Diabetes

Part 1. Definition, Diagnosis and Prevention

Victor Lawrence[a] BSc, MB BS, MRCP, Consultant Physician, The Arun Baksi Centre for Diabetes and Endocrinology, St Mary's Hospital, Isle of Wight PO30 5TG, UK

Introduction

Western countries are experiencing an explosion in the prevalence of type 2 diabetes (T2DM) linked to increasing obesity and a steady year on year rise in the incidence of type 1 diabetes (T1DM) in children. However, for reasons that are not currently understood, the situation in Sub-Saharan Africa is less clear. Many factors contribute to this. Problems reported in other African countries include:

- failure of patients to present to health care facilities (either because of rapid death in T1DM or lack of clear symptoms in T2DM sometimes linked to malnutrition);
- targeting of acute infection rather than less cost effective long term conditions in healthcare prioritisation and
- problems with the reliable supply, affordability and storage of insulin, other medications and the means to monitor treatment (e.g. finger prick blood testing).

Some population studies in Africa have suggested that type 1 diabetes is a rare condition. Sadly, this is more likely to be due to the fact that those affected die undiagnosed within a few weeks and so are rarely counted. Some studies have suggested under-diagnosis even amongst patients presenting to hospital with ketoacidosis.

In spite of this, we know that diabetes is a common condition affecting perhaps 2-6% of most populations and its under-diagnosis and under-treatment leads to rapid death in T1DM and to unnecessary suffering and premature death in T2DM. This article aims to:

- increase awareness of the condition;
- discuss symptoms and diagnostic criteria;
- consider screening and prevention of diabetes;
- point the reader in the direction of more detailed open access information (see references below).

The management of diabetes will be discussed in the next issue of the Bulletin

[a] victor.lawrence AT iow.nhs.uk

Definition of diabetes

Diabetes is a disorder of the regulation of blood glucose. The World Health Organisation (WHO) defines diabetes on the basis of an oral glucose tolerance test (OGTT) (Table 1). The American Diabetes Association (ADA) defines diabetes and impaired fasting glucose on the basis of fasting plasma glucose (FPG) only - which may be more cost effective as a screening tool (Table 2) - usually reserving OGTT to patients with abnormal fasting glycaemia.

Type 1 diabetes is characterised by an absolute deficiency of insulin and type 2 diabetes by resistance to insulin action. Most commonly (approximately 80% of the time), T1DM presents in childhood with rapid (few weeks) weight loss, lethargy, polyuria, polydipsia, blurred vision, ketosis (acetone on breath, not always detectable) and profound dehydration or shock.

Type 2 diabetes usually affects older individuals, especially if obese, and has a more insidious onset with fatigue, polyuria, polydipsia, weight loss and infections (e.g. boils, candida). If the disease is not recognised, it may present at a later stage with established diabetic complications including renal failure, peripheral neuropathy or diabetic retinopathy or cataract. Some secondary causes of diabetes (that is, diabetes being secondary to another illness or condition) occur commonly in populations where alcohol is abused or malnutrition is common (Table 3).

Table 1. Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia (WHO)

Condition	**Glucose concentration, mmol l^{-1} (mg dl^{-1})**		
	Whole blood	Whole blood	Plasma*
	Venous	Capillary	Venous
Diabetes Mellitus:			
Fasting	>=6.1 (>=110)	>=6.1 (>=110)	>=7.0 (>=126)
or			
2-h post glucose load	>=10.0 (>=180)	>=11.1 (>=200)	>=11.1 (>=200)
or both			
Impaired Glucose Tolerance (IGT):			
Fasting (if measured)	<6.1 (<110)	<6.1 (<110)	<7.0 (<126)
and			
2-h post glucose load	>=6.7 (>=120) and <10.0 (<180)	>=7.8 (>=140) and <11.1 (<200)	>=7.8 (>=140) and <11.1 (<200)
Impaired Fasting Glycaemia (IFG):			
Fasting	>=5.6 (>=100) and <6.1 (<110)	>=5.6 (>=100) and <6.1 (<110)	>=6.1 (>=110) and <7.0 (<126)
and (if measured)			
2-h post glucose load	<6.7 (<120)	<7.8 (<140)	<7.8 (<140)

Table 2. Criteria for the diagnosis of diabetes mellitus (ADA)

1. Symptoms of diabetes plus casual plasma glucose concentration >11.1 mmol/l (200 mg/dl). 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

