Reviews in Medicine

New concepts in diabetes mellitus II: complications

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The presentation of the preliminary results of the Diabetes Control and Complications Trial (DCCT) at the American Diabetes Association Meeting in Las Vegas on 13 June 1993 was a most exciting landmark. Although several smaller studies had previously demonstrated the benefit of tight control, this one defined with confidence the magnitude of the effect. Prior to the DCCT report, a meta analysis of 16 randomized trials of intensive therapy showed that long-term intensive blood glucose control significantly reduced the risk of diabetic retinopathy and nephropathy progression.⁷⁸ The DCCT reported on 1,441 insulin-dependent patients, half of them receiving conventional insulin treatment (one or two injections a day) and the other half placed on an intensified controlled regimen (three or more injections a day or the use of an insulin infusion pump). The 9-year study showed that, if blood glucose levels were maintained at nearer normal levels by intensive therapy, there was an approximate 60% reduction in risk of retinopathy, nephropathy and neuropathy. A decrease in macrovascular complications (considered together) was also observed. The benefits of intensive therapy were seen in all categories of subjects regardless of age, sex or duration of diabetes. Although there was no significant difference in neurobehavioural and psychological measurements, or quality of life, the incidence of severe hypoglycaemia was tripled in patients treated intensively (62 versus 19 per 100 person years).

Further evidence was provided in July from the Stockholm Diabetes Intervention Study⁷⁹ which followed 102 patients with insulin-dependent diabetes mellitus (IDDM) and non-proliferative retinopathy randomly assigned to either intensified insulin treatment or standard insulin treatment for almost 8 years. Nephropathy, the deterioration of nerve conduction velocities and the progression of serious retinopathy were all significantly retarded in the group of patients who received intensified treatment.

Thus, it had been established conclusively that the risk of microvascular complications can be reduced by tightening blood glucose control. This should be acceptable for the patient, provided that frequent or severe hypoglycaemia can be avoided. The Wisconsin study⁸⁰ has already shown that the mechanisms by which hyperglycaemia in non-insulin-dependent diabetes mellitus (NIDDM) causes microvascular damage are similar to those seen in IDDM and one would therefore expect a similar outcome to intensive therapy. Whether there will be a similar benefit of intensive therapy in NIDDM will hopefully be demonstrated by the UK Prospective Diabetes Study.⁸¹

Retinopathy

The St Vincent Declaration has focused interest on screening for retinopathy⁸² particularly now that failure to detect retinopathy by annual screening has been considered as inadequate care and the subject of negligent claims by the courts.

A cost-effective alternative to ophthalmologist screening would seem to be the retinal camera. An American study compared 45° fundus photographs and the standard ophthalmologists examination to detect non-proliferative and proliferative retinopathy.⁸³ In a primary care setting with a large clinic population, screening with retinal photographs through dilated pupils was found to be an appropriate and cost-effective alternative to screening by an ophthalmologist in this setting. In Tayside a non-mydratic mobile screening unit was found to be a practical and effective method of assessing diabetic retinopathy, particularly in a widely spread population. It also enables screening of elderly NIDDM and less mobile members of the community who are less likely to be under hospital care, but who nevertheless have a equally high morbidity from retinal disease.⁸⁴

The importance of optimization of blood glucose control in young IDDM patients was emphasized in a cross-sectional study in Norway in 1992 which determined the prevalence of retinopathy and evaluated its association with various risk factors

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Complications of diabetes

- The Diabetes Control and Complications Trial demonstrated that long-term intensive blood glucose control led to a 60% reduction in the risk of microvascular complications but a three-fold increase in severe hypoglycaemia.
- Peripheral neuropathy is present in more than 50% of NIDDM subjects aged over 60 years.
- Early and effective anti-hypertensive therapy in IDDM patients with microalbuminuria can reduce end-stage renal failure and lead to substantial increases in life expectancy.
- Microalbuminuria in NIDDM is an independent predictor of cardiovascular mortality.
- A double-blind study in patients who had reported hypoglycaemic unawareness found no difference between human and porcine insulin in the presentation of hypoglycaemia or the neurohumoral, symptomatic, and cognitive responses to hypoglycaemia.

in young diabetic patients.⁸⁵ A total of 371 subjects (60% of the sample available, mean age 19.8 years, mean duration of diabetes 10.5 years) volunteered for a clinical examination. Retinopathy was found in 32.8% of the sample, including 7.3% of those less than 13, the youngest of whom was 9.6 years old. In addition, patients with retinopathy had a significantly higher mean age reflecting a longer mean duration of diabetes and had a higher mean HbA1c.

