Update on type 2 diabetes

Type 2 diabetes is increasingly common and we need to offer our patients better outcomes.

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The number of people with type 2 diabetes continues to grow throughout the world, South Africa being no exception. As health care practitioners, we need to meet the challenge of assisting those individuals with diabetes who are in our care to achieve better outcomes, such as enhanced quality of life, and reductions in morbidity, largely due to microvascular complications, and premature mortality, primarily due to macrovascular disease.

This article focuses on recent developments in the management of type 2 diabetes; specifically, the legacy effect and macrovascular disease, glycaemic targets and macrovascular disease, glycaemic management (specifically focusing on initiation of insulin therapy and the group of agents shortly to be introduced in South Africa, the incretins and DPPIV inhibitors) and the role of self-monitoring of blood glucose (SMBG).

These results provided the evidence that underpinned a subsequent concerted drive to improve glycaemic and, indeed, blood pressure control in people with type 2 diabetes.

Legacy effect and macrovascular disease

Ten years ago, the UKPDS, a randomised trial of newly diagnosed people with type 2 diabetes allocated to either intensive (sulphonylurea-insulin group) or conventional (diet alone) glycaemic therapy, unequivocally demonstrated that improved glycaemic control (between-group median HBA_{1C} difference at the end of 10 years was 0.9%) reduced the progression or development of microvascular complications.[1] However, the effect was not extended to ischaemic heart disease, stroke or mortality in people in the sulphonylurea-insulin arm. Yet, when the same patients in the UKPDS with co-existent hypertension were randomised to tight or less tight regimens for blood pressure control, lower blood pressure (154/87 v. 144/82 mmHg) resulted in more global benefits, i.e. for both microvascular and macrovascular outcomes.[2] These results provided the evidence that underpinned a subsequent concerted drive to improve glycaemic and, indeed, blood pressure control in people with type 2 diabetes.

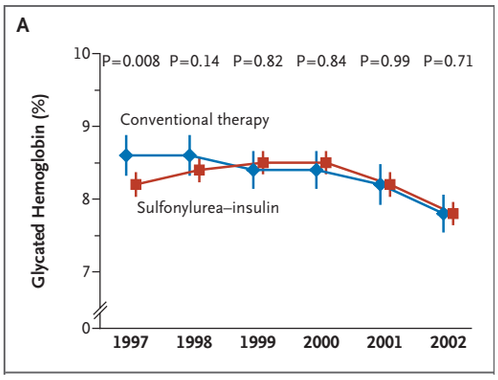

Fig. 1. Mean glycated haemoglobin (HBA_{1c}) levels for patients who were originally assigned to receive either sulfonylurea-insulin or conventional therapy at the end of the UKPDS in 1997 and completion of follow-up in 2002. (Copyright 2008 Massachusetts Medical Society. All rights reserved.)

Once the difference in blood pressure between groups disappeared, the early benefit of tight blood pressure control on micro- and macrovascular endpoints were lost.

Late last year the 10-year follow up of the UKPDS was published.[3] In this, 3 277 of the original 4 209 UKPDS participants were reviewed by questionnaire after 6 - 10 years of care provided in their community, during which time no effort was made to continue their prior randomised treatment. As seen in Fig. 1, the difference in HBA_{1C} between groups at the end of the UKPDS disappeared within 1 - 2 years, although there was an ongoing downward trend in levels in both groups. The notable findings of the follow-up study were that: in the group originally treated with sulphonylureas and/or insulin, significant risk reductions appeared over time for death from any cause (13%, p=0.007) and myocardial infarction (15%, p=0.01), while the risk reduction (24%) in microvascular outcomes persisted. The UKPDS included a sub-study in overweight participants who were initially randomised to diet or metformin therapy. In this, the originally described benefits on myocardial infarction and death from any cause in the metformin-treated group persisted at follow-up (33%, p=0.005, and 27%, p=0.002 respectively). In type 1 diabetics too, the appearance of a delayed benefit of earlier improved glycaemic control on macrovascular events has been reported from the extended follow-up of the landmark DCCT trial (a trial comparing intensive and conventional insulin therapy on microvascular and macrovascular endpoints which failed to impact on the latter despite a prominent reduction of the former).[4] Interestingly, the persistent

Table I. Legacy effect of earlier glucose control after median of 8.5 years post-trial follow-up

	End of UKPDS 1997		End of follow-up 2007	
Aggregate endpoint	**RRR**	***p***	**RRR**	***p***
Microvascular disease	25%	0.0099	24%	0.001
Myocardial infarction	16%	0.052	15%	0.014
All-cause mortality	6%	0.44	13%	0.007

RRR= relative risk reduction. Adapted from UKPDS 80. *N Engl J Med* 2008; 359.

and delayed beneficial impacts of intensive glycaemic control in the UKPDS were not replicated for blood pressure control. Once the difference in blood pressure between groups disappeared, the early benefit of tight blood pressure control on micro- and macrovascular endpoints were lost.[5]

We are uncertain as to the mechanism of the so-called 'legacy effect' of glucose control (Table I). Nevertheless, these findings do suggest the presence and importance of a metabolic memory and emphasise that early intensive management of glycaemia should become the norm in patients with type 2 diabetes. However, given the evidence emerging in the literature, an entirely glucocentric approach is not desirable, and a multi-pronged strategy which also includes aggressive blood pressure and lipid lowering is imperative, if we are to achieve the desired outcomes mentioned above.