2. Fasting plasma glucose (FPG) >7.0 mmol/l (126 mg/dl). Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h post-load glucose 11.1 mmol/l (200 mg/dl) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

Insulin resistance in comparison to insulin deficiency

It is important to recognise that many individuals are hard to define as having pure insulin resistance or pure insulin deficiency particularly in the secondary forms of diabetes (Table 3). Clinical judgement, testing of urine ketones and monitoring of the response to treatment (e.g. blood glucose levels, HbA1c, weight and general wellbeing) is required to determine whether insulin treatment will be required from the outset, later on or not at all. Many patients who are initially treated as type 2 diabetes with oral hypoglycaemic agents (OHAs) will later require insulin, and some requiring insulin for treatment of HHS (see below) will later be adequately managed on tablets and diet alone.

Table 3. Etiological Classification of Diabetes Mellitus (simplified classification based on WHO)

I. Type 1 diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
- A. Immune mediated
- B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
- A. Genetic defects of ß-cell function (MODY, mitochondrial disorders, other)
- B. Genetic defects in insulin action (e.g. Leprechaunism, congenital lipoatrophic disorders)
- C. Diseases of the exocrine pancreas (e.g. pancreatitis, trauma, pancreatectomy, neoplasia, fibrocalculous pancreatopathy)
- D. Endocrinopathies (e.g. acromegaly, Cushing's syndrome, thyrotoxicosis)
- E. Drug- or chemical-induced (e.g.glucocorticoids, thiazides, phenytoin, antiretroviral therapy)
- F. Infections (e.g. Congenital rubella, Cytomegalovirus, HIV/AIDS)
- G. Uncommon forms of immune-mediated diabetes (e.g. anti insulin receptor antibodies)
- H. Other genetic syndromes sometimes associated with diabetes (e.g. Prader-Willi syndrome)

IV. Gestational diabetes mellitus (GDM)

Modified from WHO Study Group on Diabetes Mellitus
http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

Diagnosis and screening

Diagnosis in acute settings

Many patients will present to a hospital with a metabolic emergency: diabetic ketoacidosis (DKA) in T1DM or hyperosmolar hyperglycaemic syndrome (HHS, previously sometimes called HONK) in T2DM. Secondary forms of diabetes may take either form. Patients with long standing type 2 diabetes commonly lose the ability to produce insulin over time and require insulin treatment in spite of having previously been well controlled with dietary modification or oral hypoglycaemic agents (OHAs) such as sulphonylureas or metformin. Excellent guidance in the treatment of these conditions, and many other aspects of diabetes is provided by the ADA with open access online (see references below).

Diabetic ketoacidosis

The clinical features of DKA include dehydration, shock, vomiting, abdominal pain, acidosis (with Kussmaul breathing or, in some cases, ketones on the breath), and cerebral impairment. Biochemical features of ketoacidosis include hyperglycaemia, ketosis (ketonaemia and ketonuria), metabolic

acidosis and uraemia. Creatinine concentrations may not be accurately measurable in the presence of heavy ketonaemia. Typical blood results in DKA are shown in Table 4.

Table 4. Typical initial laboratory values in diabetic ketoacidosis

Plasma [glucose] = 37mmol/L
Plasma [K^+] = 5.3mmol/L:whole body depletion typically 6.0 mmol/kg body weight
Plasma [Na^+] = 131 mmol/L: whole body depletion typically 8.0 mmol/kg body weight
Plasma [urea] > 15 mmol/L
Plasma [creatinine]> 150μmol/L (if possible to measure in the presence of heavy ketonaemia)
Plasma [ketones] >15 mmol/L
Plasma [Mg^{2+}] <0.70 mmol/L: whole body depletion typically 0.5 mmol/kg body weight
Plasma [P_i] >1.2 mmol/L: whole body depletion typically 1.0mmol/kg body weight
Serum amylase 500-1000 IU/L
Serum osmolality = 323 mmol/kg
Whole body water depletion 75-100 mL/kg body weight = 7L in typical adult
Arterial blood gases
[H^+] > 50 nmol/L (pH <7.30)
P_aCO_2 = 3.2kPa
P_aO_2 > 12kPa
[HCO_3] <18mmol/L
Anion gap ([Na^+] + [K^+]) – ([$C1^-$] + [HCO_3^-]) > 20 mmol/L

The key to successful management is, of course, recognition of the condition in the first place and early institution of fluid, electrolyte and insulin replenishment.

