Diabetes today — a review and update

LI Robertson
Coloured Diabetes Department,
Addington Hospital, Durban.

Summary

A practical approach to the understanding of diabetes mellitus, its terminology, diagnosis and etiology as well as clear guidelines to the management of the diabetic patient in general practice.

KEYWORDS: Diabetes Mellitus; Obesity in Diabetes; Diabetic Diet; Glucose Tolerance Test.

LI Robertson MBChB MFGP (SA)
300 Sparks Road
Sydenham
4091
NATAL

Curriculum Vitae

Dr Robertson studied at Cape Town University where he received the MB ChB in 1954. He did some post-graduate training at Mc Cord Zulu Hospital (Durban) and St Monica's Home (Cape Town), received the MFGP (SA) in 1975 and has been in Private Family Practice in Durban since 1957. He has a wide interest in different fields of medicine, and at the moment still holds the following posts: Senior Medical Officer – Diabetes Dept (Addington Hospital), Medical Director — Child Guidance & Research Centre (Durban/Westville), Medical Director — Institute of Human Sexuality. He also makes time to serve on several committees. He is Vice-chairman of the council of SA Academy of Family Practice/Primary Care; he is an elected member of the SA Medical and Dental Council and gives time to many other committees serving the community. Dr Robertson has presented many papers at Medical Conferences, has published several scientific papers and contributed to two medical textbooks. He is married to Barbara and they have 4 children.

Part I
Introduction and non insulin-dependent diabetes mellitus

Diabetes mellitus is a common disease which affects upwards of 30 million people worldwide. Most of these lack even the rudiments of care. All of them can be helped. With reasonable care much chronic disability could be prevented.

IDDM = exogenuous-insulin-dependent diabetes mellitus
NIDDM = non-insulin-dependent diabetes mellitus

Diabetes today — a review and update

One of the factors which has impeded our understanding of the disease is that we have tended to regard diabetes as a single disease with a single cause. Epidemiological, clinical and immunological investigations have revealed evidence of several causal mechanisms. Thus, if we regard the two main types of primary or idiopathic diabetes mellitus, we find that in Type 1 diabetes (or insulin-dependent diabetes mellitus — IDDM), auto-immunity to islet cells plays an integral part in the pathogenesis. Furthermore, susceptibility to IDDM is conferred by genes in the HLA-D region of the major histocompatibility complex on chromosome 6, particularly HLA-DR 3 and HLA-DR 4. Whilst we have not as yet identified any such strong evidence of HLA association in Type 2 diabetes mellitus (or non-insulin- dependent diabetes mellitus — NDDM), the evidence of genetic transmission is, if anything, even stronger here, as shown by David Pyke's twin studies.[1] What has emerged in recent years is the interesting fact that different environmental factors unmask the inherent genetic susceptibility to the two diseases.

In the case of IDDM, certain viral infections appear to initiate the auto-immune destruction of islet cells which will ultimately result in the disease. Strong contenders as environmental precipitators of NIDDM in a genetically susceptible individual are a sedentary lifestyle, and certain dietary factors such as a high caloric intake, a diet lacking in fibre and rich in refined carbohydrate and simple sugars, as well as obesity, increased ageing of a population, and, possibly, certain as yet not clearly defined environmental toxins. There is one factor, difficult to quantify, which is a common environmental precipitator of both types of diabetes mellitus, and that is stress.

Diabetes following on alcoholic pancreatitis is, in this country, a common form of secondary diabetes with certain interesting features which shall be discussed later.

Diabetes mellitus affects more than 30 million people today.

TERMINOLOGY

Over the years, many terms and abbreviations for the various types and phases of diabetes have been coined, used for a while, and later discarded, creating much confusion. Thus we no longer use the terms 'chemical diabetes', 'juvenile-onset diabetes', 'maturity-onset diabetes', 'latent diabetes', 'pre-diabetes' or 'potential diabetes.'

Most diabetic patients lack even the rudiments of care.

The two main types of idiopathic or primary diabetes are either called Type 1 or insulin-dependent diabetes mellitus, commonly abbreviated to IDDM, or Type 2 or non-insulin-dependent diabetes mellitus, or NIDDM. My objection to the term 'non-insulin-dependent' stems from the fact that no human, indeed no mammal, can possibly survive without insulin. Indeed, many forms of insect life are dependent on insulin for glucose homeostasis. So, while for purposes of convenience I shall be using the abbreviations IDDM and NIDDM for the rest of this review, it shall be tacitly understood that the terms indicate ***exogenous***-insulin-dependent or non-dependent, in each case.

