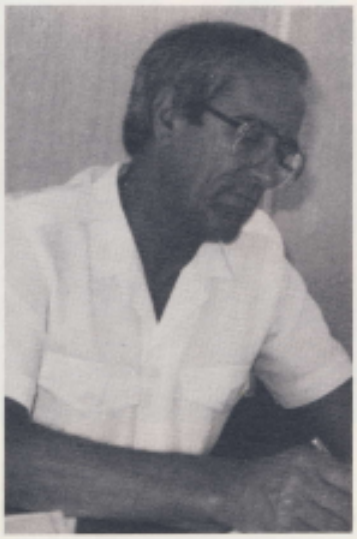
Diabetes today — a review and update (Part III)

— LI Robertson



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Summary

This is the third part of 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; Glucose Tolerance Test; Insulin; Hypoglycemia; Self Medication; Self Assessment; Alcohol drinking; Pancreatitis; Nutrition disorders; Pregnancy in diabetes; Eye diseases; Hypertension.

The previous two articles dealt with the two common and idiopathic forms of diabetes – NIDDM and IDDM. There are three important forms of secondary diabetes which warrant discussion, viz the form following on alcoholic and other types of pancreatitis, and two important forms of the disease related to malnutrition.

SECONDARY DIABETES CAUSED BY ALCOHOL-INDUCED CHRONIC PANCREATITIS

This type of diabetes, which is common in the Cape Coloured population and supplies a varying proportion of the diabetes clinic clientèle in other parts of South Africa, has several interesting and distinct clinical features. There may or may not be a history of a distinct episode of acute pancreatitis. The diabetic manifestations may appear soon after the initial episode or after many years of alcohol abuse of the pancreas. Pancreatic calcification may or may not be visible on straight x-ray of the abdomen. It is my conviction that the islet-cell damage in alcoholic pancreatitis is patchy rather than diffuse as in the auto-immune wipe-out seen in classical Type 1 diabetes. This view is supported by the fact that we have documented numerous cases where, after initially requiring hundreds of units of insulin for control, the insulin requirements rapidly decreased until control became feasible using either oral hypoglycaemic agents or diet alone, *provided there was total cessation of alcohol intake.* To me this suggests that the initial assault on the islets was patchy and that a considerable number of islets were only partially damaged or oedematous and recovered later. We have also observed this sequence of events in cases of chronic and acute pancreatitis unassociated with alcohol-intake, such as with gall-bladder pathology. Patients with this type of diabetes are not prone to ketosis or micro-angiopathy, and appear also to be protected against coronary heart-disease.

MALNUTRITION-RELATED DIABETES

There are two types, both of which are common in tropical, developing countries, generally occuring in young patients.

1. Fibro-calculous pancreatic diabetes

This type, with the distinctive features of stone formation in the main pancreatic duct and its

branches, and extensive pancreatic fibrosis, has been reported from Bangladesh, Brazil, India, Indonesia, Jamaica, Madagascar, Nigeria, Sri Lanka, Thailand, Uganda, Zaire and Zambia. Males affected outnumber females by 3 to 1. Patients are grossly underweight with other stigmata of malnutrition. Although they require high doses of insulin for control, ketosis is not a feature. Again, as with chronic pancreatitis from alcohol abuse, one's impression is that the islet destruction is patchy, with sufficient residual insulin secretion to prevent ketosis. Epidemiological observations hint strongly at an association of the disease with cassava-root consumption. Cassava-root contains several cyanide-forming glucosides, and it has been suggested that high cassava intake in the absence of an adequate protein intake results in the accumulation of cyanide in the body. Sorghum, yarn and millet may also be implicated.