Hyperosmolar hyperglycaemic syndrome

HHS typically presents with very high blood glucose levels, severe dehydration, altered mental status and electrolyte disturbance in older individuals with type 2 diabetes. The condition is commonly associated with another intercurrent illness which should be suspected and diagnosed (e.g. infection, stroke). Ketonuria is light or absent although a type A lactic acidosis may be present in more severe cases as a result of shock. Treatment is broadly similar to DKA although slower rates of fluid resuscitation and insulin infusion are usually appropriate in these typically more frail individuals.

In both DKA and HHS it is important to monitor serum electrolytes, particularly Na+ and K+ at diagnosis and in response to treatment. Details of the treatment are on the ADA website.

Diagnosis in other settings

It is important to recognise that diabetes may present in other settings than those outlined above. For example, patients with uncontrolled diabetes may fail to recover well from surgical procedures because of poor wound healing (fibroblast function) and susceptibility to infection (neutrophil function). Patients at risk should ideally be identified and treated to prevent surgical mishap. Similarly, patients with diabetes are more at risk of developing a range of other infections. This possibility should be remembered particularly where an individual has a history of recurrent skin and superficial infections or urinary tract infection without other precipitant.

Pregnancy

Pregnancy is another setting where patients not known to have diabetes may present for medical care. It is particularly important to diagnose diabetes because of a serious potential threat to the health of both mother and child if the condition is not recognised and treated appropriately. Diabetes in pregnancy may be pre-existing (already diagnosed type 1 or type 2 diabetes) or gestational.

Gestational diabetes mellitus (GDM) is defined as any form of disturbance of blood glucose regulation with onset or first recognition during pregnancy. Most often, this will mean a form of diabetes developing at around 26-28 weeks gestation and remitting at birth. However, sometimes a pregnant woman has type 1 or type 2 diabetes which will, of course, not remit at delivery. Clues to this include symptoms of diabetes which pre-date the onset of pregnancy or a proven gluco-regulatory disturbance developing before the 26th week of gestation.

Women with pre-existing diabetes should ideally:

- plan their pregnancies so that control of blood glucose may be optimised prior to conception (ideally, FPG 3.5- 5.9 mmol/l and 1 hour post prandial capillary blood glucose <7.8 mmol/l) and
- take folic acid 5 mg prior to conception and up to the end of the first trimester.

Poor control of pre-existing diabetes may be associated with a 10 fold or higher incidence of major congenital anomalies (typically cardiac or neural tube defects). DKA during pregnancy is usually fatal to the foetus and frequently to the mother.

Suspect gestational diabetes when the risk factors listed in Table 5 exist although the precise screening programme should reflect the prevalence of the disorder and resources available for its diagnosis and treatment.

Table 5. Risk factors for GDM

History of a large baby (e.g. over 4.0 kg)
Family history of diabetes in a first degree relative
Obesity
Unexplained previous late foetal loss
Older mother (e.g. over 30)
Previous gestational diabetes

Prevention

Type 1 diabetes is not thought to be preventable at the current time. Immunosuppressant therapy has been tried in the past with some success but the dangers of such treatment generally outweigh the benefits. Many cases of type 2 diabetes are however preventable with good diet, maintenance of normal weight and healthy amounts of exercise. Some studies have shown an additional effect of metformin in addition to these measures although this is not a substitute for a healthy lifestyle. People at risk from diabetes will usually have a family history of the condition, be overweight/obese or both. For example, the risk of type 2 diabetes for a woman with BMI >35 [kg.m-2] is approximately 93 times that of a lean woman. Centrally distributed adiposity carries an independent additional risk.

However, not all obese people have diabetes and genetic factors (most easily assessed by family history) are thought to play a significant part. Women with a history of gestational diabetes carry a 50% lifetime risk of diabetes. Where resources for screening are available, the groups likely to have the highest undiagnosed prevalence of diabetes are those with obesity and women with a history of gestational diabetes

References and further reading

The following freely accessible on-line resources provide a wealth of further information and links to other relevant sites:

- American Diabetes Association (ADA) *Clinical Practice Guidelines* http://www.diabetes.org/ for-health-professionals-and-scientists/cpr.jsp
- ADA *Guidelines on Diabetic Emergencies* http://care.diabetesjournals.org/cgi/content/full/27/suppl_1/s94
- National Diabetes Information Clearing House http://diabetes.niddk.nih.gov/

See also items on page 17.