The relationships between glycated haemoglobin (HbA1), fasting or 2-hour plasma glucose post-oral glucose load, and diabetic retinopathy were examined by cross-sectional and prospective analyses among Pima Indians with NIDDM.⁸⁶ This population, with a very high prevalence of NIDDM, has been studied longitudinally since 1965 with standardized examinations every 2 years. In the cross-sectional analysis, data from the last examination of 789 subjects with HbA1, fasting and 2-hour blood glucose, and fundus photo were used. In the prospective analysis, 227 diabetic subjects free of retinopathy at their first diabetic examination were followed up. HbA1, fasting and 2-hour plasma concentrations were similar in their associations with both the prevalence and incidence of retinopathy. It has been confirmed that systolic blood pressure increases prevalence and severity of retinopathy in NIDDM. Ophthalmoscopy and fundal photographs were performed among a group of patients matched according to diabetes duration, HbA1 and albumin excretion rate. Those subjects with a systolic blood pressure above 140 mmHg had a higher prevalence of proliferative retinopathy particularly during their first 10 years of disease.⁸⁷

Neuropathy

The prevalence of diabetic peripheral neuropathy in the UK hospital clinic population, published in

1993, was determined by a cross-sectional multi-centre study involving 6,487 diabetic patients examined in 118 clinics.⁸⁸ The overall prevalence of neuropathy was 22.7% in IDDM and 32.1% in NIDDM. As expected, neuropathy increased with both age and duration of diabetes, until it was present in more than 50% of NIDDM subjects aged over 60 years. Neuropathy was detected clinically and a scoring system used to correlate this with vibration perception threshold as measured at two separate centres.

Several scoring systems now exist to diagnose diabetic polyneuropathy and estimate the degree to which the nerves are affected. In a study of 78 patients with symptomatic polyneuropathy one such scoring system was used to compare the four sensory modalities. Pinprick sense, light touch sense, and ankle jerks were the most important parameters in the clinical diagnosis, and clinical sensory deficits could not be inferred from the results of neurophysiological testing of sensory nerve function.⁸⁹

The calculation of a clinical neuropathy score from a computerized clinical information system has been shown to be simple, valid and a relevant method for diabetes care both in hospital and the community. When combined with palpation of peripheral pulses at risk patients for foot ulceration can be identified and targeted.⁹⁰

The debate continues on the pathogenesis of diabetic neuropathy. It has long been thought to be the result of tissue damage due to prolonged hyperglycaemia mediated by the consequences of polyol (for example, sorbitol) pathway activation and excessive glycation of circulating or membrane-bound proteins. In addition nerve regeneration by insulin-like growth factor 1 (IGF-1) can be defective. A study of Crosby *et al.*⁹¹ found that in IDDM that there were clear abnormalities in the regulation and circulating levels of IGF-1 and insulin-like growth factor binding-protein (IGFBP-1), and that the changes, particularly in IGFBP-1 which is acutely regulated by insulin, were more pronounced in patients with peripheral neuropathy.

The evidence that microvascular disease may have a role in the pathogenesis of neuropathy is increasing. Sural nerve biopsies taken from neuropathic diabetic patients show the pathological features of microangiopathy and are hypoxic compared with controls. Peripheral nerve function has been shown to be associated with tissue hypoxia and, by improving oxygenation, nerve conduction can be improved over a short period of time.⁹² The microvascular damage occurs particularly in the endoneurium. Malik *et al.*⁹³ showed significant correlation between morphometric measures of microangiopathy and neuropathic severity assessed by functional and

pathological means. The evidence on the effectiveness of aldose reductase inhibitors in the treatment of neuropathy remains inconclusive. A 12-month randomized trial of an aldose reductase inhibitor found no beneficial effect in patients with chronic symptomatic diabetic neuropathy in motor and sensory nerve conduction velocities, vibration perception thresholds, symptom scores or autonomic function.¹⁷ However, Sima *et al.* described significant improvement in axonal recovery and sural nerve conduction velocities in ten sorbinil (an aldose reductase inhibitor) treated patients compared with no such effects seen in six placebo-treated patients.⁹⁴

