmHg)
- 1st Degree relative with diabetes
- Previous gestational diabetes
- Documented coronary artery disease
- All individuals with impaired glucose tolerance or impaired fasting glucose should be screened annually (7).

### DIAGNOSIS

In a patient with typical symptoms of hyperglycaemia, diabetes mellitus can be diagnosed on any one of the following criteria:

- Casual plasma glucose  $\geq 11.1$  mmol/L
- Fasting plasma glucose (FPG)  $\geq 7.0$  mmol/L
- 2-hour plasma glucose following an oral glucose tolerance test (OGTT)  $\geq 11.1$  mmol/L

Venous blood should be collected in appropriate tubes for plasma glucose determination by a standardised laboratory based method. When typical symptoms of hyperglycaemia are absent, a second confirmatory test on another day is required. Fasting plasma glucose remains the diagnostic test of choice for establishing and documenting the onset of diabetes.

### INTEGRATED MANAGEMENT OF DIABETES

Diabetes care should be structured and organised around purpose-built Diabetes Centres, where an interdisciplinary team approach to the management of diabetes can be effectively organised with minimal inconvenience to the patient. The management team should include the primary care doctor, diabetes educators with direct access to diabetes specialists and other support professionals, and health-care providers such as cardiologist, ophthalmologists, neurologists, nephrologists, podiatrists, phar-

macists and social workers.

### GLYCAEMIC CONTROL: SELF-MONITORING OF BLOOD GLUCOSE

Abbott/MediSense Laboratories, YSI, Bayer Corporation, Boehringer Mannheim, The Roche Group, Home Diagnostics, Inc., LifeScan Inc., Inverness Medical, and Kyoto Daiichi produce the more popular commercial blood-glucose meters. The measurement requires a 3- to 10- $\mu$ L drop of blood and usually takes <1 min. Although all meters take a whole-blood sample to calculate blood glucose, some of the newer meters and/or test strips have been calibrated to provide the result as a plasma equivalent. Plasma-calibrated meters and/or test strips make it easier for comparison between glucometer and laboratory reported results. A plasma-calibrated meter will report a reading ~12% higher than a whole blood calibrated meter (8).

The precision of such devices is highly operator-dependent and this requires meticulous adherence to the manufacturer's instructions. Besides poor technique and inadequate amount of blood sample, other common errors are due to defective or expired test strips, incorrect calibration and instrument failure. Initial training for the use of blood glucometers should be provided by qualified staff rather than having the patient read through the manufacturer's manual. The importance of meter calibration should be highlighted. Annual reviews appear to be necessary to verify users' competency, provide an update of the advances of home glucose devices, and evaluate the correlation between capillary glucose levels on the glucometer with a simultaneous venous sample analysed by a central laboratory. Calibration checks of meters should also be conducted with standard solutions according to the manufacturer's recommendations.

Self-monitoring of capillary blood glucose (SMBG) by patients should be an integral part of diabetes self-care. Charting of day-to-day trend should form the basis of fine-tuning the appropriate therapy and to assess the efficacy of treatment (9).

A suggested regime for home monitoring is as follows:

- For patients with type 1 diabetes and most insulin-treated type 2 patients, a frequency of one to two days per week is recommended.
- For non insulin-treated patients, SMBG may be performed less frequently but it should be done sufficiently to facilitate reaching glucose target levels.
- For patients with unstable metabolic control, changes in daily routine, alterations of treatment regimens or inter-current illness, the frequency of SBGM should be increased.

### GLYCAEMIC CONTROL: GLYCATED HAEMOGLOBIN TESTING

In the 1990s, in the Diabetes Control and Complications Trial (DCCT) (10) and United Kingdom Prospective

Diabetes Study (UKPDS) (11) demonstrated that glycaemic control impacts on the development of microvascular complications. Healthcare professionals have been reaffirmed in focusing their efforts on improving the glycaemic control of their patients. Unlike the rapid fluctuation of glucose in blood, the measurement of glycated haemoglobin quantifies average glycaemia over the preceding 2-3 months. This tool complements and provides a more stable index compared to blood glucose testing, which indicates day-to-day glycaemic excursions.