Secondary diabetes caused by alcohol-induced chronic pancreatitis is common amongst the Cape coloured population

2. Protein-deficient pancreatic diabetes

In this form of malnutrition-related diabetes there is an early onset, between 15 and 25 years of age, and resistance both to the action of insulin as well as to ketosis. It has been reported from Bangladesh, Brunei, Dar-es-Salaam, Fiji, Ghana, India, Indonesia, Jamaica (hence its previous title, "J-type diabetes"), Kenya, Malawi, Malaysia, Nigeria, Papua New Guinea, South Africa, Uganda, Tanzania and Zaire. More common in males in Asia, in other parts there is an equal sex incidence, whilst in Jamaica more females are affected.

Poor control of diabetes during pregnancy carries a high risk of foetal death

Whilst both forms of malnutrition-related diabetes have wasting and stigmata of malnutrition, this protein-deficiency type is neither associated with calcification nor with recurrent bouts of abdominal pain.

PREGNANCY AND THE DIABETIC

Poor control of diabetes during pregnancy carries a risk close to certainty of foetal death, and the causes range from infertility through delayed implantation of the ovum to malformations, pre-eclampsia, macrosomia and neonatal hypoglycaemia.

Further, the diabetic's own control is affected by pregnancy, with hypoglycaemia common in the first trimester and hyperglycaemia in the last. The renal threshold is depressed throughout, and there is a real risk of any retinopathy progressing. Hypertension is common.

Many IDDM patients fail to experience or perceive early warning symptoms even when these are obvious to an observer

The management of the pregnant diabetic is beyond the scope of this paper as these patients should be under the care of an obstetrician well-versed in diabetic care, but it is interesting to observe the historical aspects of the management of the diabetic in pregnancy.

The initial approach was to forbid pregnancy. The following attempts stemmed from Denmark when it was appreciated that the majority of problems occured in the last trimester. Hospitalisation, frequent blood-glucose monitoring, and tight control resulted in a radical salvaging of babies. Since the late 1970s and the introduction of accurate home blood-glucose monitoring, attempts were made to manage patients at home, and to allow more spontaneous deliveries. At present, now that the perinatal mortality has been reduced to those virtually entirely due to congenital abnormalities, our attention has switched to reducing the frequency of those abnormalities by insisting on tight glycaemic control prior to conception.

Sexual dysfunction is rarely a feature of diabetes in the female

DIABETIC COMPLICATIONS

1. Short-term complications of diabetes

The insulin-dependent diabetic's life is a constant battle to maintain a blood-sugar level which, whilst steering away from hyperglycaemic levels that would encourage long-term microangiopathic complications, is high enough to prevent the most dreaded complication of all for the average diabetic, namely, hypoglycaemia.

- Hypoglycaemia

As we have seen, our conventional exogenous insulin therapy makes frequent biochemical hypoglycaemia almost inevitable, and intermittent symptomatic hypoglycaemia all too common. It is also a very dangerous, albeit uncommon, complication in the older patient on sulphonylureas.

The causes, in the IDDM patient, may be insulin overtreatment, erratic insulin absorption (particularly with depot insulin preparations), or subnormal counter-regulatory hormone responses to low blood sugars (e.g. glucagon, adrenaline, cortisol and growth hormone). Furthermore, many patients fail to experience (or perceive) early warning symptoms, even when these are obvious to an observer.

Children lend to be more pronne to hypoglycaemia

Symptoms

These may be divided into *adrenergic* symptoms (pallor, sweating, tremor, palpitations and a gnawing 'hunger' pain in the epigastrium) and *neurogenic* symptoms such as lightheadedness, poor concentration, dysarthria, incoordination, diplopia, peri-oral tingling or even epilepsy, transient pareses, and ultimately, coma.

It should be remembered that after some five to ten years of diabetic life the early warning catecholamine-induced symptoms may disappear and the patient may go straight into the neuroglycopaenic phase, with sometimes disastrous consequences. Also, the newer human insulins do appear to produce fewer adrenergic symptoms with hypoglycaemia.

Children are more prone to hypoglycaemia. Older people do not tolerate it well, and often hypoglycaemia present as failing mental function. Remember, too, that in the long-term IDDM patients require less insulin as the renal function deteriorates. Exercise may predispose to 'hypos' by speeding insulin absorption and promoting peripheral glucose uptake.

