Meeting the challenges of glycaemic control in type 2 diabetes

A report from a symposium sponsored by GlaxoSmithKline held at the Inaugural National Conference of the Primary Care Diabetes Society 12 November 2005, Wishaw, Warwickshire

Targets in type 2 diabetes: Are they tight enough?

'Targets have a role in the management of chronic diseases, particularly type 2 diabetes,' stated Dr Mark Savage (Consultant Physician in Diabetes & Endocrinology at North Manchester General Hospital) during a symposium titled *Meeting the challenges of glycaemic control in type 2 diabetes*, which was held at the Inaugural National Conference of the Primary Care Diabetes Society. The evidence-based targets that exist for type 2 diabetes cover glycaemic control, blood pressure and lipid levels, as was mentioned by Dr Martin Hadley-Brown (GP in Thetford, Norfolk), the symposium's chair, in his introduction. Current targets, as well as standards set out in the new General Medical Services (nGMS) contract, are shown in *Table 1*. Dr Savage focused on targets for glycaemic control.

Targets for glycaemic control

The UK Prospective Diabetes Study (UKPDS) showed that tight glycaemic control was linked to significantly reduced risk in a range of end points. In an epidemiological extrapolation (Stratton et al, 2000) of results from the UKPDS, explained Dr Savage, a 1% reduction in HbA_{1c} was associated with a risk reduction of 21% for any diabetes-related end point, a risk reduction of 37% for microvascular end points and a risk reduction of 43% for peripheral vascular disease. Despite these benefits, though, the National Diabetes Audit for 2003–2004 found that only 23% of people in England with diabetes achieved HbA_{1c} <6.5% (Health and Social Care Information Centre, 2005).

In the management of diabetes, lifestyle interventions are known to be of universal benefit (through their insulin-sensitising properties), but data from the UKPDS revealed that almost all people with type 2 diabetes will eventually need pharmacotherapy to achieve good glycaemic control (Turner et al, 1999). However, people on monotherapy, said Dr Savage, 'are not achieving targets.' In a study highlighted by Dr Savage (Sattar et al, 2005), 59.3% of 7563 people with type 2 diabetes across 126 general practices in Scotland who were on monotherapy did not have HbA_{1c} <7.0%. Moreover, Turner et al (1999) found that the majority of people on monotherapy in the UKPDS did not have HbA_{1c} <7.0% after 9 years; combination therapy is thus needed for

Below: Dr Mark Savage

Table 1. Targets and standards in type 2 diabetes.

	Targets[1–4]	nGMS standards[5]
HbA_{1c}	<6.5%	≤7.4%
Fasting plasma glucose	≤6.0 mmol/l	-
Blood pressure	<130/80 mmHg	<145/85 mmHg
Triglycerides	<2.3 mmol/l	-
Total cholesterol	<4.0 mmol/l	≤5.0 mmol/l
LDL-cholesterol	<2.5 mmol/l	-
HDL-cholesterol	>1.0 mmol/l	-

1. International Diabetes Federation (IDF; 2005) Global Guideline for Type 2 diabetes. *IDF, Brussels*
2. Department of Health (2002) National Service Framework for Diabetes: Standards. Supplementary Information. Clinical care of adults with diabetes. *DoH, London.*
3. Diabetes UK (2000) Recommendations for the management of diabetes in primary care. 2nd ed. *Diabetes UK, London.*
4. Williams B et al (2004) Journal of Human Hypertension ***18****: 139–85*
5. British Medical Association (BMA; 2003). Investing in General Practice. The new General Medical Services Contract. *BMA, London*

glycaemic targets to be achieved in the long term, noted Dr Savage.

Another finding to come out of the UKPDS was that when glucose levels are above normal, any reduction in HbA_{1c} is of benefit in reducing microvascular complications (UKPDS Group, 1998), said Dr Savage. But what happens when glucose levels are in the currently defined 'normal' range? Or, to put it another way, is there a reason for further improvements in glycaemic control, beyond that recommended by current evidence-based targets? The European Prospective Investigation into Cancer and Nutrition (EPIC) is one study to explore complications of diabetes in people with normal glycaemic control.

'Regular review is essential if people with [type 2 diabetes] are to achieve HbA_{1c} targets and receive the best possible treatment.'

Table 2. The EPIC study: HbA_{1c} concentration predicts mortality continuously across the whole population.