The term "glycated haemoglobin" refers collectively to a sequence of stable adducts, which are formed between haemoglobin and sugars, where glycated haemoglobin A1c (HbA1c) is the most important indicator of the degree of severity of diabetes. The fraction of HbA1c in healthy adults is ~5%, but it can increase two- to threefold in patients with diabetes mellitus. The availability of glycated haemoglobin (HbA1c) has revolutionised diabetes management. Ion exchange, affinity chromatography, and electrophoresis are the major analytical methods for HbA1c determination. Technical issues of assay standardisation no longer hamper and limit the clinical application of glycated haemoglobin. In 1996, the US National Glycohemoglobin Standardization Program (NGSP) Steering Committee implemented a programme that would enable laboratories to report DCCT-traceable standardised glycohaemoglobin results.

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 method used, the glycated components measured (HbA1, or HbA1c), the non-diabetic reference interval, and potential assay interferences.

The following schedule is recommended for glycated haemoglobin testing (12):

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

Table 1 shows the adopted classification of glycaemic control based on reference ranges established by leading local institutions, which have established reference intervals for non-diabetic populations. These values were determined by standardised assays on the Biorad Variant® and Variant Express® (7).

### MANAGEMENT OF CONCOMITANT CONDITIONS

#### Diabetic Dyslipidaemia

The recently announced Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) has put an increased emphasis on the management of lipids in persons with diabetes. Those with multiple metabolic risk factors (the metabolic syndrome) are identified as candidates for intensified therapeutic lifestyle changes.

Table 1

Test	Assessment of Glucose Control			
	Ideal (non-diabetic levels)	Optimal (target goal for majority of patients)	Sub-optimal (adequate goal for some patients)	Unacceptable (action needed in all patients)
Glycated Haemoglobin (HbA1C in %)	4•5-6•4	6•5-7•0	7•1-8•0	>8•0
Pre-meal glucose* (mmol/L)	4•0-6•0	6•1-8•0	8•1-10•0	>10•0
2h post-meal glucose* (mmol/L)	5•0-7•0	7•1-10•0	10•1-13•0	>13•0

\* capillary blood sampling

Table 2

Performance Parameter	Recommended Frequency
Home glucose monitoring (fasting)	1 - 4 times a week
Glycated haemoglobin (HbA1c)	2 - 4 times a year
Urine albumin: creatinine ratio	4 times a year
Lipid profile	4 times a year
Serum creatinine	4 times a year

The status of persons with type 2 diabetes has been recognised to be equivalent to that of having established coronary heart disease (CHD). The primary target of therapy is the identification of low-density lipoprotein cholesterol (LDL-C), for which the goal for persons with diabetes is < 2•6 mmol/L (100 mg/dL), irrespective of whether or not there is documented CHD<sup>13</sup>.

Most Singaporean diabetics have some degree of dyslipidaemia/ hypercholesterolaemia. Consequently, atherosclerotic heart disease is a substantial risk to the diabetic population and accounts for over 75% of hospitalisations for diabetic complications. People with diabetes are far more susceptible to coronary heart disease (CHD) than the general population and suggests that long-term, aggressive control of lipid levels is as critical as that of glycaemic control. Aggressive lipid lowering, although a desirable goal, does not yet appear to be standard practice.

### Microalbuminuria

Microalbuminuria is an important risk factor for the development of progressive diabetic nephropathy. It is usually detected in 30% of patients with type 1 diabetes between 5-15 years after diagnosis. In type 2 diabetes, there is already a high prevalence of dipstick positive albuminuria, at the time of diagnosis<sup>14</sup>. Early detection of microalbuminuria allows identification of selected patients who would benefit from aggressive intervention to forestall the onset of overt renal disease. Microalbuminuria is defined as either an albumin concentration of 20-200 mg/L or an albumin: creatinine ratio of > 3•5 (women) and > 2•5 g/mmol (men) on first void morning urine. Albumin excretion

rates (AER) of 20-200 ug/min or 30-300 mg/day are also commonly used to define microalbuminuria.

### Summary

Table 2 summarises the suggested biochemical surveillance parameters in the management of diabetes mellitus. Diabetes is a chronic illness with numerous serious complications resulting in significant morbidity and mortality. Addressing issues of medical effectiveness of treatment and continuous improvement of the quality of care of patients with diabetes have been shown to have significant positive impact on the patient, the community and health service provider.

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