

## Type 2 diabetes: important aspects of care

In Wales, around 3.5% of people suffer from diabetes and many remain undiagnosed.<sup>1</sup> The incidence of diabetes is increasing in all age groups<sup>2</sup> and it has been predicted that the number of people with diabetes in the UK may reach three million by 2010.<sup>3</sup> Most adverse outcomes associated with diabetes are the result of vascular (microvascular and macrovascular) complications. Long-term microvascular complications include visual impairment (diabetic retinopathy), progressive renal failure (diabetic nephropathy) and nerve damage (diabetic neuropathy). Macrovascular complications include coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease (PVD). The risk of stroke is up to three times higher in people with diabetes, compared with people without the disease, and the mortality rate from CHD is up to five times higher.<sup>1</sup> In addition to the personal costs, it has been estimated that diabetes and its complications accounts for around 9% of acute sector NHS costs.<sup>1</sup> The presence of diabetic complications in a patient increases NHS costs more than five-fold.<sup>1</sup>

This bulletin discusses the evidence regarding several important aspects of care for patients with type 2 diabetes:

- ◆ Control of blood pressure (BP).
- ◆ Use of metformin.
- ◆ Self-monitoring of blood glucose (SMBG).

### Control of blood pressure

Up to 70% of adults with type 2 diabetes have raised blood pressure (BP), which is a risk factor for both macrovascular and microvascular complications.<sup>2</sup> Cardiovascular disease (CVD) is the major cause of morbidity and mortality in people with diabetes and many people with type 2 diabetes are at increased risk of a coronary event even if they do not have manifest CVD.<sup>4</sup>

### Summary

- ◆ Although the management of blood glucose is important, it should not be considered in isolation. The management of diabetes is multifactorial and should include smoking cessation, weight control, exercise and the control of cardiovascular disease (CVD) risk factors, such as blood lipids and blood pressure (BP).
- ◆ Tight control of BP is at least as important as, if not more important than, intensive control of blood glucose in type 2 diabetes.
- ◆ Studies of hypertension in patients with type 2 diabetes show that tight BP control reduces the risk of cardiovascular events and death.
- ◆ There is evidence to show that use of the metformin reduces the macrovascular complications of diabetes.
- ◆ The effect on outcomes seen with metformin would not appear to be explained in terms of glycaemic control alone.
- ◆ Self-monitoring of blood glucose (SMBG) should not be a stand-alone intervention.
- ◆ SMBG can be useful when it serves an identified purpose in a patient's self-management programme. Impact is maximized in patients who receive appropriate education.

The United Kingdom Prospective Diabetes Study (UKPDS) has shown that tight control of BP is at least as important as, if not more important than, intensive control of blood glucose in type 2 diabetes.<sup>5,6</sup>

*Studies of hypertension in patients with type 2 diabetes show a clear and consistent effect; tight BP control reduces the risk of cardiovascular events and death.*

As part of the UKPDS, 1148 patients with type 2 diabetes who were also hypertensive were enrolled. Patients were randomised to tight control of their BP (target BP <150/85 mmHg) or less tight control (target BP <180/105 mmHg) and were followed up for a median of 8.4 years.<sup>5</sup>

Tight BP control (mean BP 144/82 mmHg) reduced macrovascular and microvascular disease compared to less tight control (mean BP 154/87 mmHg). The incidences of any clinical end-point related to diabetes, of deaths related to diabetes, and of stroke were significantly reduced in the tight control group. Six patients needed to be treated with tight BP control over 10 years to prevent one patient developing any diabetes-related complication (NNT 6). To prevent one death from a cause related to diabetes the NNT was 15, and to prevent one stroke the NNT was 20. Reductions in myocardial infarction (MI), PVD, and all-cause mortality were not statistically significant. There was a significant reduction in the incidence of microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure; NNT 14). However, most of this benefit was from the reduction in retinopathy requiring photocoagulation.<sup>5</sup>

In the Hypertension Optimal Treatment (HOT) study, 18 790 hypertensive patients were randomly assigned to one of three BP target groups (diastolic BP of  $\leq 90$  mmHg,  $\leq 85$  mmHg or  $\leq 80$  mmHg).<sup>7</sup> There was no difference in cardiovascular morbidity and mortality between the three groups; however, active lowering of BP was beneficial in a subgroup of 1501 patients with diabetes. Major cardiovascular events were significantly reduced from 24.4 per 1000 patient-years in the  $\leq 90$  mmHg group to 11.9 events per 1000 patient-years in the  $\leq 80$  mmHg group (NNT 8 over 10 years). Cardiovascular mortality was also significantly reduced from 11.1 to 3.7 events per 1000 patient-years, (NNT 14).<sup>7</sup>

