DIABETES FESTIVAL: 11–12 NOVEMBER 1999

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SESSION 1

Professor R. Williams, Leeds, Dr A. Morris, Dundee and Dr D. Pearson, Aberdeen

DIABETES AND THE POPULATION

At present 5.8% of the total healthcare budget is spent on diabetes care. By 2010 projections suggest that this percentage will have to increase to 10.1%. Therefore, reducing the cost to the health services of diabetes is an important goal. This may be achieved in part by primary prevention of diabetes, e.g. reducing levels of obesity in the population, but it may perhaps be easier to limit the cost by implementing efficient secondary prevention strategies which reduce the cost of complications of diabetes and limit the excess hospital usage made by diabetic patients.

Much of the epidemiological data for diabetes was originally obtained from the Framingham cohort. Whilst this information is important, it is essential to remember that there were only 237 individuals with diabetes included in it. The Diabetes Audit and Research in Tayside (DARTS) project has collected accurate epidemiological information about the entire population with diabetes in Tayside. The success of this project is down to the assimilation of pre-existing data from various sources which include clinic attendances, hospital admissions, the diabetic 'eye van' biochemical data, prescription encashment (from the Medicines Monitoring unit (MEMO)) and primary care as a key source. The co-ordination of the collation of data sources is facilitated by the use of a unique patient identifier for all patients in Tayside known as the CHI number. This population-based database has identified:

- An association between the prevalence of type 2 diabetes and social deprivation which may be driven by increased levels of obesity.
- A two to three fold increase in the adjusted relative risk of cardiovascular complications in the diabetic population compared to a similar non-diabetic population, with females aged less than 50 years of age having the highest increase in relative risk.
- That more than 70% of diabetic patients exceed the BP target of 130/80mmHg, and that the combined British cardiovascular risk tables probably underestimate the true risk in diabetic patients (SIGN 40).
- That for patients receiving multiple oral treatments only 8% of patients are fully concordant with treatment.

DIABETES AND PREGNANCY

The St Vincent Declaration aims for pregnancy outcomes in the diabetic population to be similar to the background population. Despite setting this target some ten years ago, information regarding pregnancy outcomes in patients with diabetes is still lacking: information from individual centres is available but this information may be subject to selection bias. The Scottish National Audit of Pregnancies in Patients with Diabetes ran between April 1998 and March 1999, and involved collaboration between physicians, midwives and obstetricians. The audit has recorded information on 268 pregnancies resulting in 209 live deliveries, and although analysis of all the data is not yet complete, a number of important statistics have emerged.

- Perinatal mortality rate for patients with diabetes is still higher than the general population, at 18.9/1,000 compared with 7/1,000.
- Despite the target issued by SIGN 9 that women with diabetes should have a planned pregnancy overall, only 42% of the pregnancies studied were planned and only 25% of women attended formal pre-pregnancy counselling.
- SIGN 9 guideline states that folic acid supplementation should be given to all women but only 50% were receiving folic acid and only 14% were receiving the recommended 5 mg dose of folic acid.
- Guidelines state that rubella status should be checked in all women but in the women audited only 43% had been so checked.
- Euglycaemic status was achieved in very few of the women studied.
- Spontaneous deliveries occurred in only 22% of diabetic pregnancies with 64% delivering by caesarean section.
- The majority of babies delivered were above the fiftieth centile for weight.

These figures would appear to show that we are not achieving the various targets set for diabetic pregnancies but they will now form the building blocks for improving our practice. Further national audits are an essential stimulus to improving care.

KEY POINTS

- Diabetes healthcare costs will be 10.1% of overall health costs by 2010.
- Only 237 diabetic patients were in the original Framingham cohort.
- Type 2 diabetes is associated with social deprivation possibly driven by increased levels of obesity.
- Seventy per cent of patients with diabetes exceed the BP target of 130/80.
- Only 18% of patients are concordant with multiple oral treatments.
- Perinatal mortality is still 2.5 times that in the non-diabetic population.
- Sixty-four per cent of diabetic women in Scotland are delivered by Caesarean section.

SESSION TWO

Professor I. Campbell, Kirkcaldy, Dr J. Walker, Edinburgh, Dr S. Marshall, Newcastle, Professor J. Tooke, Exeter

COMPLICATIONS OF DIABETES

The Royal College of Physicians Register was established in 1989. The registry includes data from insulin-treated patients, and provides data for trials, study of epidemiology and medical audit. The morbidity data is linked to SMR (Standardised Mortality Ratio). There are now more than 4,000 patients on the Register. Those who required insulin treatment and were <35 years of age at onset are categorised as having type 1 diabetes. Those requiring insulin and are >35 years of age are categorised as having type 2 diabetes. Information on height, weight, blood creatinine and cholesterol, microalbuminuria and retinal screening information is recorded for each individual.