Nocturnal hypoglycaemia often may go unnoticed and result in high blood glucose levels on rising

Nocturnal hypoglycaemia can be a particular problem, usually around 3 a.m. to 4 a.m. Many episodes at this hour go unnoticed, and counter-regulatory response not infrequently results in **high** blood glucose levels on rising and before breakfast. The potential dangers of treating these high morning levels by *increasing* the night intermediate insulin without checking the 3 a.m. to 4 a.m. glucose levels will not escape the wary physician.

On page 105 you will find a detailed check-list for your diabetic patients to observe in managing hypoglycaemic episodes. Note that glucagon is never used by a patient, for the simple reason that a patient who can mix and administer glucagon does not need it. Persons who give the glucagon need ample opportunity to practise giving injections (viz insulin) so that a situation where their first injection ever is in a situation which threatens the life of a loved one can be avoided. If glucagon is ineffective in five to ten minutes, the patient needs I.V. glucose. After glucagon, remember to replenish depleted muscle and hepatic glycogen stores by a carbohydrate feed. Do not use glucagon in hypoglycaemia induced by oral hypoglycaemics, as it promotes insulin release.

Long-term hyperglycaemia results in a constant spectrum of pathological effects

Lastly, beware of the effects of alcohol in producing hypoglycaemia, and beta-blockers in masking warning symptoms.

- Hyperglycaemia and ketoacidosis

Diabetic ketoacidosis results from excessive production of ketoacids. Dehydration and hyperglycaemia are the rule, and lactic acidosis may also be present. The clinical features are: vomiting, thirst, polyuria, weakness, acute loss of mass, impaired consciousness, abdominal pain, visual disturbances, muscle-cramps, hypotension, Kussmaul's breathing, hypothermia and a smell of ketones on the breath. Evidence of infection may or may not be present.

Management should be conducted in an adequate hospital setting, and involves fluid replacement, insulin – preferably by intravenous infusion – and correction of electrolyte disturbances. The dose of insulin is 0,1 iu/kg/hour initially, and when the change-over to subcutaneous insulin is made, the I.V. insulin infusion should overlap by one hour at least, to allow the subcutaneous dose time to take effect.

1. Long-term complications of diabetes

Long-term hyperglycaemia, irrespective of its cause, results in a constant spectrum of pathological effects, but, as we have already seen, there are differences

in both pattern and timing of complications between IDDM and NIDDM. The latter is more likely to affect larger rather than small vessels, is more likely to affect the lens and macula of the eye and, perhaps most important, complications in NIDDM appear to develop more rapidly, and are often present at the time the diabetes is first diagnosed. Finally, different categories of diabetes have a particular predilection for, or resistance to, various complications, and there are also ethnic differences. Thus, diabetes due to alcoholic pancreatitis has a relative resistance to vascular complications, and the South African Black with IDDM also has a relative resistance to CAD. On the other hand, NIDDM in our Natal Indian population is associated with an inordinately high incidence of cataracts, maculopathy and CAD.

It has become increasingly evident that early on in the life of the diabetic, possibly even prior to the onset of hyperglycaemia, there are detectable alterations in the retina, the peripheral and/or autonomic nerves and the kidneys. We can thus, using fluorescein angiography, detect capillary leakage very early on in many Type I diabetics. Ziegler and his co-workers have shown, within days of the initial episode of ketoacidosis which heralds the clinical onset of IDDM, changes in ulnar and sural nerve-conduction-velocity, as well as subtle changes in autonomic function. Though most of these alterations in function reverse themselves once the metabolic dysfunction is corrected, the abnormal sural NCV was still present after three months. We are also aware of the fact that transient alterations in renal function, as evidenced by sporadic micro-albuminuria, may occur early on as well. At a 'micro-functional' level it would then appear that virtually *all* diabetics have *benign* eye, nerve and renal complications. What is not clear, and the subject of much research at the moment is, why, in a percentage of diabetics, the complications take on a *malignant* form and proceed to organ damage.