### *What is the target BP in diabetes?*

- ♦ The National Institute for Health and Clinical Excellence (NICE) recommends a target BP of  $\leq 140/80$  mmHg, or  $\leq 135/75$  mmHg in patients with concomitant microalbuminuria or proteinuria.<sup>4</sup> Drug treatment is recommended in patients with BP  $>160/100$  mmHg. Drug treatment is not recommended initially in patients with BP between 140/80 mmHg and 160/100 mmHg, unless they have, or are at high risk of, CVD.<sup>4</sup>
- ♦ The British Hypertension Society recommends a lower target of  $\leq 130/80$  mmHg for all patients with diabetes.<sup>8</sup>

Observational analysis of UKPDS data found that, for any of the macrovascular or microvascular complications studied, there was no threshold systolic BP below which risk no longer decreased, nor was there a level above which risk no longer increased. This suggests that the nearer to normal the systolic BP, the lower the risk of complications, and that any reduction of raised BP is likely to be of benefit.<sup>9</sup>

### *What treatments are recommended?*

In the UKPDS, the initial BP-lowering treatment used in the tight control group was atenolol or captopril. The benefits of this hypertensive treatment in diabetic patients might be related to effects on the kidney. However, many patients required additional agents to adequately reduce their BP – 29% of patients in the tight control group required three or more antihypertensives.<sup>5</sup>

NICE guidance suggests that ACE inhibitors, angiotensin II receptor antagonists, beta-blockers or thiazide diuretics can be used as first-line treatments in the management of hypertension in patients with type 2 diabetes. ACE inhibitors should be used first-line if patients have concomitant microalbuminuria or proteinuria.<sup>4</sup>

Lowering BP is a key component of diabetes management, which should be multifactorial and should include smoking cessation, weight control, exercise, management of other cardiovascular risk factors such as blood lipids (see WeMeReC Bulletin May 2005), and the control of blood glucose. People with type 2 diabetes may not be aware of the association between diabetes, raised BP, and the increased risk of developing vascular complications. Unlike blood glucose control, the control of BP is considered by some patients to be beyond personal control; education of patients is important.<sup>10</sup>

## Control of blood glucose

Epidemiological studies of the general population have shown that high blood glucose concentrations are associated with an increased risk of CVD.<sup>11,12</sup> Similarly, a UKPDS prospective, observational study of 4585 patients with type 2 diabetes found that the risk of both macrovascular and microvascular complications was strongly associated with hyperglycaemia (as measured by mean haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) concentrations).<sup>13</sup> However, this study has been criticised for its lack of methodological rigour.<sup>14,15</sup> These results are not supported by data from randomised analyses of UKPDS data. For example, in the UKPDS study of intensive blood glucose control with sulphonylureas or insulin compared with conventional dietary treatment, intensive glucose control (maintaining a median 7.0% HbA<sub>1c</sub> over the first 10 years after diagnosis of diabetes) substantially reduced the frequency of microvascular endpoints but not diabetes-related mortality, MI, or stroke.<sup>6</sup>

Although the management of blood glucose is important, it should not be considered in isolation. It should be a part of the multifactorial management of diabetes, which also includes the control of CVD risk factors such as high BP and blood cholesterol concentrations.

## Use of metformin

Metformin improves insulin sensitivity and suppresses hepatic glucose output. It is associated with fewer hypoglycaemic attacks and less weight gain than sulphonylureas.<sup>16</sup>

*Metformin has been shown to reduce the macrovascular complications of diabetes.*

The UKPDS study showed that treatment with metformin improved outcomes in overweight people with type 2 diabetes. Intensive treatment with metformin, aiming for fasting plasma glucose <6 mmol/l (n=342), was compared with treatment with diet alone (n=411) for a median follow-up of 10.7 years. The study showed significant reductions in the risk of any diabetes-related endpoint (29.8 vs 43.3 per 1000 patient-years), diabetes-related death (7.5 vs 12.7 per 1000 patient-years, all-cause mortality (13.5 vs 20.6 per 1000 patient-years) and MI (11 vs 18 per 1000 patient-years).<sup>16</sup>

A secondary analysis showed that, compared with chlorpropamide and glibenclamide or insulin, metformin had a greater effect on any diabetes-related endpoint, all-cause mortality, and stroke, although the effect on stroke was not significant in any of the groups compared to conventional treatment comprising dietary advice.<sup>16</sup>

The HbA<sub>1c</sub> levels in both the metformin and the sulphonylurea or insulin groups were similar. Therefore, the effect on outcomes seen with metformin would not appear to be explained in terms of glycaemic control alone.

