TYPE 1 DIABETES MELLITUS

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The term type 1 diabetes mellitus has replaced insulin-dependent diabetes (IDDM), juvenile-onset diabetes mellitus (JODM) and early-onset diabetes mellitus. The previous names were based on the fact that type 1 diabetics need insulin for life and usually present before the age of 30. The new classification represents an attempt to 'introduce an appropriate, uniform terminology and a functional, working classification of diabetes that reflects the current knowledge about the disease'.

Type 1 diabetes mellitus is a disorder characterised by β-cell destruction, usually leading to absolute insulin deficiency. Carbohydrate metabolism is severely deranged and patients require insulin in order to survive.

CLASSIFICATION

Type 1 diabetes mellitus is now divided into type 1A (autoimmune) and type 1B (idiopathic). Type 1A diabetes results from cell-mediated autoimmune destruction of the β-cells of the pancreas. Markers of this process include islet cell, insulin, glutamic acid decarboxylase and tyrosine phosphatase autoantibodies. At least 1 of these autoantibodies is found when hyperglycaemia is initially detected. The disease has strong HLA associations (see below).

Type 1B diabetes is less frequent than type 1A, has no known cause, and most patients are of Asian or African descent. Patients with type 1B diabetes tend to have diabetic ketoacidosis as their initial clinical presentation, lack autoimmune markers at diagnosis, and have physical characteristics more typical of patients with type 2 diabetes. After recovery from their initial episode many of these patients seem to achieve acceptable glycaemic control for many years using either diet alone or diet plus oral hypoglycaemic agents.

PATHOGENESIS

Type 1A diabetes mellitus results from a cell-mediated autoimmune attack on β cells. It is believed to arise as a result of a combination of genetic and environmental factors. Susceptibility is inherited, and is associated with HLA DR and DQ, and to a lesser extent with a number of other genetic loci termed 'insulin-dependent diabetes mellitus (IDDM) susceptibility genes'. It is thought that a susceptible individual needs to be exposed to an environmental trigger for diabetes to occur. These triggers include viruses (e.g. enteroviruses, coxsackie, and congenital rubella), and toxins or foods (dietary exposure to non-human proteins in early infancy). T-cell activation leads to inflammation, mononuclear cell infiltration of pancreatic islands (insulitis) and to a humoral (B cell) response, possibly secondary to the insulitis, with production of autoantibodies to insulin. There is loss of insulin secretory reserve and ultimately absolute insulin deficiency with type 1 diabetes.

There are approximately 171 million people with diabetes worldwide. In South Africa about 4 million people are known to have diabetes mellitus. The crude prevalence in a study in Umtata, Eastern Cape, was 2.45%. Diabetes mellitus was responsible for 1.6% of deaths in South African females and 0.9% in males. The 'disability-adjusted life years' (DALY) rate for diabetes mellitus in South Africa ranks second in the world after the American region.

The prevalence of type 1 diabetes mellitus varies greatly in different socio-economic and geographical areas. One to 6% of Africans living on the African continent have diabetes, and approximately 25% of these patients are treated with insulin. It has been suggested that roughly half of these have type 1B diabetes.

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PATHOPHYSIOLOGY

Diabetes is strongly associated with certain human leukocyte antigens (HLA). While certain HLA types may confer risk, others have been found to protect against diabetes. Local studies suggest that HLADRB1*09 and HLA-DQB*0302 have the strongest association with type 1 diabetes in black South Africans. Non-HLA susceptibility loci include the 'IDDM susceptibility genes'. Although environmental triggers have been sought the association between putative agents such as viruses, toxins, early infant diet and diabetes is still unclear.

Type 1 diabetes is heterogeneous and polygenic. The relative risk for developing diabetes is 33% in identical twins, but the chance of a child developing type 1 diabetes when another first-degree relative has the disease is only 5 - 10%. The risk is higher when the father has the disease (8%) than when the mother is diabetic (3%).

CLINICAL FEATURES

The onset of type 1 diabetes is usually abrupt. Symptoms due to hyperglycaemia (polyuria, polydipsia, polyphagia, blurred vision) are common, as are fatigue and unusual weight loss. Impaired growth in children may also be seen.