DIAGNOSIS

The clinical diagnosis of diabetes in children, and IDDM in adults is straightforward as the vast majority present with the acute and classical symptoms of increased thirst and urine volume, accompanied by inexplicable weight-loss, and have heavy glycosuria, often ketonuria and high levels of blood sugar. All that is required is a high index of suspicion.

The oral glucose tolerance test (OGTT) is rarely, if ever, necessary (or appropriate) for the diagnosis. In fact, it needs to be emphasised that, in the clinical setting, the OGTT and all the confusion with regard to its methodology and standardisation, is only necessary for the diagnosis of a small proportion of borderline cases of NIDDM patients, whilst its only other uses are in pregnancy and in epidemiological settings to screen for diabetes or impaired glucose tolerance (IGT.)

ORAL GLUCOSE TOLERANCE TEST

The OGTT should be administred in the morning after at least three days of unrestricted diet (greater than 150 g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 10 to 16 hours, during which water may be drunk. Smoking is not permitted during the test. The presence of factors that influence interpretation of the results of the test must be recorded (*eg* medications, inactivity, infection, etc.)

After collection of the fasting blood sample, the subject should drink 75g of glucose in 250-300mℓ of water over the course of 5 minutes. For children, the test load should be 1,75g of glucose per kg body weight up to a total of 75g of glucose. Blood samples must be collected 2 hours after the test-load[2]

INTERPRETATION

(See Table 1)

Dr RA Jackson, a former South African now at the Middlesex Hospital, showed in 1973, that standardisation with regard to which forearm veins were used was important. If one took blood from the dorsum of the hand or from one of the superficially draining veins on the medial or lateral sides of the forearm or ante cubital region, the blood so obtained was virtually arterialised, and had (in the non-fasting state) a higher glucose content. On the other hand, blood from the deep ante cubital vein itself (draining as it does the forearm muscles) is mixed venous and shows lower glucose levels than arterialisee blood after glucose load.[3]

In the general practice setting, an OGTT is best performed using one of the reflectance meters such as the 'glucometer' or 'reflolux' or 'glucocheck', which measure

TABLE 1
DIAGNOSTIC VALUES FOR THE ORAL GLUCOSE TOLERANCE TEST

	Glucose concentration (mmol/ℓ)			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes mellitus				
Fasting value	≥ 6,7	≥ 6,7	≥ 7,8	≥ 7,8
2 hrs after 75g glucose load	≥ 10,0	≥ 11,1	≥ 11,1	≥ 12,2
Impaired glucose tolerance				
Fasting value	< 6,7	< 6,7	< 7,8	< 7,8
2 hrs after 75g glucose load	6,7-10,0	7,8-11,1	7,8-11,1	8,9-12,2

For epidemiological or population screening purposes the 2-hour value after 75g oral glucose may be used alone or with the fasting value. The fasting value alone is considered less reliable since true fasting cannot be assured and spurious diagnosis of diabetes may more readily occur.

(From "Diabetes Mellitus", WHO Technical Report Series, No. 727, 1985).

capillary blood and give the most reproducible results.

The issue of interpretation can be further simplified. Thus, if you obtain fasting levels on at least two occasions of less than 6,7 mmol/ℓ then DO NOT PROCEED with the OGTT as the patient does not have diabetes.

Similarly, a fasting level of more than 7,8 mmol/ℓ on two occasions indicates that the patient is a diabetic. Again, DO NOT PROCEED with the glucose load.

A random blood sugar of more than 12,2 on your reflectance meter also indicates that the patient is a diabetic and that the OGTT is unnecessary. However, as the diagnosis condemns your patient to a lifetime of treatment, you should confirm the raised random level on one more occasion, much as you would repeat blood pressure recordings on a few more occasions should a single high reading be discovered.

Much chronic disability resulting from diabetes mellitus could be prevented with only reasonable care.