This Register has allowed the characterisation of the individuals treated with insulin.

- Fifty-five per cent of the patients with type 1 diabetes are male. The sex distribution for those with type 2 diabetes is equal.
- Disappointingly, 33% of individuals with type 1 diabetes and 29% of those with type 2 diabetes are current smokers.

The registry is currently involved in writing a programme that will analyse the effects of microalbumin concentrations, risk factors for macrovascular disease, deprivation and pregnancy in insulin-treated individuals. The registry has also formed the basis for the multicentre MRC funded POPODAD study which aims to assess whether aspirin or antioxidant therapy, either separately or combined, are more effective than placebo in preventing arterial disease progression.

DIABETIC KIDNEY DISEASE

Diabetic nephropathy engenders huge costs. It is the commonest cause of renal replacement in the UK accounting for 40% of all transplants. Diabetic nephropathy will affect 25% of individuals with type 1 diabetes and 25% of individuals with type 2 diabetes who survive > 25 years. Maintenance of good glycaemic control is effective in reducing the impact of diabetic renal disease, but even in individuals with good glycaemic control, micro-albuminuria still occurs in 10-12% of individuals. Microalbuminuria is a predictor for end-stage renal disease, and microvascular and macrovascular disease. The measurement of microalbumin levels has now become incorporated into clinical practice. The Royal College of Physicians Registry has recently co-ordinated a prospective multicentre cohort study in type 1 patients with the aim of determining the levels of microalbumin predictive of the progression to nephropathy or the development of proliferative retinopathy or maculopathy. In total 1,201 patients were followed for a mean of four years. The key findings were that 3.8% of the patients studied progressed to have nephropathy and 7.8% developed eye complications over the four-year study period. The risk factors for nephropathy were a disease duration greater than 15 years, elevated HbA1c, and microalbumin concentrations above 7.4mg/l. Microalbumin did not predict the development of retinopathy.

ACE inhibitors are currently the mainstay of treatment for secondary prevention for patients with established microalbuminuria, and this may be a function of lowering blood pressure by these changes. Despite intervention with ACE inhibitors a significant proportion of individuals still progress to develop end-stage renal disease. This suggests that other factors may be involved:

- Undertreatment of co-existing risk factors such as hypertension, hypercholesterolaemia, poor glycaemic control and underprescription of ACE inhibitors has been shown in individuals with existing diabetic nephropathy.
- Familial Predisposition: twin studies have shown that in twins who have type 2 diabetes, if one twin develops nephropathy, there is an 80% risk that the other twin will also develop nephropathy. Therefore a single genetic influence seems likely.
- Clustering of other risk factors: patients with nephropathy tend to do badly with increased complication rates, hypertension, dyslipidaemia and increased insulin resistance.

The mechanisms underlying the clustering of risk factors are unclear but it has been suggested that the sodium/lithium (Na/Li) counter transporter may be involved. Abnormal Na/Li counter transport has been noted in individuals with diabetic nephropathy and the same defect has also been noted in family members of the affected individuals. Thus increased Na/Li kinetics may be used to predict the development of increased microalbumin excretion. The inherited factor may be a 33kDA protein, which may be tropomyosin; this in turn may cause abnormal cycling of the GLUT4 mechanism thereby resulting in insulin-resistance.

In order to reduce the impact of diabetic renal disease it is essential to identify those who are at risk, and improve primary and secondary prevention. Increasing our understanding of the mechanisms involved will allow the development of novel treatment strategies including possible gene therapy.

CURRENT CONCEPTS OF THE CAUSATION OF DIABETIC ANGIOPATHY

Diabetic angiopathy comprises macroangiopathy and microvascular disease.

a) Diabetic macroangiopathy

This refers to atherosclerosis which in individuals with diabetes is accelerated; the disease is also more distal and females are not spared. The same process also affects individuals with impaired glucose tolerance. Increased oxidative stress and glycation in these individuals contribute to altered vascular haemodynamics.

The major contributors to diabetic macroangiopathy are:

- Hypertension.
- Adverse lipid profiles.
- Increased oxidised LDL.
- Procoagulant blood.
- Endothelial injury that results in the formation of foam cells and the release of growth factors.