Cause of death	HbA_{1c} (%)				χ^2 (linear trend), *P* value
	<5	5–5.4	5.5–6.9	≥7	
All causes					
Age-adjusted ratio/100	1.65	2.33	3.43	4.35	40.8, <0.001
Relative risk	1.00	1.41	2.07	2.64	
Cardiovascular disease					
Age-adjusted rate/100	0.50	1.27	1.24	2.54	31.8, <0.001
Relative risk	1.00	2.53	2.46	5.04	

In the investigation's Norfolk cohort, 4662 men aged between 45 and 79 years were followed up for mortality from all causes and mortality from cardiovascular disease (Khaw et al, 2001; see *Table 2*). Baseline HbA_{1c} level was related to subsequent mortality from all causes and cardiovascular disease across the whole population, with the lowest rates seen in people with HbA_{1c} <5.0%. Furthermore, the increased risk of mortality associated with diabetes seemed to be mostly attributable to HbA_{1c} levels, Dr Savage explained.

In brief, then, the UKPDS has shown that tight glycaemic control can reduce the burden of type 2 diabetes; many people with the condition, however, are not achieving evidence-based glycaemic targets. Lifestyle intervention and monotherapy have both been shown to be inadequate as ways of getting people with type 2 diabetes to targets in the long term. Interestingly, results from the EPIC Norfolk cohort suggest that there are benefits of improvements in glycaemic control beyond current targets.

Can we do better?

In caring for people with type 2 diabetes, 'are we going to go for a goal-led approach or a failure-led [reactive] approach?' asked Dr Savage. Campbell (2000) encouraged healthcare professionals to adopt the goal-led approach. More specifically, Dr Savage noted, this goal-led strategy could incorporate early, intensive combination therapy to 'treat to target' and therefore avoid the microvascular complications arising from poor glycaemic control. In addition, Sattar et al (2005) used their findings on glycaemic control to conclude that 'an aggressive, target-based approach […] should be given strong consideration.'

The use of early, intensive interventions to achieve glycaemic targets is one part of the optimal management strategy for type 2 diabetes described by Dr Savage. Another major part is the continual assessment of insulin resistance.

Finally, Dr Savage pointed out, traditional approaches to the frequency of review have not offered good glycaemic control in the long term to the majority of people with type 2 diabetes. It is thus important to note that regular review

is essential if people with the condition are to achieve HbA_{1c} targets and receive the best possible treatment.

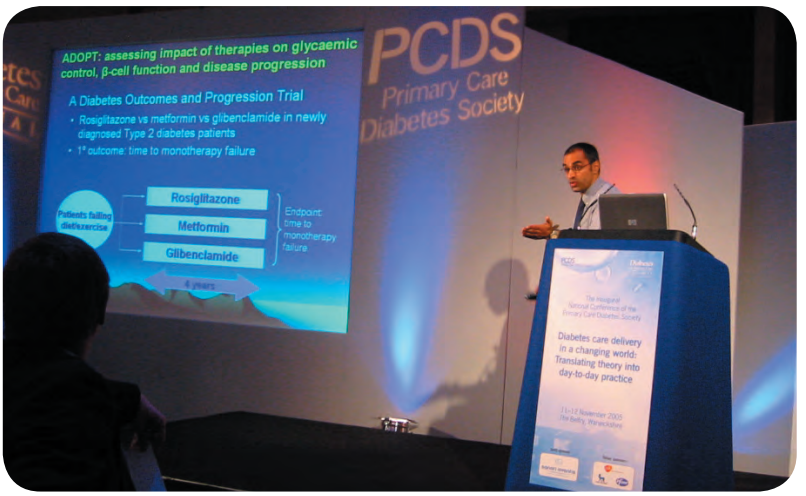
The natural history of beta-cell dysfunction: Is there potential for change?

'Insulin resistance is the root cause of type 2 diabetes,' said Prof Naveed Sattar (Professor of Metabolic Medicine at the University of Glasgow), as he outlined the natural history of type 2 diabetes. This progressive condition is characterised by a period of insulin resistance, which is initially compensated for by the increased secretion of insulin from pancreatic beta-cells. Eventually, due to beta-cell dysfunction, the pancreas can no longer produce the required amount of insulin to maintain normoglycaemia. Hyperglycaemia results, explained Prof Sattar, and is accompanied by an increased risk of micro- and macrovascular complications associated with type 2 diabetes. 'Obesity – specifically visceral obesity – is the type 2 diabetes risk factor *par excellence*,' he said.

Visceral obesity and insulin resistance

It is now known that insulin resistance is closely linked to visceral obesity, which presents clinically as increased waist circumference, explained Prof Sattar. He alluded to the results of Banerji et al (1997), who demonstrated an inverse non-linear relationship between glucose disposal and visceral adipose tissue volume in a study of people with type 2 diabetes. In contrast, said Prof Sattar, the group also found that glucose disposal was not significantly associated with total subcutaneous fat volume – therefore highlighting the importance of visceral obesity, which, in a study of Japanese-American men (Fujimoto et al, 1999), was also shown to be an independent predictor of coronary heart disease.