A kinder and very useful procedure in general practice is to do a blood sugar estimation on a reflectance meter 2 hours after a substantial meal. Readings less than 8,8 mmol/ℓ indicate the absence of the disease whilst levels of over 12,2 on your capillary sample, point to a diagnosis of NIDDM. Levels between 8,8 and 12,2 indicate IGT (or impaired glucose tolerance.) Again, with the levels below 8,8 or above 12,2 you need not proceed to a full OGTT. There is one situation which calls for a revision of these guidelines and that is the patient with a "dumping syndrome" after surgery for peptic ulcer who shows a transiently high blood glucose soon after a meal (particularly a meal high in refined carbohydrate taken with fluids) and has glycosuria. By the 2 hour level his blood glucose will have returned to normal or even below normal.

The OGTT is often used in pregnancy to detect gestational diabetes, a diagnosis which should be confined to women in whom glucose intolerance is first detected in pregnancy. Reclassification is always necessary post-partum.

Type 2 diabetes mellitus — NIDDM

The majority of diabetics do not require exogenous insulin and are classified as NIDDM. Between 1-2% of all population groups are affected by the disorder and no race is immune.

Epidemiological studies have revealed interesting patterns of incidence in different populations. Among Pima Indians in the state of Arizona, and Nauruans in Melanesia, fully half of the adult population suffer from the disorder.

Within the same ethnic group, urban residents and migrants to urban areas have a higher prevalence of NIDDM than their rural counterparts. The generally undramatic clinical presentation probably leaves large pools of undiagnosed cases in many populations, and incidence rates are as much an index of awareness as of the actual frequency of diabetes. For instance, there have been no studies of the incidence of NIDDM in Caucasian populations using the WHO criteria. A recent epidemiological survey of the South African population of Indian descent in Chatsworth in Natal revealed an incidence of 11%.[4]

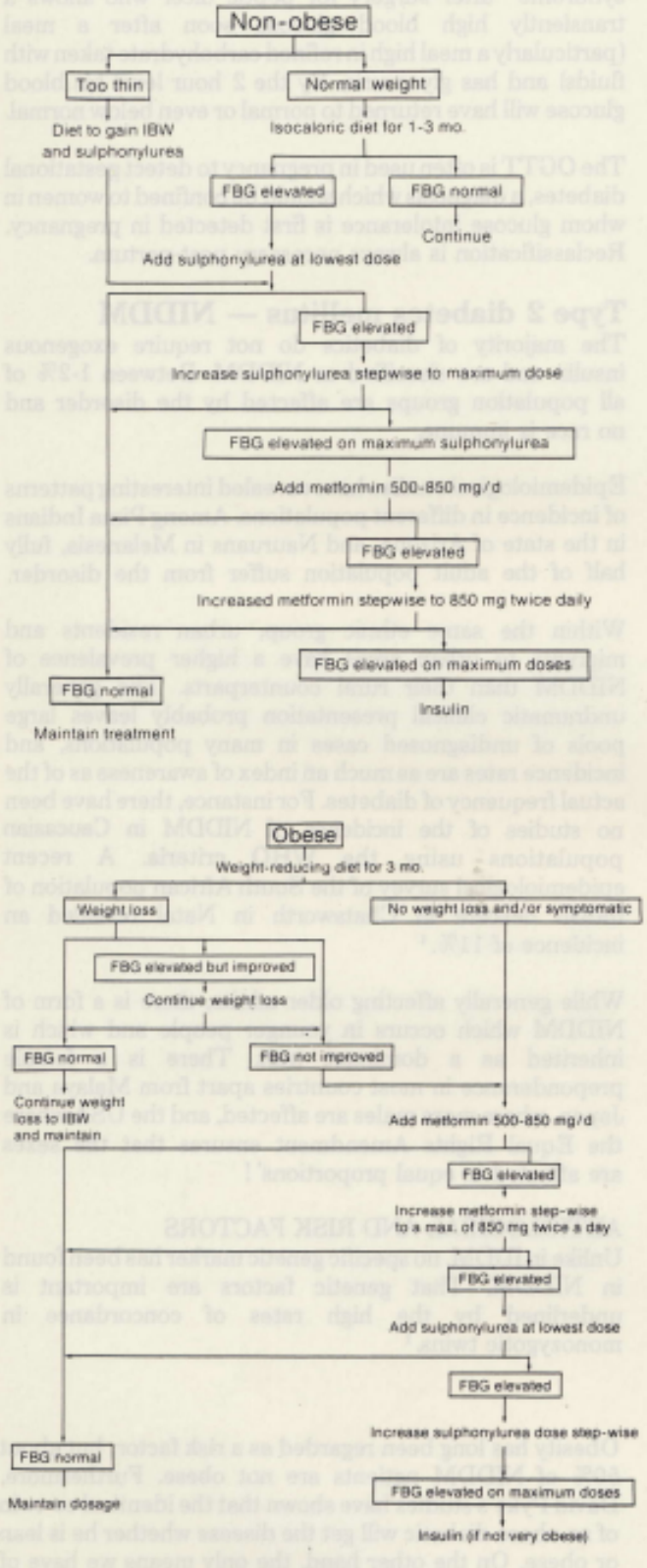
While generally affecting older adults, there is a form of NIDDM which occurs in younger people and which is inherited as a dominant trait. There is a female preponderance in most countries apart from Malaya and Japan, where more males are affected, and the USA where the Equal Rights Amendment ensures that the sexes are affected in equal proportions'!