The first event may be severe diabetic coma, the onset of which may be unexplained or accompany an intercurrent illness or surgery. Anorexia, nausea and vomiting, coupled with polyuria, result in severe dehydration. This is followed by drowsiness and coma. Examination usually reveals characteristic Kussmaul breathing and there is a smell of acetone on the patient's breath. If present, fever should suggest the presence of infection. Apart from hyperglycaemia with ketoacidosis, nonketotic hyperosmolar syndromes may complicate type 1 diabetes.

Other complications of type 1 diabetes include retinopathy with loss of vision; nephropathy leading to renal failure; peripheral neuropathy with foot ulcers, Charcot joints; and autonomic neuropathy with genitourinary and gastrointestinal symptoms and sexual dysfunction. There is a high risk of cardiovascular and peripheral vascular disease. Type 1 diabetics have an increased propensity to develop infections.

DIAGNOSTIC CRITERIA

The diagnosis of type 1 diabetes should not be difficult as most patients present with acute symptoms and markedly elevated blood glucose levels. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommend the following criteria for the diagnosis of diabetes mellitus:
- Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/l. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
                    or
- Fasting plasma glucose ≥ 7.0 mmol/l. Fasting is defined as no caloric intake for at least 8 hours.
                    or
- 2-hour plasma glucose ≥ 11.1 mmol/l during an oral glucose tolerance test performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

EVALUATION

The expert committee of the American Diabetes Association has produced a checklist which should serve as a guide to all doctors caring for patients with type 1 diabetes (Table I).

MONITORING

Monitoring of glycaemic status, by patients and health professionals, is a critical component of diabetes care. Results are used to assess management and to guide medication, diet, and exercise. Ideally monitoring should also determine the risk of complications and where present their degree and severity.

Urine testing is relatively inexpensive and easy. Urine glucose measurement provides only a rough estimate of blood glucose levels above the renal threshold, which for most patients is ± 10 mmol/l. For this reason urine testing has largely been replaced by self-monitoring of blood glucose (SMBG), which has revolutionised the management of diabetes. Patients with type 1 diabetes should attempt to achieve and maintain blood glucose levels as close to normal as is safely possible. Such optimal management can only be achieved using SMBG. The frequency varies but most patients with type 1 should measure their blood glucose 3 or more times daily.

Blood and urine glucose testing are useful for the day-to-day management of diabetes but do not provide any insight into the medium- to long-term control of hyperglycaemia. Here, measurement of glycated proteins such as haemoglobin has revolutionised the management of diabetes. HbA_{1c} is a relatively stable haemoglobin component formed from haemoglobin and glucose. The rate of formation of HbA_{1c} is directly proportional to the ambient glucose concentration. The level of HbA_{1c} in a blood sample provides an accurate history of blood sugar control over the previous 2 - 3 months. Haemoglobin A_{1c} determination is easy, relatively

Table I. Components of the comprehensive diabetes evaluation*

Medical history

• Symptoms, results of laboratory tests, and special examination results related to the diagnosis

• Eating patterns, nutritional status, and weight history; growth and development in children and adolescents

• Details of previous treatment, including nutrition and diabetes self-management education, attitudes, and health beliefs

• Current treatment of diabetes, including medications, meal plan, and results of glucose monitoring

• Exercise history

• Frequency, severity, and cause of acute complications such as ketoacidosis and hypoglycaemia

• Prior or current infections, particularly skin, foot, dental, and genitourinary infections

• Symptoms and treatment of chronic eye; kidney; nerve; genitourinary (including sexual), bladder, and gastrointestinal function; heart; peripheral vascular; foot; and cerebrovascular complications associated with diabetes

• Other medications that may affect blood glucose levels

• Risk factors for atherosclerosis: smoking, hypertension, obesity, dyslipidaemia, and family history

• History and treatment of other conditions, including endocrine and eating disorders

• Assessment for mood disorder

• Family history of diabetes and other endocrine disorders

• Lifestyle, cultural, psychosocial, educational, and economic factors that might influence the management of diabetes

• Tobacco, alcohol, and/or controlled substance use

• Contraception and reproductive and sexual history

Physical examination

• Height and weight measurement (and comparison to norms in children and adolescents)