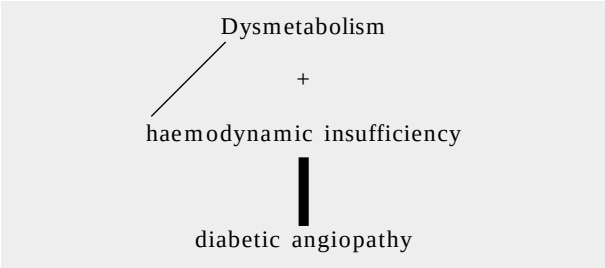

FIGURE 1
Pathogenesis of diabetic angiopathy.

b) Microvascular disease

Microvascular disease is strongly related to the degree of glycaemic control and duration of illness. Angiopathy is a result of disordered metabolism and haemodynamic insufficiency (Figure 1). The type of diabetes may influence the type angiopathy; type 2 diabetes is a more heterogeneous condition in which hypertension occurs more commonly and there is an increased risk of macrovascular disease when compared to type 1 diabetes. There is also an altered expression of microvascular disease with maculopathy occurring more frequently than proliferative retinopathy. In patients with type 1 diabetes nephropathy is a more common occurrence.

Fatty streaks are the precursors of diabetic macroangiopathy and are probably related to haemodynamic changes. The role of haemodynamic changes in microvascular disease is less clear but is probably still important, as the United Kingdom Prospective Diabetic Study (UKPDS) has shown that a reduction in blood pressure reduces the risk of developing retinopathy (Figure 2).

Endothelial function is impaired in individuals who are predisposed to develop diabetes later in life. The Barker hypothesis suggests that fetal insulin resistance may be the initiator of impaired endothelial function which may in turn result in changes in capillary density and in vascular smooth muscle. The future prospects for management of angiopathy are shown in Table 1.

In conclusion, the treatment and prevention of diabetic vascular complications requires that factors that influence the endothelium, as well as haemodynamic and metabolic parameters, be addressed.

TABLE 1
Prospects for therapy in diabetic angiopathy.

i) Macroangiopathy
• Aggressive management of lipids and glycaemia • Insulin sensitisers • Nitric Oxide enhancers • Antioxidant therapy • Reprogramming (ACE Inhibitors have been used sucessfully in low birth weight rats)
ii) Microangiopathy
• Glycaemic control • PKC inhibitors • Aldose reductase inhibitors • Prevention of the formation of advanced glycation end-products • VEGF

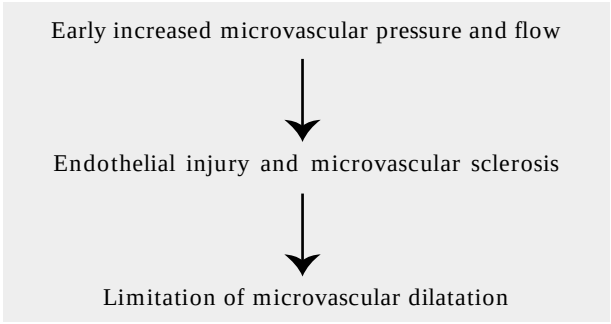

FIGURE 2
Haemodynamic hypothesis.

KEY POINTS

- One in three diabetic patients smoke.
- Microalbumin concentrations greater than 7.4 mg/l predict nephropathy.
- Glycaemic control, blood pressure, lipids and use of ACEI influence onset of diabetic kidney disease.
- Genetic factors are important in the development of diabetic kidney disease.
- Haemodynamic and metabolic factors are important in the development of angiopathy.
- Novel treatment strategies may be effective in reducing diabetic vascular complications.

SESSION 3

Professor G. Shulman, US, Professor P. Cohen, Dundee

NATURE OF TYPE 2 DIABETES

In some elegant and novel experiments Professor Shulman has used Magnetic Resonance Spectroscopy (MRS) to gain further understanding into abnormalities of carbohydrate metabolism in diabetes *in vivo*. Using hyperglycaemic, hyperinsulinaemic infusions of the stable isotope ^{1}13C-glucose it has been shown in healthy individuals that 85% of infused glucose was disposed via non-oxidative pathways, i.e. mainly stored as glycogen, whilst in type 2 diabetes the rate of disposal was 50% less, with the deficit due mainly to a lack of glycogen synthesis. He has tried to determine where in the glycogen synthetic pathway the main abnormality lies. The main possibilities are glycogen synthase, hexokinase or the membrane glucose transporters (GLUT4).