The immune system is thought to play a role in the pathogenesis of autonomic neuropathy. Zanone *et al.*⁹⁵ found that 33% of patients with autonomic neuropathy were positive for at least one autoantibody to sympathetic and parasympathetic nervous structures. Anti-sympathetic ganglia antibodies, in particular, were significantly more prevalent than in the diabetic controls with disease of similar duration and the normal subjects. In addition the diabetic subjects without complications and short disease duration were also positive for at least one antibody, and it was speculated that this may represent a group of pre-neuropathic patients. There was no correlation found with other autoantibodies including islet cell antibodies.

The awareness of impotence as a significant cause of morbidity in middle-aged diabetic men is increasing in the diabetic clinic and is known to affect up to 50% of patients. It is often a complex problem involving several mechanisms, such as psychogenic factors, vascular disease, autonomic neuropathy, hormone imbalance and drug therapy. Nocturnal penile tumescent studies, used in the differential diagnosis, can be abnormal in diabetics who have no history of coital failures, and therefore this data should be interpreted with caution.⁹⁶ Vacuum constriction devices have been shown to be successful in treating impotence particularly when intracorporeal papaverine injections are not tolerated or are ineffective as when significant vascular disease is present.⁹⁷

Nephropathy

Microalbuminuria is an established early marker of progression of overt renal disease in IDDM. Identification of patients at high risk by screening for microalbuminuria now occurs in many hospital clinics and potentially early and effective anti-hypertensive treatment in these patients can postpone or prevent clinical nephropathy. A cost-benefit analysis using a computer stimulated cohort of 8,000 patients from previously published data showed that a programme such as this would lead

to substantial increases in life expectancy and reduction in the incidence of end stage renal failure.⁹⁸

A 4-year follow-up of a cohort of 137 IDDM patients identified poor glucose control, an early rise of blood pressure and smoking as being implicated in the development of persistent microalbuminuria.⁹⁹

Blockade of the renin-angiotensin system by angiotensin I converting enzyme inhibitors may decrease microalbuminuria in normotensive diabetic patients independently of the fall in blood pressure.¹⁰⁰ Twenty-five patients received either enalapril or hydrochlorothiazide in a parallel, double-blind, double placebo study. An effective renin-angiotensin system blockade by enalapril significantly reduced the microalbuminuria of normotensive diabetic patients within one year's treatment. This did not occur in the thiazide-treated group. There was, however, a slightly greater fall in blood pressure in the enalapril-treated group.

Renal disease secondary to diabetes mellitus is more common in patients of Asian ethnic origin than Caucasians living within the UK. A study from Leicester found that the incidence rate of end-stage renal failure was much higher in Asian patients and that in all cases this was secondary to NIDDM.¹⁰¹ In addition there was a male:female ratio of 9:1 compared to an equal sex distribution in the White Caucasian group. Why Asian diabetic males should be so susceptible to end-stage renal failure is unclear. It is of interest that there is a greater prevalence of treated end-stage renal failure in other ethnic minority groups such as Black Americans and Mexican Americans and this may be related to the higher prevalence of hypertension in these groups.

Macrovascular disease

The macrovascular mortality from diabetes has long been an underestimated health problem. The 10-year mortality in the Three City Study confirmed that survival in 540 NIDDM subjects was poorer than expected for both sexes compared with population controls. Standardized mortality ratios for selected causes of death confirmed excess for cardiovascular disease, coronary heart disease and cerebrovascular disease. Only 54% of the death certificates contained any mention of diabetes in this cohort.¹⁰² Modification of risk factors confers a benefit 3–5-fold greater in diabetic compared with non-diabetic men.¹⁰³

A prospective study of the prognosis in acute myocardial function was performed in 858 patients admitted to a Coronary Care Unit in Sweden during a period of 21 months.¹⁰⁴ Of those admitted, 11% had a history of diabetes and the one year

mortality rate was 41% compared to 26% for non-diabetic patients. The clinical presentation did not differ between the two groups, the estimated infarct size and occurrence of ventricular arrhythmias was similar. Although congestive heart failure was more common in the diabetic patients, the percentage of diabetic patients who died in association with heart failure was similar to that in non-diabetic patients. The mechanisms behind the higher mortality were therefore unclear.

