Total risk factor management in patients with type 2 diabetes

Type 2 diabetes is a multisystem metabolic syndrome. Its increasing prevalence therefore presents a major challenge not only in the management of diabetes but also in the treatment of cardiovascular disease.

The number of diabetics in the UK is predicted to reach 3 million within the next 5 years (Diabetes UK, 2004). This presents not only a major challenge in the management of diabetes, but also in the treatment of cardiovascular disease (CVD) (*Table 1*).

It has been estimated that having type 2 diabetes confers approximately the same risk of coronary heart disease as already having had a heart attack (Haffner et al, 1998). Diabetic patients who suffer an acute myocardial infarction (MI) are more likely to die than non-diabetic patients (Miettinen et al, 1996), their outcome following revascularization is worse and they are at greater risk of suffering heart failure. Around 75% of type 2 diabetics die of vascular events such as MI or stroke (King's Fund, 1996).

Unfortunately, while hyperglycaemia remains the defining metabolic abnormality of type 2 diabetes, it appears that CVD risk cannot be sufficiently reduced by glycaemic control alone. This was clearly demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS, 1998a), where intensive glucose-lowering therapy achieved a substantial reduction in all diabetes-related deaths but the fall in MI incidence was of only borderline significance and there was an insignificant effect on peripheral vascular disease.

Table 1. Type 2 diabetes and cardiovascular disease

People with diabetes have up to a five-fold increased risk of developing cardiovascular disease
Middle-aged men with diabetes are five times more likely to die of cardiovascular disease than men without diabetes
Women with diabetes are eight times more likely to die of cardiovascular disease than women without diabetes
People with diabetes are five times more likely to suffer heart failure
People with diabetes are at a two–three times increased risk of having a stroke compared to those without the condition
At least 15% of deaths in people with type 2 diabetes are the result of a stroke
African-Caribbean and South Asian men with diabetes have a 40% and 70% higher risk of stroke respectively than the general population

From Diabetes UK (2004)

Other trials have shown that a reduction in CVD among diabetic patients requires aggressive and early modification of major CVD risk factors such as hyperlipidaemia, hypertension and smoking (Stamler et al, 1993). Indeed, hyperglycaemia is now considered just one risk factor for CVD in type 2 diabetes among a list that also includes:

- Obesity
- Dyslipidaemia
- Hypertension
- Hyperinsulinaemia or insulin resistance
- Haemostatic abnormalities
- Advanced glycosylation end-product (AGE) proteins
- Oxidative stress.

Managing such a diverse array of symptoms and risk factors presents a major challenge to the physician. It requires an approach in which no single risk factor is treated in isolation, but rather each is considered within the context of a multisystem metabolic syndrome.

Measuring coronary risk

It is important, on diagnosis, for each patient with type 2 diabetes to receive a comprehensive assessment of CVD risk (*Table 2*). This require assessment of the patient's clinical history, smoking status, weight, blood pressure and lipid profile. Subsequent risk assessments should be made at least annually.

Patients are defined as at high coronary risk if they already have evidence of CVD or if their 10-year coronary event risk is above 15%. Measuring this 10-year risk has been simplified by the availability of a number of risk assessment tools, which should be used to supplement rather than replace clinical judgment. These tools include:

- Joint British Societies Cardiac Risk Assessor Program (www.bnf.org)
- UK Prospective Diabetes Study Risk Engine: Risk in people with type 2 diabetes (www.dtu.ox.ac.uk)
- Joint British Societies Coronary Risk Prediction Chart (www.heartuk.org.uk/)
- Sheffield table for primary prevention of coronary heart disease (bmj.com/content/vol320/issue7236/images/large/wale3599.f1.jpeg)

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Patient education and lifestyle modification

CVD risk assessment provides an excellent opportunity to counsel patients with type 2 diabetes on the implications of their diagnosis and on the measures they can take to reduce the risk to their heart.