NICE guidelines on the management of blood glucose in type 2 diabetes recommend that metformin should be used as the first-line glucose-lowering therapy in people who are overweight (body mass index >25.0 kg/m<sup>2</sup>) and in whom blood glucose is inadequately controlled using lifestyle changes alone. For people who are not overweight, metformin should be considered as an option for first-line or combination therapy.<sup>17</sup>

Metformin is contraindicated in patients with renal impairment (serum creatinine >130 µmol/l) and those who are at risk of sudden deterioration of renal function.<sup>17</sup> This is because of a risk of lactic acidosis, which has been estimated from postmarketing surveillance data to occur in approximately 5 cases per 100 000.<sup>18</sup> However, a Cochrane systematic review, which pooled data from 176 comparative trials and cohort studies, found no cases of lactic acidosis in 35 619 patient-years of metformin use (or in 30 002 patient-years of not taking metformin).<sup>19</sup> It has been suggested that the contraindications for metformin should be revised so that the benefits of metformin can be made available to as wide a group of appropriate patients as possible.<sup>20</sup>

## Self-monitoring of blood glucose

Intensive glycaemic control is associated with a lower risk of microvascular complications,<sup>6</sup> and SMBG is considered by some to be an important component of diabetes care.

It is generally accepted that people with diabetes (type 1 or type 2) treated with insulin should monitor their blood glucose regularly to guide insulin dosing and avoid hypoglycaemia. However, there has been some controversy about whether SMBG is worthwhile for people with type 2 diabetes receiving oral treatment.

Approximately £8.5 million was spent on blood glucose testing strips for people with diabetes in Wales in 2004. This is estimated to be 6% more than the amount spent on oral hypoglycaemic agents.<sup>21</sup> Understandably, healthcare providers are looking for reassurance that this is appropriate.

Several benefits of SMBG have been suggested: that it allows patients to see the immediate impact of particular behaviours, such as dietary habits, on their

blood glucose levels and that it supports psychological well-being by increasing patients' feelings of control over their disease.<sup>22</sup> However, the evidence for the effect of SMBG on blood glucose control is not clear. Most studies have assessed HbA<sub>1c</sub> as the sole outcome when evaluating SMBG, and the effects on patient outcomes such as the occurrence of hypoglycaemia and quality of life are not well documented.

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## SMBG - the evidence

An NHS Health Technology Assessment (HTA) of blood glucose monitoring reviewed six randomised controlled trials that included comparisons of blood testing, urine testing and no testing in subjects with type 2 diabetes.<sup>23</sup> Meta-analysis of data from four of these studies showed no difference in glycosylated haemoglobin between groups of patients performing blood or urine self-monitoring and those that were not. Meta-analysis of data from three studies also showed no difference in glycosylated haemoglobin for patients performing SMBG compared with those performing urine testing. The authors concluded that, overall, SMBG may not be essential for all patients. However, they point out that the studies included in the meta-analysis had many limitations and low statistical power.<sup>23</sup>

Several studies of SMBG have been published since the HTA. A recent open randomised trial, conducted over six months, included 689 patients with type 2 diabetes who were poorly-controlled on oral anti-diabetic treatment.<sup>24</sup> The participants were randomised to two groups: one group underwent measurement of HbA<sub>1c</sub> only, and the other underwent SMBG in addition to measurement of HbA<sub>1c</sub>. The difference in HbA<sub>1c</sub> reduction between the two groups was slight but statistically significant; there was a mean reduction of 0.88% in the SMBG group vs 0.6% in the conventional assessment group. After six months, an improvement in HbA<sub>1c</sub> was shown in 57.1% of patients in the SMBG group vs 46.8% in the conventional assessment group. No serious episodes of hypoglycaemia were reported but there was an increased number of episodes of hypoglycaemia (symptomatic or asymptomatic) in the SMBG group compared to the conventional assessment group (10.4% vs 5.2%, respectively).<sup>24</sup>