Fat accumulation in the abdominal region causes an increase in the concentration of free fatty acids (FFAs) in the circulation, explained Prof Sattar. This leads to hyperglycaemia, since FFAs stimulate gluconeogenesis in the liver and inhibit the uptake of glucose by muscle. Increased amounts of FFAs, through their accumulation in muscle and liver tissue, also lead to increased triglyceride levels. Thus, said Prof Sattar, insulin resistance and visceral obesity present two challenges to pancreatic beta-cells: 'glucotoxicity' (hyperglycaemia) and 'lipotoxicity' (increased concentrations of FFAs and triglycerides).



Above: Prof Naveed Sattar

Pancreatic beta-cells: A dual challenge

The lipo- and glucotoxicity presented by visceral obesity is detrimental to beta-cell function in two ways, said Prof Sattar, explaining that the two challenges contribute to both beta-cell dysfunction and beta-cell apoptosis (see *Figure 1*). For example, he said, Dubois et al (2004) found that the stimulatory response of cultured pancreatic islet cells was reduced in the face of increasing concentrations of glucose or non-esterified fatty acids. Furthermore, hyperglycaemia results in the production of reactive oxygen species that directly damage the cellular processes of beta-cell function, leading ultimately to apoptosis via increased production of interleukin-1beta (Stumvoll et al, 2005; Zeender et al, 2004).

How might this dual toxicity be managed in people with diabetes? 'If we could reduce FFA and glucose levels,' said Prof Sattar, 'we could also reduce the toxic burden on the pancreas.'

He explained that treatment with a glitazone (rosiglitazone or pioglitazone; synthetic agonists of peroxisome proliferator-activated receptor gamma [PPARγ]) can be of benefit in several ways. Firstly, he said, glitazones have been shown to enhance insulin sensitivity in muscle, adipose and, to a lesser extent, liver tissue, thereby indirectly reducing glucotoxicity. In addition, he said, they also have a protective

The progressive nature of beta-cell decline

Prof Sattar alluded to an analysis from the UKPDS (UKPDS Group, 1995) which showed that, in people randomised to the diet-treated arm of the study (n=376), beta-cell function was already lower than 50% at the time of type 2 diabetes diagnosis. Over the next 6 years, beta-cell function declined further ($P<0.0001$).

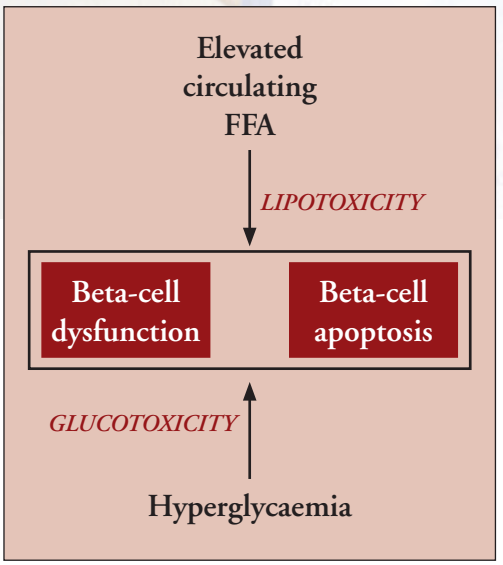


Figure 1. The dual challenges of glucotoxixity and lipotoxicity cause beta-cell dysfunction and apoptosis.

effect on beta-cell function. For example, rosiglitazone has been shown to reduce both blood glucose and FFA concentrations (Charbonnel et al, 1999), thereby indirectly helping to address both the lipo- and glucotoxicity associated with beta-cell dysfunction.

Glitazones may also have direct effects, mediated through PPARγ, which help to preserve beta-cell function, said Prof Sattar, listing increased beta-cell proliferation, increased beta-cell mass, reduced beta-cell apoptosis, increased insulin secretion and reduced proinsulin secretion as examples (Walter and Lubben, 2005).

Evaluating the potential to delay progression to type 2 diabetes

So could addressing insulin resistance and beta-cell dysfunction early on in the disease process delay or prevent the development of type 2 diabetes? Prof Sattar pointed to a range of studies, some still in progress, designed to investigate exactly this question. He outlined the results of TRIPOD (TRoglitazone In the Prevention Of Diabetes), a study in which treatment with the now-discontinued thiazolidinedione troglitazone reduced the progression to type 2 diabetes by more than 50%, compared with placebo, in women with recent gestational diabetes (Buchanan et al, 2002). The investigators concluded that this effect was associated with the preservation of beta-cell function, and appeared to be mediated by the reduction in insulin secretion demand, explained Prof Sattar.

Finally, he explained that other studies, such as the ongoing ADOPT (A Diabetes Outcomes and Progression Trial) and DREAM (Diabetes REduction Approaches with ramipril and rosiglitazone Medication) trials 'should provide us with additional robust data on the use of pharmacotherapy in delaying or preventing the onset of type 2 diabetes.' ■

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