It is important to stress that many of the risk factors for diabetes and CVD respond well to modifications in lifestyle, smoking behaviour and diet. For instance the Diabetes Prevention Program showed that obese patients undergoing a combination of weight loss and exercise achieved a 58% reduction in the onset of diabetes compared to a 38% reduction in patients treated with metformin (Tumilehto, 2001; Diabetes Prevention Program, 2002). Even a weight loss of 10% or less can improve glycaemic control, reduce blood pressure, reduce cholesterol levels and increase longevity in obese individuals (Goldstein, 1992).

Nevertheless, most patients with type 2 diabetes will, at some stage, require long-term pharmacotherapy involving antidiabetic drugs, antihypertensive agents and cholesterol-lowering agents.

Pharmacological treatment

The treatment goals when managing patients with type 2 diabetes are to combat microvascular complications through tight control of the patient's blood glucose while also reducing macrovascular risk through management of the patient's blood pressure and blood lipid profile.

Many patients newly diagnosed with type 2 diabetes will already have manifestations of CVD and will need to be treated accordingly.

Table 2. National Institute for Clinical Excellence guidelines for assessment and management of cardiovascular disease (CVD) risk in patients with type 2 diabetes

At diagnosis take full clinical history including details of CVD
Arrange annual review
Estimate CVD risk at least annually
Use risk assessment charts to estimate 10-year coronary event risk
Classify people with manifest cardiovascular disease as being at higher 10-year coronary event risk
Maintain tight blood glucose control (haemoglobin A1c <6.5–7.5%)
Screen for renal disease and manage accordingly
Measure blood pressure and manage accordingly
Measure lipid profile and manage accordingly
Review and discuss other modifiable risk factors, particularly smoking
Offer smoking cessation advice where appropriate
Offer lifestyle management advice
For individuals who are overweight or obese, encourage weight loss and increased physical activity

From National Institute for Clinical Excellence (2002)

Individual assessment of each patient will determine treatment priorities and reveal which risk factors require the most aggressive intervention. However, it is important not to view each treatment goal in isolation. Each intervention should be assessed not only in terms of its effect on the target symptom but also with consideration of its impact across the entire metabolic spectrum.

For example while beta-blockers are effective antihypertensive agents and undoubtedly have a place in the treatment of type 2 diabetics (particularly in patients who have already suffered an MI; MacDonald et al, 1998), side effects such as insulin resistance and peripheral vasoconstriction have led to suggestions that their use should be limited. Combined-effect beta-blockers, such as carvedilol, a beta-blocker with alpha-1 blockade, are known to reduce insulin resistance and induce peripheral vasodilatation and may therefore be a better choice for patients with type 2 diabetes.

Similarly it may be appropriate to consider the differing effects of antidiabetic agents on patients' lipid profiles when choosing a medication to combat hyperglycaemia.

Control of blood lipids

The importance of lipid-lowering therapy in patients with type 2 diabetes has become increasingly evident in recent years. Indeed US guidelines (Snow et al, 2004) for statin therapy in type 2 diabetes now recommend that all patients with type 2 diabetes should be considered for statin therapy regardless of their CVD risk. It is expected that the forthcoming joint British guidelines will also take this view.

The typical lipid profile of a patient with type 2 diabetes exhibits moderately elevated levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol.

Low-density lipoprotein (LDL) cholesterol tends not to be elevated in type 2 diabetes, but it does show evidence of increased atherogenicity. This is partly the result of an increased rate of glycation of apolipoprotein B (Lyons, 1992) which delays LDL clearance from the plasma and increases the susceptibility of LDL particles to oxidation.

Diabetic dyslipidaemia is also notable for its predominance of smaller, denser LDL particles which are more susceptible to oxidation than the larger particles. Oxidation plays a key role in the development and progression of the atherosclerotic plaque.

LDL cholesterol is therefore an important CVD risk factor in type 2 diabetes and strenuous efforts should be made to reduce it. Indeed LDL cholesterol has been identified as the primary target for lipid management by the American Diabetes Association (1998) which has set a therapeutic goal of 2.6 mmol/litre.

In the UK treatment targets are to reduce total cholesterol to below 5 mmol/litre and LDL to below 3 mmol/litre. However, the new joint guidelines, due later this year, are expected to set lower targets.