A smaller randomised trial including 250 patients, investigated the effect of meal-related SMBG (before and one hour after main meals on two days per week) on glycaemic control and well-being in non-insulin-treated type 2 diabetic patients.<sup>25</sup> The control group received non-standardised counselling on diet and lifestyle. The trial ran for six months, with six months of follow-up. A greater reduction in HbA<sub>1c</sub> was observed in the SMBG group compared to the control group (mean reduction 1% vs 0.54% respectively). SMBG also improved some measures for depression and well-being. However, an eating diary and a structured counselling programme were provided only to the monitoring group and, therefore it cannot be inferred that the SMBG was solely responsible for the improvement in glycaemia control in this group.<sup>25</sup>

A large cross-sectional study of 3567 patients found that, in non-insulin treated patients with type 2 diabetes, SMBG did not improve metabolic control and was reported by patients to be associated with higher levels of frustration, worries and depression.<sup>26</sup> The authors suggest that the correlation with poorer psychological well-being could be related to patients feeling powerless when they are unable to improve unsatisfactory results.<sup>26</sup> Although the authors acknowledge that the study may be subject to confounding factors, they conclude that their data does not support the use of SMBG in patients with type 2 diabetes who are not treated with insulin. They suggest that SMBG is more appropriate for patients with type 2 diabetes who use insulin and are able to use the information from SMBG to adjust their insulin doses for daily glycaemic control.<sup>26</sup>

In view of the lack of clear evidence of the effect of SMBG on glycaemic control in people with type 2 diabetes who are not using insulin, a multidisciplinary group of healthcare professionals have produced advice on SMBG.<sup>27</sup> They suggest that not all people with type 2 diabetes require SMBG, but that there are certain situations where monitoring would be prudent, for instance, in people taking sulphonylureas (due to the increased risk of hypoglycaemia with these agents), during periods of illness, following changes in therapy, and where regular HbA<sub>1c</sub> testing is not available.<sup>27</sup>

*“Self-monitoring of blood glucose should not be a stand-alone intervention and should be used, with appropriate education, as part of integrated self-care.”<sup>17</sup>*

SMBG is useful when it serves an identified purpose in the patient’s self-management programme. To maximise the positive effects of SMBG, patients need to understand the role of monitoring and how to interpret and respond to readings.<sup>28</sup>

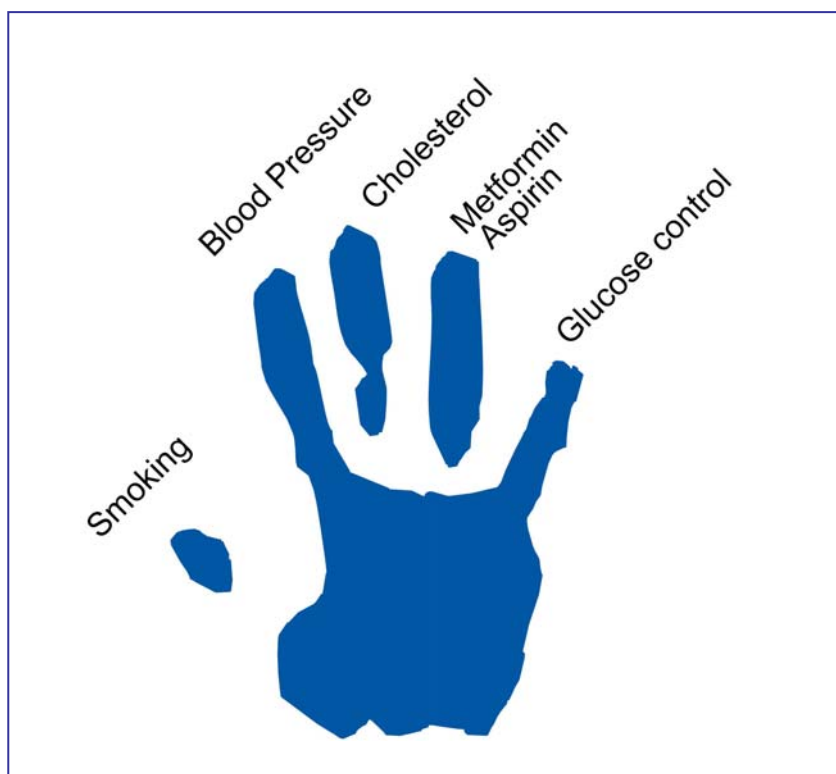


Fig. 1 A teaching aid for patients and students, illustrating where to obtain the most value for treatment effort with type 2 diabetes (working from left to right).

Adapted from Shaughnessy and Slawson. Lending a hand to diabetes. A pocket full of possibilities: “Just-in-Time” information at the point of care. Information Mastery Conference, Cardiff 2005.

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