Using ^{31}P MRS, increased glucose 6-phosphate concentrations were demonstrated after glucose infusions in control subjects. A similar increase was shown in glucose 6-phosphate in patients with type 2 diabetes, which suggests that for the small number of unselected patients in this study, glycogen synthase was not the main site of the defect. Other work in insulin-resistant children of patients with type 2 diabetes contradicts these findings, suggesting that at least in some patients glycogen synthase may be more critical.

In further studies of infused ^{1}13C-glucose with 13C-mannitol as an extracellular marker, Professor Shulman has shown that intracellular glucose concentrations are very low in patients with type 2 diabetes, indicating a difficulty in getting glucose into cells, and suggesting that GLUT4 transport may be impaired and may be the main contributor to hyperglycaemia.

It has been demonstrated repeatedly that insulin

TABLE 2
Pathways controlling Glycogen synthase and other anabolic enzymes.

PIP:	Phosphatidylinositol phosphate
PDK:	Phosphoinositide dependent protein kinase
PDE:	Phosphodiesterase
PFK:	Phosphofructokinase
PKB/PKC:	Protein Kinase B and C
GSK:	Glycogen Synthase kinase

sensitivity is inversely proportional to plasma free fatty acid concentrations. In experiments using euglycaemic hyperinsulinaemic clamps, free fatty acids (FFA) were infused in either low or high concentrations. High FFA concentrations were associated with reduced glucose sensitivity, reduced glucose 6-phosphate concentrations, and reduced intracellular glucose concentrations, compared to subjects infused with low FFA concentrations. This implies FFA may have a direct deleterious effect on GLUT4 transporters and this may be the mechanism whereby FFA cause insulin resistance. Other studies show that FFA may have additional effects on intracellular insulin signalling pathways, including protein kinase C and P13 kinase resulting in insulin insensitivity.

Professor Cohen described the details of the post-insulin receptor intracellular signalling pathway in detail. Glycogen synthase is active when not phosphorylated, and is deactivated by phosphorylation. There are at least nine phosphorylation sites on the enzyme. He described the meticulous experiments performed to unravel the detail of the control of glycogen synthase by a number of protein kinases (Table 2). A number of factors may influence this pathway. For instance, cells lacking PDK1 will not respond to insulin, but will respond to IGF1. Also PKB appears to become active when bound to the membrane by PIP3 and PDK1. Drugs may also influence the pathway e.g. drugs inhibiting GSK3 would act to increase glycogen synthesis, and are already being considered. This site, amongst many others, provides potential for therapeutic interventions in the future.

KEY POINTS

- Type 2 diabetes is associated with impaired glycogen synthesis.
- Abnormalities in GLUT4 transport and glycogen synthase are probably the main post-insulin receptor factors contributing to type 2 diabetes.
- High concentrations of free fatty acids directly impair GLUT4 function, and other intracellular enzymatic pathways.
- At least nine phosphorylation sites help determine the activity of glycogen synthase.
- An intricate pathway of protein kinases help control glycogen synthesis, protein synthesis and lipolysis.

SESSION 4

Professor S. Brink, US, Dr B. Frier, Edinburgh

INSULIN THERAPY AND HYPOGLYCAEMIA

There was a consensus in this debate that in a selection of diabetic patients, tight control may not be advantageous. There was less agreement as to how many patients with diabetes this applied to, and what level of glycaemia should be aimed for. The DCCT (Diabetes Control and Complications Trial) was a highly selected population with only 0.2 severe hypoglycaemic events per year in the conventional treatment group, compared to 1.1–1.6 per year in a standard clinic setting. The impact of severe repeated hypoglycaemia is decreased quality of life, possible cognitive dysfunction, precipitation of cardiovascular events and subsequent avoidance tactics resulting in poor control. Thus lies the clinical challenge of identifying patients at risk, who are identified in Table 3.

TABLE 3
Risk factors for severe hypoglycaemia.

- Extremes of age
- Hypoglycaemia unawareness
- Ischaemic heart disease or cerebrovascular disease
- Advanced diabetic complications
- (Possibly) long duration of diabetes

KEY POINTS

- There are predictable patient groups who are at risk from tight glycaemic control (see Table 6).
- A possible association exists between repeated prolonged hypoglycaemia and long-term cognitive impairment.
- On average a young patient with type 1 diabetes has 1.1–1.6 episodes of severe hypoglycaemia per year.
- Recurrent severe hypoglycaemia induces hypoglycaemic unawareness.