Statins are the first-line therapy of choice. The use of statins can reduce cardiovascular events and death by 25% in high-risk patients with type 2 diabetes (Heart Protection Study Collaborative Group, 2002). In the Scandinavian Simvastatin Survival study (4S) simvastatin reduced cardiovascular mortality by 34% overall but 55% in the diabetic patients (Scandinavian Simvastatin Study Group, 1994). The Collaborative Atorvastatin Diabetes Study (CARDS) found that atorvastatin 10 mg daily in type 2 diabetics reduced acute coronary heart events by 36% (Colhoun et al, 2004).

Control of blood glucose

Tight control of blood glucose is essential to reduce the risk both of diabetic complications and CVD. According to the UKPDS (1998a) for every absolute 1% reduction in haemoglobin A1c the risk of myocardial infarctions reduces by 14% while the risk of heart failure reduces by 16%.

First-line antidiabetic treatment is metformin, which not only offers highly effective blood glucose control but is also known to have favourable effects on lipid levels and high sensitivity measurements of C-reactive protein. In the UKPDS trial (1998a) metformin was the most beneficial treatment for obese patients and was associated with substantial decreases in cardiac events and mortality in obese patients.

Metformin should be given initially at 500 mg daily after the evening meal and the dose increased gradually until normoglycaemia is achieved (maximum dose 1 g twice daily) or until the patient cannot tolerate the side effects. Metformin is contraindicated in patients with heart failure, alcohol dependence and renal impairment (creatinine >130 mmol/litre).

Unfortunately, many patients find metformin difficult to tolerate. In the UKPDS 20–30% of people stopped using the drug because of gastrointestinal or anorexic side effects (UKPDS, 1998b). For those who can tolerate the drug, monotherapy with metformin is not always sufficient to achieve satisfactory control of blood glucose and a second or even third agent may need to be added to the regimen.

The choice of second-line antidiabetic agent is currently controversial. According to advice from the National Institute for Clinical Excellence (2003), where monotherapy with metformin fails, a sulphonylurea should be added. If this dual therapy fails then a thiazolidinedione (TZD) should be substituted for the sulphonylurea.

However, the association of hyperinsulinaemia with vascular events has led to doubts over the wisdom of using insulin secretagogues such as the sulphonylureas. These doubts are further fuelled by questions over the effect that sulphonylureas may have on the myocardium under conditions of relative ischaemia. Some sulphonylureas have been shown to block energy-sensitive potassium channels in the myocardium and coronary arteries. Under acute ischaemia this effect could worsen the impact of the cardiac event (Matz, 1998).

Many diabetologists have therefore begun looking to the TZDs pioglitazone and rosiglitazone as their second-line antidiabetic agent of choice. In addition to their benefits on hyperglycaemia, TZDs offer the additional benefits on patients' lipid and triglyceride profiles. These potential benefits include a decreased plasma insulin level, decreased triglyceride concentration, increased HDL cholesterol levels, decreased lipid oxidation and improved endothelial and vascular function.

In one retrospective study of patients with type 2 diabetes, triglyceride levels decreased by 23% in patients who received pioglitazone and by 6% in those who received rosiglitazone (Boyle et al, 2002). HDL cholesterol levels increased by 6% in the pioglitazone group although they decreased by 0.26% in the rosiglitazone group.

Pioglitazone may offer greater benefit to the lipid profile than rosiglitazone – a study at the American Heart Association 2004 conference demonstrated significant improvements in triglycerides, HDL cholesterol, non-HDL cholesterol, and LDL particle size and concentration for patients taking pioglitazone *vs* those taking rosiglitazone (Goldberg et al, 2004).

Ongoing trials such as the PROactive (pioglitazone) which is due to report at the European Association for the Study of Diabetes (EASD) in Athens in 2005, ACCORD (rosiglitazone) and RECORD (rosiglitazone) should help determine whether these biochemical differences translate into significant clinical benefit.

The use of insulin in patients with type 2 diabetes should be reserved for those in whom oral therapy fails to establish glycaemic control. Insulin may be combined with oral treatment to improve control.

Acarbose may also occasionally be considered as an alternative in people unable to use other oral drugs although problems with flatulence make this an unpopular choice.