AETIOLOGICAL AND RISK FACTORS

Unlike in IDDM, no specific genetic marker has been found in NIDDM. That genetic factors are important is underlined by the high rates of concordance in monozygotic twins.[1]

Obesity has long been regarded as a risk factor, but about 50% of NIDDM patients are not obese. Furthermore, David Pyke's studies have shown that the identical co-twin of an obese diabetic will get the disease whether he is lean or obese. On the other hand, the only means we have of influencing whether genetically susceptible persons will get the disease or not is by preventing them from becoming or remaining obese. Obesity can induce resistance to insulin by reducing the number of insulin-receptors on the target cells (a reversible situation, as reduction in mass has been shown to increase the number of receptors) and also through decreasing glucose transport at a post-receptor level.

TABLE II



Management of NIDDM (diabetes mellitus type II). (Note: (*i*) a normal fasting blood glucose (FBG) value (3,5 - 6,0 mmol/l) reflects good control; (*ii*) as a rough guide, ideal body weight (IBW) can be regarded as height in metres without the figure 1 preceding the decimal — 1,75 m = 75 kg, 1,51 m = 51 kg); and (*iii*) assessments should be done monthly until stabilization — thereafter FBG should be determined every 3 months and haemoglobin A_{1c} every 6 - 12 months.)

Other factors which appear to unmask genetic susceptibility to NIDDM are environmental ones, such as a sedentary life-style, dietary factors, stress, urbanisation and acculturation.

Although the disease is often discovered during pregnancy, parity per se is probably not a risk factor.

PATHOPHYSIOLOGY

The non-exogenous insulin dependent diabetic is characterised by a combination of inadequate and/or delayed insulin secretion, and resistance of peripheral tissues to its actions[5] due to receptor and post-receptor defects. In a few patients the synthesis of an abnormal, biologically less-active insulin as a result of mutation of the insulin-gene, has been shown to be responsible for the NIDDM[6]

Recently different environmental factors unmasked the inherent genetic susceptibility.

CLINICAL PRESENTATION

The vast majority of Type 2 diabetics are diagnosed by the incidental finding of glycosuria and confirmed by hyperglycaemia. Occasionally, the thirst and excessive urination of the Type 1 diabetic's presentation is found in NIDDM or the patient may have vaginal candidosis or monilial balanoposthitis which alert the doctor to the diagnosis. Loss of weight is seldom a feature of this disorder and, indeed, if there has been severe weight-loss, it may be an indication that we are dealing with a patient who, although manifesting most of the characteristics of the Type 2 disorder, may in fact require insulin for his optimal control.

Whilst the complications of diabetes will be dealt with in a separate section later, it needs to be emphasised that there are differences in the type and timing of these complications in NIDDM as compared with the average case of IDDM. Thus, the vascular effects tend to involve large vessels (accounting for the high incidence of coronary artery disease and mortality therefrom,) and the ophthalmological complications are more likely to involve the lens and macula. But the most important distinction is that whereas in the case of IDDM microvascular complications tend to manifest after a decade or more, in NIDDM the complications are not infrequently present at the time of diagnosis.

MANAGEMENT OF NIDDM

It is a fair comment to make that as many serious errors are made in the management of the Type 2 diabetic, as with the incorrect or inappropriate use of insulin in the case of the insulin-dependent diabetic. One has witnessed situations in which the widespread abuse of potentially valuable medications, often against the advice of the manufacturers, has resulted in large numbers of

patients who would have benefitted from their use being denied them due to their removal from various Provincial codes.