• Sexual maturation staging (during pubertal period)

• Blood pressure including orthostatic measurements and comparison to age-related norms

• Fundoscopic examination

• Oral examination

• Thyroid palpation

• Cardiac examination

• Abdominal examination (e.g. for hepatomegaly)

• Evaluation of pulses by palpation and with auscultation

• Hand/finger examination

• Foot examination

• Skin examination (for acanthosis nigricans and insulin-injection sites)

• Neurological examination

• Signs of diseases that can cause secondary diabetes (e.g. haemochromatosis, pancreatic disease)

Laboratory evaluation

• HbA_{1c}

• Fasting lipid profile, including total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol, liver function tests with further evaluation for fatty liver or hepatitis if abnormal

• Test for microalbuminuria in type 1 diabetic patients who have had diabetes for at least 5 years

• Serum creatinine and calculated GFR in adults (check creatinine in children if proteinuria is present)

• Thyroid-stimulating hormone (TSH) in all type 1 diabetic patients

• Electrocardiogram in adults, if clinically indicated

• Urinalysis for ketones, protein, sediment

Referrals

• Eye exam, if indicated

• Family planning for women of reproductive age

• Diabetes educator, if not provided by physician or practice staff

• Behavioural specialist, as indicated

• Foot specialist, as indicated

*Modified from American Diabetes Association. Standards of Medical Care in Diabetes – 2006. *Diabetes Care* 2006; **29** (Suppl 1) : S5-42.

inexpensive and can be done at any time of day. Its level correlates strongly with the risk for eye, kidney, and nerve disease in people with type 1 diabetes mellitus.

MANAGEMENT

Management of type 1 diabetes, whether in a quaternary or primary setting, is dependent on teamwork and the principles of a primary health care approach (Fig. 1).

- Should be by a team of physicians, nurses, dietitians and pharmacists
- Is critically dependent on patients and their family being part of a therapeutic alliance
- Patient and family education is vital
- Care is life-long and often spans childhood, adolescence and adulthood and must be tailored to the patient's:
    - age
    - school or work schedule and conditions
    - physical activity
    - eating patterns
    - social situation and personality
    - cultural factors, and
    - presence of complications of diabetes or other medical conditions

(Standards of Medical Care in Diabetes–2006. *Diabetes Care* 2006; 29 (Suppl 1, S5-42.)

Fig. 1. Management of type 1 diabetes mellitus.

Table II. Correlation between HbA_{1C} level and mean plasma glucose levels*

HbA$_{1C}$ (%)	Mean plasma glucose (mmol/l)
6	7.5
7	9.5
8	11.5
9	13.5
10	15.5
11	17.5
12	19.5

* Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA$_{1c}$: analysis of glucose profiles and HbA$_{1c}$ in the Diabetes Control and Complications Trial. *Diabetes Care* 2002; **25**: 275–278.

Aims of management

There is overwhelming evidence that good glycaemic control reduces microvascular and neuropathic complications of diabetes. The recommended targets for adults are summarised in Table III.

NON-DRUG MANAGEMENT

Education

Patient education is a vital component of care. Educators should have insight into the patient's cultural background, socio-economic status and educational level. Education should where possible be in the patient's mother tongue.

Table III. Recommended targets for adults*

Glycaemic control	
Haemoglobin A$_{1C}$	< 7.0%
Preprandial capillary plasma glucose	5.0 – 7.2 mmol/l
Peak postprandial capillary plasma glucose	< 10.0 mmol/l
Blood pressure	< 130/80 mmHg
Lipids	
LDL	< 2.6 mmol/l
Triglycerides	< 1.7 mmol/l
HDL	> 1.1 mmol/l

Diabetes Care 2006; **29** (Suppl 1): S5-42.

Points to cover should include an explanation of the disease, what to do when feeling unwell, how and when to take injections, how to recognise hyper- and hypoglycaemia, foot care and the need to join Medic Alert.

Diet

Dietary intervention is fundamental in the management of diabetes mellitus. Dietary guidelines should be individualised according to the patient's age, sex, weight and physical activities. Diets must be culturally acceptable and affordable. Rigid diabetic diets are difficult to follow and often lead to non-adherence.