In NIDDM, microalbuminuria has been shown to be an independent predictor of cardiovascular mortality for the first time in a prospective study of 141 subjects.¹⁰⁵ The mechanism of the link is postulated to be that increased urinary albumin loss is a marker of a generalized increase in vascular permeability, which might predispose to greater penetration into the arterial wall of atherogenic lipoprotein particles. Lipoprotein(a) (Lp(a)) levels, a known independent risk factor for macrovascular disease, were raised in a study of 26 NIDDM patients with microalbuminuria and albuminuria compared with non-diabetic controls.¹⁰⁶ Heesen *et al.*¹⁰⁷ found that with increasing Lp(a) levels, higher prevalences of preproliferative retinopathy and evidence of coronary heart disease were found in a larger group of 194 NIDDM subjects but no relationship was found with other diabetic complications including albuminuria. Lp(a) levels in NIDDM subjects were compared with controls in a population based study (San Antonio Heart Study).¹⁰⁸ No significant increase in Lp(a) levels were seen in the diabetic subjects and there was no relationship with duration of diabetes or the level of fasting glycaemia. Although the exact mechanism may be unclear the evidence suggests that the role of screening for microalbuminuria in NIDDM could be to identify a group of patients who are at high risk and for whom risk factors for cardiovascular disease must be rigorously addressed.

In the non-diabetic population, coagulation appears to be disturbed in patients with ischaemic heart disease. Fibrinogen concentrations are frequently elevated in diabetes, regardless of diabetes duration, but particularly in those with NIDDM and pre-existing vascular complications. Even patients with uncomplicated IDDM have significantly elevated levels.¹⁰⁹ In a study of 122 diabetic patients (both IDDM and NIDDM subjects) red cell aggregation was measured by a photometric method and compared with 100 matched non-diabetic controls.¹¹⁰ Significant increases in red cell aggregation were found and these correlated with triglycerides, VLDL, and inversely with HDL, and in the NIDDM patients also with body mass index and hypertension. In addition, triglycerides, body mass index, and smoking showed an independent association with red cell

aggregation and thus this may be a further mechanism by which some cardiovascular risk factors could promote cardiovascular disease in diabetics. It has been suggested that diabetics have increased free radical activity, a putative factor in the pathogenesis of macrovascular disease. However, a study by MacRury *et al.*¹¹¹ failed to find an additive effect of diabetes on the increased free activity associated with vascular disease when comparing diabetics and non-diabetics with peripheral disease, although activity was shown to be increased in both groups.

A large community survey of ten general practices in East Dorset identified 1,150 diabetic subjects with peripheral vascular disease. The prevalence in IDDM was 8.7% and in NIDDM was 23.5% which, after adjusting for age, was not significantly different.¹¹² A survey of lower limb amputation found that during 1989–1991 diabetic patients comprised 39% of amputees and 42% of all operations.¹¹³ Of the 48 diabetic amputees, 88% had evidence of peripheral vascular disease and 15% had diabetes first diagnosed when they were admitted for amputation. The mortality rate within 30 days after diabetic amputation was 10% and the median life expectancy following amputation was 22 months. Foot examination and assessment was found to be inadequately recorded in 47% of cases. In the presence of hypertension, the risk of peripheral vascular disease in NIDDM rises substantially. Increased serum total cholesterol, LDL-cholesterol and lower HDL-cholesterol were found to be independently associated with peripheral vascular disease.¹¹⁴ Effective screening for lipid abnormalities and adequate intervention is likely to reduce morbidity and mortality.

The diabetic foot

As many as 20% of diabetic-related admissions to hospital are for management of foot problems. Recent studies have cast doubt that *Staphylococcus aureus* may be the dominant infecting organism.¹¹⁵ A study of the frequency with which multiple organisms can be isolated from severe foot infections in diabetics found that an average of 3.4 organisms were found per infection in a district general hospital, and that both *S. aureus* and anaerobic organisms were isolated from 58% of the ulcers. The implication is that effective anaerobic antibiotic cover must be provided in the initial regimen until a bacteriological report is available. Early diagnosis of osteomyelitis is difficult but essential as prompt antibiotic treatment can prevent amputation. In a prospective study of 16 foot ulcers in 12 patients, osteomyelitis was confirmed by bone biopsy in 44%, even though the diagnosis was not suspected clinically in any case.¹⁰⁶

Leucocyte scanning was 100% sensitive in detecting osteomyelitis and was superior to magnetic resonance imaging (MRI) which was only 29% sensitive. The positive and negative predictive values for the leucocyte scan were also greater than those of MRI.