Diabetic nephropathy

About one-third of diabetics diagnosed before the age of 25 will die from diabetic nephropathy.

Diagnosis

Whilst the average duration of diabetic life prior to end-stage-renal-disease is 20 years, we not uncommonly find reversible abnormalities of renal function

within a few years of the diagnosis of diabetes. A raised GFR may occur a few years before histological changes are present in the glomeruli. Further, whilst persistent proteinuria is seldom present before 15 years of IDDM, death from renal disease (or the need for dialysis) follows within three to five years. More optimistically, there is a direct correlation between nephropathy (and indeed all microangiopathic complications) and quality of glycaemic control.

So, check for proteinuria at every visit, insist on tight control, and treat hypertension vigorously. In diabetics you should aim at diastolic pressures of 80 and lower, as 90 mm is unacceptable. Once there is albuminuria, reduce protein intake to 50 g or even 40 g per day, avoid contrast media and refer to a nephrologist or specialised renal unit.

Diabetic retinopathy

Diabetes is the commonest cause of new cases of blindness seen in eye departments. Symptoms vary from gradual diminution of visual acuity to sudden deterioration and blindness.

First, a word of caution. Fluctuating or deteriorating visual acuity is a common way of presentation in cases of NIDDM in particular. Do not refer patients for optometric assessment before excluding diabetes. Short-term changes in VA due to varying osmotic pressures often settle after glycaemic control is achieved, and the patients may be spared much unnecessary expense in wasted spectacle lenses.

Check your diabetic's eyes on a Snellen's chart twice a year and examine the fundi following dilatation,

It remains a problem why in some diabetic patients complications become malignant and proceed to organ damage

(using 0,5 to 1 per cent tropicamide every six to twelve months). Referral to an ophthalmologist should be considered for every patient with background retinopathy involving the peri-macular area and whenever you suspect the presence of new-vessel formation. Choose your ophthalmologist carefully. I would personally only refer my diabetic patients to an

ophthalmologist skilled in the use of laser, as the timing of this treatment is often critical and delays occasioned by further referral may be disastrous.

Retinopathy and nephropathy are microvascular complications which usually follow the same time-pattern.

Diabetic neuropathy

About 15 per cent of diabetics (particularly older patients with long-standing disease) have severe manifestations of diabetic damage to peripheral and/or autonomic nerves. However, if we use more subtle methods of assessing nerve damage, such as nerve-conduction-velocity-studies (NCV) or checking the vibration-threshold (VT) – using a biothesiometer – we find that neuropathy is the commonest diabetic complication of all, and there are few diabetics indeed who do not show subtle changes in NCV or VT after three to four years of diabetic life.

Again, there is some correlation with quality of control, but not nearly as clear-cut as in nephropathy or retinopathy. Neuropathy may be symmetrical and diffuse (and may affect motor and/or sensory nerves), or may be focal, affecting one nerve (mononeuropathy).

Diabetes is the commonest cause of new cases of blindness seen in eye departments

The autonomic nervous system is not uncommonly affected in long-standing, poorly controlled diabetes, resulting in cardiovascular dysfunction (loss of normal beat-to-beat variation, and the potential for sudden cardiorespiratory arrest, such as with unaccustomed exercise or during surgery), gastrointestinal effects (diarrhoea and gastrostasis) and genitourinary effects (reduced bladder tone, retrograde ejaculation and impotence). Excessive sweating, especially on the face, is another feature of the involvement of the autonomic nervous system.