It is essential for the family practitioner to remember that the management of nearly all cases of NIDDM does not, in the first instance, involve the use of either oral hypoglycaemic drugs or insulin. Rather the initial emphasis should be on the correction of faulty nutritional habits and attention to weight reduction and physcial activity where appropriate, taking into account each patient's needs, as well as cardiovascular status. Dietary aspects will also be dealt with in greater detail separately, but at this juncture it should be noted that our previous blanket restriction of all carbohydrates is no longer considered good diabetic practice. The emphasis is now on reducing dietary fat to about 30% of total daily energy intake, with the substitution of foods containing polyunsaturated vegetable oils for those containing saturated fats such as dairy products. Protein should account for approximately 15-20% of the daily intake, and carbohydrates rich in natural fibre should constitute the remaining food energy. The discerning doctor will note that these general principles describe a diet which represents good nutrition for non-diabetics as well.

The Witwatersrand Diabetes Group recently published their algorithm for handling NIDDM.[7] It is an admirably lucid summary of the current 'state of the art' in diabetes management. There are three sulphonylureas which are used in hospital diabetes departments and their "lowest" and "maximum" doses are:

Sulphonylurea	Starting dose	Maximum dose
Gliclazide ('diamicron')	40mg daily	160mg b.d.
Glibenclamide ('daonil', 'euglucon')	2,5 mg daily	10mg b.d.
Tolbutamide ('rastinon', 'artosin')	0,5g daily	1,5g daily

The only biguanide currently on Provincial code is Metformin ('glucophage'), and the lowest and starting doses are 0,5g daily and 3g daily (in divided doses of 1 g t.i.d.).

There are certain clearly defined principles which should be adhered to in the use of oral hypoglycaemics:

(1) Always start with the lowest dose.

(2) Re-assess after at least two weeks before increasing dose.

(3) When using sulphonylureas at their maximum doses consider reducing the dose if you are not getting the desired drop in FBG. This is advisable as the sulphonylurea may, by its appetite enhancing effect, make dietary compliance difficult.

(4) Use sulphonylureas with great caution in the elderly or in diabetics with compromised renal function. The cumulative effect of the longer-acting sulphonylureas, in particular, may result in catastrophic hypoglycaemia, a potentially fatal disorder in the older diabetic.

(5) Biguanides should be avoided in diabetics with renal, hepatic or cardiac dysfunction due to the danger of lactic acidosis, again a disorder with a high mortality rate, particularly in the older patient. There is some evidence that metformin is less culpable in this regard than phenformin ('insoral'), but more years of metformin use will show whether this impression is correct. The higher doses of metformin are often not well-tolerated because of gastro-intestinal side-effects, especially diarrhoea.

Many of my colleagues will, I know, consider the following a heretical statement, but it is my personal conviction that we have over-reacted with regard to the banning of the use of phenformin and chlorpropamide ('diabinese') from our Provincial codes. Chlorpropamide is a potent and useful sulphonylurea and was our therapeutic mainstay for many years. It was due to the abuse of the drug in high and multiple doses daily, with no regard either for the manufacturers' instructions or the drug's long half-life which resulted in the deaths of a few elderly diabetics from irreversible hypoglycaemia. Used with caution at doses of 100 mg once daily in the younger cases of NIDDM, it is at least as effective as the newer and more expensive sulphonylureas. Many of the same remarks apply to the restrictions on the use of phenformin, when its abuse in doses higher than those advocated by the manufacturer in cases with severe renal impairment, caused fatalities from lactic acidosis. For years we were getting as good results with 50 mg of phenoformin daily, as are now obtained with twenty to thirty times higher doses of metformin.

Recent, and as yet unpublished work by Jackson and his associates in London suggest that neither fasting nor oral hypoglycaemic drugs actually improve glucose tolerance. Whilst glucose tolerance curves appear better after fasting, sulphonylureas or biguanides, closer examination reveals that they are in fact superimposable and are only different from the pre-treatment curves by virtue of the fact that they commence at a lower baseline or fasting level. Similarly, whilst the "area under the curve" also appears smaller, the true incremental area under the curve is identical.[8] This is of importance when we consider the most logical method of monitoring the progress of NIDDM patients on treatment. It now becomes clear that post prandial or random blood glucose levels are not as useful as fasting levels, and it is our practice to do the fasting blood glucose every month or two months and supplement these tests with a glycated haemoglobin estimation every 6 months.

A few patients with NIDDM appear to eventually run out of ßeta cell reserve and require insulin, but this will be discussed when we consider the use of insulin in a later section.

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