A further advance in the treatment of outpatient unilateral diabetic foot ulcers was the demonstration of the effectiveness of the 'half shoe' or 'heel shoe.' This is a practical method of providing pressure relief to the ulcer whilst allowing mobility and is better tolerated by patients than other aides to relieve weight bearing such as crutches and plaster casts.¹¹⁶ The impact of 'half shoes', only available to the investigators since 1989, was compared in 26 patients with a comparative retrospective control group given standard treatment alone. The overall healing time and the rate of hospitalization were significantly lower in the 'half shoe' treated group.

Hypoglycaemia

Hypoglycaemia is the commonest side effect of insulin therapy and is the complication that patients fear most. A retrospective study in Edinburgh in 600 randomly selected insulin-treated patients attending a large outpatient clinic, documented the frequency of severe hypoglycaemia.¹¹⁷ A total of 29.2% of the sample reported a total of 964 episodes (1.6 episodes per patient per year) of severe hypoglycaemia in the preceding year. The frequency in IDDM was twice that seen in a small subgroup of insulin-treated NIDDM. The resulting morbidity was determined in a subset of 302 patients. Those who had experienced severe hypoglycaemia reported a rate of injury of 0.04 injuries per person per year, 6.6% had reported hypoglycaemic-related convulsions, and there were five road traffic accidents caused by hypoglycaemia. The reliable predictors of severe hypoglycaemia were a previous history of severe hypoglycaemia or hypoglycaemic-related injury, convulsion and the duration of diabetes. These affected patients tended to have a lower mean glycated haemoglobin but this did not reach significance.

The prevalence of severe hypoglycaemia and loss of awareness of hypoglycaemia in insulin-treated NIDDM patients was ascertained by Hepburn *et al.*¹⁴ A total of 104 NIDDM subjects were compared with a similar number of IDDM subjects matched for duration of insulin therapy and found

no difference in the incidence of severe hypoglycaemia between the two groups; but the length of exposure to insulin therapy was relatively short. The range and prevalence of specific symptoms of hypoglycaemia were similar in both NIDDM and IDDM subjects. In both groups lack of awareness of hypoglycaemia was significantly associated with duration of insulin therapy.

The possibility that converting to the use of human insulin might also increase hypoglycaemic unawareness has been the subject of much controversy and public debate. In order to attempt to resolve this issue a double-blind clinical and laboratory study of human and porcine insulin in patients who had reported hypoglycaemic unawareness was performed.¹¹⁸ In 17 patients with IDDM of more than 5 years duration no difference was found in the presentation of hypoglycaemia or the neurohumoral, symptomatic and cognitive function responses to hypoglycaemia. This confirmed most other clinical and laboratory studies and definitively lays to rest the question of a peculiar action of human insulin which differs from porcine insulin. However, it does not change pragmatic clinical advice to an individual uncomfortable with his or her treatment. The British Diabetic Association strongly recommends that patients reporting unhappiness of any kind with one insulin should be changed to another.

To clarify the effect of ethanol on blood glucose regulation in IDDM subjects, a cross-over study was performed.¹¹⁹ Plasma ethanol concentration was raised to about 120 mg% by intravenous administration. This had no detectable effect upon blood glucose regulation. The authors suggest that the frequently observed association between alcohol and hypoglycaemia is a consequence of the associated events – missed meals, errors in insulin dose or inability to respond to early warning signs of hypoglycaemia when inebriated.

Conclusions

Knowledge about diabetes has increased exponentially over the last decade. In the context of unstable and changing health care systems, the challenge lies in ensuring adequate delivery of diabetes care to all affected individuals. The role of research in simplifying this task by moving towards a genuinely satisfactory treatment for both IDDM and NIDDM should be evident from this review of the efforts of one year.

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