SESSION 5

Dr R. Nesto, US, Dr B. Fisher, Paisley, Professor L. Ritchie, Aberdeen, Professor R. Holman, Oxford

PREVENTION OF CARDIOVASCULAR DISEASE

Various speakers once again exemplified the adverse outlook for diabetic patients with ischaemic heart disease. Blood pressure is an important risk factor as shown in the UKPDS. The HOT trial indicated a reduction in myocardial infarction (MI) by 50% just by lowering diastolic blood pressure from 90 to 80 mmHg; a similar finding was noted in the HOPE study. A poor understanding of the underlying mechanisms still exists. Presentation with the anginal event, angiographic findings were no different between diabetic and non-diabetic patients, although the outlook for the former is worse. This tends to indicate that lack of plaque stability, rather than plaque size, is the risky feature in diabetics. In patients matched for extent of myocardial infarction and number of coronary vessels affected, left ventricular wall function was significantly worse in diabetic patients at six months post-infarct compared to controls. This implies a dysfunctional remodelling process in diabetic patients, which may suggest a particular benefit if diabetic patients were treated with ACE inhibitors and ß-blockers. Indeed day one use of ACE inhibitors and ß-blockers have been shown to reduce six week post-MI mortality in diabetic patients.

No particular benefit was shown in screening for asymptomatic ischaemic heart disease as there is no proven

intervention of benefit, other than treating the risk factors that should be addressed anyway. This is especially the case as one, poorly controlled, trial estimated the cardiovascular risk in diabetes for primary prevention to be identical to secondary prevention in non-diabetics.

Important aspects in delivering such care revolve around close integration with primary care involving effective IT systems and clear leadership, with targeting delivery of care.

UKPDS

Dr Holman presented some less well-recognised elements of the UKPDS. It would appear that ß-cell loss from the pancreatic islets starts about 12 years before diagnosis of type 2 diabetes. Intensive treatment was associated with weight gain, but this was only 2–3 kg more than the conventionally treated group. Hypoglycaemia was another problem of intensive control with a 30% risk of any form of hypoglycaemia and 3% risk of severe hypoglycaemia compared with a 3% and 2% risk respectively in the conventional group. Thus the additional risk of severe hypoglycaemia was not drastically worse for the intensively controlled group compared with conventional treatment. The role of risk factors on the occurrence of cardiovascular events was addressed. A 10mmHg increase in BP was associated with a 13% increased risk of a cardiovascular (CV) event, and a close relationship was distinguishable between mean HbA1c throughout the trial and CV events, with a 1% increase in HbA1c being associated with 14% increase in CV events. Of further interest was that there was no threshold effect in HbA1c. The UKPDS showed that the order of importance of intervention of CV risk factors in preventing CV events in patients with diabetes was lipids> HbA1c> blood pressure > smoking.

The cost of life saved by controlling blood pressure in a diabetic patient was £900, compared to £6,000 for breast cancer screening, indicating the cost-effectiveness of blood pressure lowering in diabetes.

The particular advantages of metformin in the UKPDS study seem to relate to reducing endogenous insulin concentrations rather than to specific changes in glucose or cholesterol concentrations. This may reflect improved insulin sensitivity.

KEY POINTS

- Lowering diastolic BP from 90-80 mmHg significantly reduces the risk of cardiovascular events (CV) in diabetes (HOT study).
- Left ventricular function is more likely to deteriorate post-MI in diabetes, indicating a probable remodelling problem.
- The risk of a primary CV event in diabetes is equal to the risk of a secondary event in non-diabetic patients.
- Intensive glycaemic control in type 2 diabetes increases weight by only 2–3 kg.
- Intensive glycaemic control in type 2 diabetes increases risk of minor hypoglycaemia from 3-30%, and major hypoglycaemia from 2-3% (UKPDS).
- Cost of life saved by aggressive BP control in diabetes is £900 (c.f. £6,000 for breast cancer screening).

SESSION 6

Professor G. Alberti, Newcastle

DIABETES IN THE TWENTY-FIRST CENTURY

In the developing world type 2 diabetes is becoming an increasing problem as populations abandon their traditional 'hunter-gatherer' way of life in favour of a more sedentary westernised lifestyle. The cost of treating diabetes and its complications presents a large economic burden on these already poor and disadvantaged countries. The key to reducing these costs is therefore prevention. Simple messages such as 'Eat less and walk more' appear to be more successful than complex dietary instructions. Cheap but effective medication has to be made more freely available in less well-developed countries.