Symptoms

Pain, especially in the legs and feet, and tingling are the symptoms you will be called on to deal with most often in the diabetic with neuropathy. The treatment

Instructions to patient for mixing soluble and complexed insulins

- *Swab rubber tops of both vials with a spirit swab.*
- *Mix the longer-acting (cloudy) insulin by rolling between the palms.*
- *Inject the same volume of air into this bottle without inverting the bottle and do not withdraw any insulin.*
- *Inject the appropriated volume of air into the bottle of clear insulin and withdraw past the correct dose and then tap out any air-bubbles and push back into the bottle until the correct dose remains.*
- *Insert the needle into the cloudy insulin bottle and draw out very carefully until the correct* ***combined*** *dose is reached, being sure there is no excess.*
- *Inject the mixture immediately.*
- ***If any mistakes are made discard the insulin and start again.***
- *Do not use spirits for cleansing the skin – just use soap and water.*
- *Carefully replace the plastic tip protecting the needle and return the insulin bottles to the refrigerator keeping some distance away from the freezer compartment.*

we find most successful is a combination of pyridoxine 50 mg t.i.d., carbamazepine ('Tegretol') 200 mg b.d., and tight glycaemic control. The pain in sensory neuropathy is self-limiting and the severer symptoms not infrequently subside after about a year with or without medication. The judicious use of tricyclic anti-depressants such as amitriptyline 25 mg nocte is often beneficial.

Do not refer patients for optometric assessment before having excluded diabetes

Sexual dysfunction in diabetes

Except for transient loss of desire during phases of marked hyperglycaemia and dyspareunia during episodes of vaginal candidosis, sexual dysfunction is rarely a feature of diabetes in the female. In males, loss of desire and erectile dysfunction may be a transient feature during periods of poor control. A small number of diabetic males have impotence as the presenting feature, and in our sexual dysfunction unit we have seen 13 males, referred for impotence, where diabetes (NIDDM) was discovered during investigation of the dysfunction. There is no doubt that a number of male diabetics have impotence as a result of long-term diabetes, but one should caution against the bland assumption that this indicates purely organic impotence and that nothing short of a penile implant will alleviate the problem. The realities of life for the diabetic involve loss of job mobility and insurability, which may well have an emasculating effect, whilst the knowledge that his disorder may have effects on sexual function aggravates performance anxiety. Our experience, both in the diabetes department as well as in our sex dysfunction unit, is that predominantly organic impotence in the diabetic is far less likely to be due to vascular insufficiency, but is more commonly due to autonomic neuropathy, as penile-brachial indices in a large number of affected diabetic males have not shown the expected lower levels. Careful history-taking in these patients reveals that prior to the erectile dysfunction there was a period of retarded ejaculation and/or retrograde ejaculation. In a small group of 15 diabetic males with retrograde ejaculation we found the use of a small dose of an alpha-adrenergic stimulant such as ephedrine HCI before bedtime succeeded in reversing the bladder neck dysfunction, allowing of anterograde ejaculation, first in the "safer" setting of masturbation and later in coitus.

The realities of life for the diabetic involve loss of job mobility and insurability

In the severer cases of organic impotence the use of prosthetic implants may be considered. At the recent IDM meeting in Madrid, a new device producing passive engorgement of the penis using a plastic mould and a vacuum pump (after which a rubber-band at the base of the penis maintains the "erection") was viewed with interest, and the publication of the method is awaited with eagerness by all who deal with these unfortunate patients.

Check for proteinuria at every visit, insist on tight control and treat hypertension vigorously!

Sites of preference for injecting insulin

*(1) **Anterior abdominal wall.** Especially for physically active diabetics. The rate of absorption is twice as fast as from the thighs and 1½ times as fast as from the arms. The area immediately round the umbilicus should be avoided. Patients with more than 2 cm of subcutaneous tissue should be encouraged to inject at right angles to the skin as there is a danger of injecting too superficially and causing microabscesses.*

*(2) **The thighs.** Suitable for the physically inactive diabetic and for the night-time injections for the active diabetic.*

*(3) **The upper arms.** There is a risk of insulin lipodystrophic swellings as patients tend to confine the injections to one arm, eg the left arm if they are right-handed.*

The family doctor should check every IDDM patient's injection sites at every visit to ensure that rotation of sites and proper injection technique is being observed.

References

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