Recommended energy intake

This should be explained in terms the patient can understand. Complex carbohydrates should provide 50 - 60% of energy intake; total fat 30 – 35% and saturated fat < 7%. Protein should contribute the remaining 15 - 20%. Attention should be paid to meeting vitamin and mineral requirements.

Exercise

Regular aerobic exercise has been recognised as an important component of the management of diabetes. Current recommendations suggest at least 150 min/week of moderate-intensity aerobic physical activity (50 – 70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (> 70% of maximum heart rate). The physical activity should be distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity.

DRUG MANAGEMENT

Insulin is the mainstay of the management of type 1 diabetes mellitus. In South Africa all varieties of insulin are biosynthetic. They are produced using a recombinant DNA technology and the human molecular structure. Only a single strength, 100 units/ml, is available. Table IV lists the insulin preparations available in South Africa.

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Table IV. Characteristics of insulin preparations available in South Africa*

Trade name	Manufacturer	Onset	Peak	Duration	Route	Solubility
Ultra fast-acting insulin						
Humalog	Eli-Lily	15 min	1 h	3 – 4 h	SC	Soluble
NovoRapid	Novo Nordisk	10 min	45 min	3 – 5 h	SC	Soluble
Fast-acting insulin						
Actrapid HM	Novo Nordisk	30 min	2.5 – 5 h	8 h	IV/IM/SC	Soluble
Humulin R	Eli Lily	20 – 30 min	1 – 3 h	5 – 7 h	IV/IM/SC	Soluble
Intermediate to long-acting insulin						
Humulin N	Eli Lily	1 h	2 – 8 h	18 – 20 h	SC	Suspension
Lantus	Aventis	1 h		22 – 24 h	SC	Suspension
Monotard HM	Novo Nordisk	2.5 h	7 – 15 h	22 – 24 h	SC	Suspension
Protaphane HM	Novo Nordisk	1.5 h	4 – 12 h	24 h	SC	Suspension
Biphasic insulin						
Actraphane 30/70 HM	Novo Nordisk	30 min	2 – 12 h	20 – 24 h	SC	Suspension
Humulin 30/70	Eli Lily	30 min	1 – 8 h	14 – 15 h	SC	Suspension
Humualog Mix25	Eli Lily	15 min	0.5 - 2.5 h	14 – 16 h	SC	Suspension
NovoMix 30	Novo Nordisk	10 – 20 min	1 – 4 h	up to 24 h	SC	Clear
Ultra long-acting insulins						
Ultratard HM	Novo Nordisk	4 h	8 – 24 h	28 h	SC	Suspension

*Adapted from Gibbon CJ, ed. South African Medicines Formulary 7th ed. Cape Town: Health and Medical Publishing Group, 2005.

Insulin regimens

Patients with type 1 diabetes will require insulin for life. The insulin regimen should:

• mimic normal blood insulin concentrations
• provide adaptability
• must fit the needs of the individual
• suit the patient's circumstances
• initially be given at 03 - 0.6 units/kg/day (adjusted according to response).

For type 1 diabetics:

• Twice-daily injections of a mixture of a short- and an
    intermediate-acting insulin is most commonly used,
    especially for young and middle-aged patients with a
    long life expectancy. Patients unable to mix their own
insulins may use premixed short- and intermediate-acting
insulins. Two-thirds of the daily dose of insulin is given approximately 30 minutes before breakfast and one-third before supper.

• Where the above regimen leads to late evening or
    early morning hypoglycaemia the intermediate-acting
    insulin dosage before supper should be reduced. If early-
morning hyperglycaemia occurs the short-acting insulin
may be given before supper and the intermediate insulin
at bedtime (about 22h30) together with a snack.

• A 'basal bolus regimen' provides good control in well-motivated patients with SMBG. An intermediate-acting insulin is injected before bedtime, supplem-ented by 3 preprandial short-acting insulin injections: alternatively, an ultra long-acting insulin is injected before bedtime providing 24-hour basal insulin requirements, supplemented by 3 preprandial short-acting insulin injections.

Insulin syringes should be 0.5 ml or 1 ml size with ultrathin 12-mm long needles. Insulin may be injected in any part of the body with loose skin such as the abdomen, thighs, arms and buttocks. The anterior abdomen is recommended for subcutaneous injections. The advent of pen injector devices has made insulin injections much less unpleasant for the patient.