Control of blood pressure

Hypertension (blood pressure over 140/90 mmHg) is twice as common in people with diabetes than in people without. Moreover, controlling blood pressure is particularly important in diabetic patients.

The combination of hypertension and diabetes doubles the risk of developing microvascular and macrovascular complications, and doubles the risk of mortality when compared to non-diabetic people with hypertension. Fortunately even small reductions in the blood pressure of diabetic patients can yield significant cardiovascular benefits.

For instance, in the Hypertension Optimal Treatment (HOT) study (Hansson et al, 1998), non-diabetic patients whose diastolic blood pressure was controlled to 80, 85, or 90 mmHg had similar rates of cardiovascular

events. For diabetic patients, however, the level of antihypertensive control had a much greater cardiovascular impact. Those whose diastolic blood pressure was reduced to 80 mmHg showed a 51% reduction in cardiovascular events, including myocardial infarction and cardiovascular death, compared with those whose blood pressure was reduced to 90 mmHg. Patients with a treatment goal of 80 mmHg also did significantly better than patients with a goal of 85 mmHg.

The benefits of aggressive antihypertensive management in diabetes were confirmed in the UKPDS, (1998a), where tight blood pressure control reduced the relative risk of diabetes-related deaths by 32%, stroke by 44% and heart failure by 56%.

The British hypertension guidelines state that patients with diabetes should be considered for drug treatment if their systolic blood pressure is sustained above 140 mmHg and/or their diastolic blood pressure is sustained above 90 mmHg (Williams et al, 2004). The treatment goals are systolic blood pressure below 130 mmHg and diastolic blood pressure below 80 mmHg (Williams et al, 2004). Reducing blood pressure to 125/75 mmHg may produce additional benefit in patients with chronic renal disease of any aetiology associated with proteinuria of ≥1 g per 24 hours (Williams et al, 2004).

Angiotensin-converting enzyme (ACE) inhibitors are most commonly recommended as first-line therapy for people with diabetes and hypertension. However, the Antihypertension and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002), which included over 12 000 people with hypertension and type II diabetes, found that the thiazide-like diuretic chlortalidone was superior to ACE inhibitor lisinopril for several cardiovascular disease outcomes.

Almost all patients with hypertension and diabetes will require a combination of blood pressure-lowering drugs to achieve the recommended treatment targets. According to the British Hypertension Society this combination is likely to include a thiazide/thiazide-like diuretic and an ACE inhibitor or angiotensin receptor blocker. Longer-acting calcium channel blockers, beta-blockers and alpha-blockers are also considered suitable therapies.

KEY POINTS

- Rising rate of diabetes is likely to result in increasing prevalence of cardiovascular disease.
- Risk factors for cardiovascular disease in type 2 diabetes should not be treated in isolation but in the context of a multisystem metabolic syndrome.
- Total risk factor management of type 2 diabetes should include lifestyle.modification and aggressive treatment of hyperlipidaemia, hypertension, thrombosis risk and renal disease.

Control of thrombosis risk

Diabetes is associated with a number of prothrombotic changes that increase the risk of cardiovascular events. The use of low-dose aspirin (75 mg/day) is recommended for all people needing secondary prevention of ischaemic CVD, and for primary prevention in people with hypertension over the age of 50 years who have a 10-year CVD risk ≥ 20% (Williams et al, 2004).

Control of renal disease

Elevated urinary albumin excretion (even below the threshold currently used to define microalbuminuria) is now recognized as a predictor of cardiovascular morbidity and mortality. There is now good evidence that angiotensin II receptor antagonist-based antihypertensive therapy can delay the progression of microalbuminuria, a benefit that is complementary to those achieved by improved blood pressure control (Williams et al, 2004).

Conclusions

With an ageing population and obesity levels that have trebled in the past 20 years the UK is facing a likely pandemic of type 2 diabetes. This, in turn, could lead to a dramatic escalation in macrovascular complications such as coronary heart disease and stroke. Preventing this chain of events will require physicians to view type 2 diabetes as part of a multisystem vascular syndrome in which each metabolic abnormality should be aggressively treated. BJHM

Conflict of interest: Professor Betteridge has received honoraria for lectures and sat on advisory boards for all the major companies involved with lipid-lowering drugs.

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