Diabetic diary

Patients should keep a diary containing all sugar measurements, insulin doses and untoward symptoms. The data should be reviewed at each visit.

Complications of diabetes mellitus

The complications of diabetes are dealt with elsewhere in this edition of *CME*.

CONCLUSION

Type 1 diabetes mellitus is most commonly first seen before the age of 30. It is caused by an absolute deficiency of insulin. Management should be holistic and is best provided by a multidisciplinary team. Patients benefit from a regimen based on a primary health care approach.

Further reading

Bradshaw D, Groenewald P, Laubscher R, *et al*. Initial burden of disease estimates for South Africa, 2000. *S Afr Med J* 2003; **93**: 682-688.

Daneman D. Type 1 diabetes. *Lancet* 2006; **367**: 847–858.

Erasmus RT, Blanco Blanco E, Okesina AB, Matsha T, Gqweta Z, Mesa JA. Prevalence of diabetes mellitus and impaired glucose tolerance in factory workers from Transkei, South Africa. *S Afr Med J* 2001; **91**:157-160.

Gerstein HC. Glycosylated hemoglobin: finally ready for prime time as a cardiovascular risk factor. *Ann Intern Med* 2004; **141**: 475-476.

Gibbon CJ, ed. *South African Medicines Formulary*. 7th ed. Cape Town: Health and Medical Publishing Group, 2005.

Goldstein DE, Little RR, Lorenz RA, *et al*. Tests of glycemia in diabetes. *Diabetes Care* 2003; **26** (Suppl 1): S106-108.

Pirie FJ, Hammond MG, Motala AA, Omar MA. HLA class II antigens in South African blacks with type 1 diabetes. *Tissue Antigens* 2001; **57**: 348-352.

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; **26**: S5-20.

Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA$_{1c}$: analysis of glucose profiles and HbA$_{1c}$ in the diabetes control and complications trial. *Diabetes Care* 2002; **25**: 275–278.

Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF. Diabetes in Africans. Part 2: Ketosis-prone atypical diabetes mellitus. *Diabetes Metab* 2002; **28**: 5-12.

Standards of Medical Care in Diabetes – 2006. *Diabetes Care* 2006; **29** (Suppl 1): S5-42.

Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**:1047–1053.

IN A NUTSHELL

The term type 1 diabetes mellitus has replaced insulin-dependent diabetes (IDDM), juvenile-onset diabetes mellitus (JODM) and early-onset diabetes mellitus. The previous names were based on the fact that type 1 diabetics need insulin for life and usually present before the age of 30.

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Type 1A diabetes mellitus results from a cell-mediated autoimmune attack on β-cells. It is believed to arise as a result of a combination of genetic and environmental factors.

In South Africa about 4 million people are known to have DM. The crude prevalence in a study in Umtata, Eastern Cape, was 2.45%. Diabetes mellitus was responsible for 1.6% of deaths in South African females and 0.9% in males. The 'disability-adjusted life years' (DALY) rate for diabetes mellitus in South Africa ranks second in the world after the American region.

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The onset of type 1 diabetes is usually abrupt. Symptoms due to hyperglycaemia (polyuria, polydipsia, polyphagia, blurred vision) are common, as are fatigue and unusual weight loss. Impaired growth in children may also be seen.

The diagnosis of type 1 diabetes should not be difficult as most patients present with acute symptoms and markedly elevated blood glucose levels.

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Urine testing has largely been replaced by self-monitoring of blood glucose (SMBG), which has revolutionised the management of diabetes. Patients with type 1 diabetes should attempt to achieve and maintain blood glucose levels as close to normal as is safely possible.

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There is overwhelming evidence that good glycaemic control reduces microvascular and neuropathic complications of diabetes.

Education, diet and exercise are important in the non-drug treatment of type 1 diabetes mellitus.

Insulin therapy is the mainstay of drug treatment of type 1 diabetes mellitus.

In South Africa all varieties of insulin are biosynthetic. They are produced using a recombinant DNA technology and the human molecular structure. Only a single strength, 100 units/ml, is available.

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