Glycaemic targets and macrovascular disease

Three large trials published within the past 18 months have specifically addressed the question of whether intensive versus standard glycaemic control impacts on cardiovascular disease outcomes in people with established type 2 diabetes. The ACCORD, ADVANCE and the Veterans Affairs Diabetes Trial (VADT) included people with a mean duration of diabetes of 8 - 11 years. The ACCORD and ADVANCE trial participants also had either a previous cardiovascular (CVD) event or significant CVD risk while 40% of the VADT participants had experienced a previous cardiovascular event and 72% had hypertension.[6-8] The three trials failed to demonstrate a beneficial impact of lowering the mean HBA_{1c} to ~6.5% on a combined CVD endpoint over a median of 3.5 - 5 years.[4-6] Attempts to lower HbA_{1c} to 6.5 % in the ACCORD study increased mortality, although this was not replicated in the other two studies. On the other hand, patients with shorter duration of diabetes, lower baseline HBA_{1c} and without previous macrovascular disease experienced a reduction in the CVD endpoint.

Current guidelines are that the target for glycaemic control in people with type 2 diabetes is an HBA_{1c}<7% and that a level of ≥7% should be a call to action. However, glycaemic targets need to be individualised. In people with limited life expectancy, severe hypoglycaemic episodes, hypoglycaemic unawareness, severe co-morbidity and advanced complications of diabetes less stringent goals should be sought. [9,10]

Glycaemic treatment

Many agents are available to help the patient and clinician achieve glycaemic goals in the setting of type 2 diabetes and it is important to base prescribing habits on evidence. International and local societies advocate the initiation of treatment in newly diagnosed type 2 diabetic patients with lifestyle modification plus metformin.[10] This is contrary to previous algorithms that initiated treatment with lifestyle measures alone and is based on a number of factors. Lifestyle changes are superior to treatment with any drug in preventing or delaying progression to type 2 diabetes in the pre-diabetes phase. Once the person is diabetic, lifestyle changes alone are usually unsuccessful in achieving glycaemic targets, probably due to the difficulties experienced in introducing and maintaining these changes. Furthermore, data from the UKPDS have shown the many beneficial effects of metformin. There is no evidence for the use of insulin as monotherapy for the initial treatment of a patient with type 2 diabetes, but in patients who present with features of severe uncontrolled diabetes (catabolic, fasting glucose >13.9 mmol/l or HbA_{1c} >10%) treatment should be initiated with lifestyle modification and insulin, with the insulin therapy possibly being replaced by oral agents once the glucose levels are controlled.

The debate begins if the HbA_{1c} remains >7% in patients on first-line therapy with metformin and lifestyle modification. The algorithm allows for the addition of a sulphonylurea, thiazolidinedione or insulin. The addition of another oral agent at this stage is accepted practice. However, the introduction of insulin at this stage is more contentious. Both lipo- and glucotoxicity are proposed to induce β-cell failure while the natural history of type 2 diabetes is that β-cell function gradually deteriorates. There is evidence for the use of insulin when added to oral agents, but the question is how and when to initiate the insulin.[11] In order to preserve β-cell function, early treatment with an agent that will control glycaemia is ideal. Studies have shown that insulin therapy, when used early in the treatment protocol, may preserve β-cell function and has led to increased insulin sensitivity, two of the major pathogenic factors in type 2 diabetes. Unfortunately, weight gain and more frequent hypoglycaemic episodes are two of the unwanted adverse effects associated with insulin therapy. Nevertheless, despite no solid evidence base for its early use, but recognising the importance of early glycaemic control, insulin is increasingly becoming part of the early treatment for patients with type 2 diabetes.

Complicating the issue further, is which insulin to use and what regimen to prescribe. The 4-T study was designed to answer this question – it compared the initiation of insulin as additive therapy with oral hypoglycaemic agents using a basal, biphasic or prandial regimen. The 1st-year results showed a significant decrease in HbA_{1c} using a biphasic or prandial regimen (7.2 - 7.3% v. 7.6%) but at the cost of an increased risk of hypoglycaemic episodes.[12] This led the authors to conclude that biphasic or prandial insulin exposed the patients to an unnecessary high risk of hypoglycaemia without clinically important benefit (only a 0.3% lowering of the HBA_{1c}).

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The algorithm does not, at this stage, suggest a role for the newer agents such as the incretins and DPPIV inhibitors.

Incretins

In the 1960s various research groups showed that the insulin secretory response to an oral glucose load was greater than to an intravenous glucose load, providing the first clinical proof that an oral glucose load could stimulate the release of insulin secretagogues from the gastrointestinal tract. This has been termed the 'incretin effect'. Glucose-dependent insulinotropic peptide (GIP) was the first and glucagon-like peptide 1 (GLP-1) the second, and final, incretin to be characterised. GIP and GLP-1 are released

from intestinal enteroendocrine cells in response to a glucose load and account for over 50% of insulin secreted in response to a meal. In addition, GLP-1 slows gastric emptying, inhibits glucagon release, induces the feeling of satiety, decreases β-cell apoptosis and stimulates β-cell proliferation. Both incretins have a short half-life as they are rapidly degraded by dipeptidyl peptidase 4 (DPPIV).

In patients with type 2 diabetes the incretin effect is diminished or absent – GIP being unable to stimulate insulin secretion (i.e. β-cell resistance) while GLP-1 maintains the ability to stimulate insulin secretion, but its levels are low. The search for a treatment for T2DM using GLP-1 has centered on finding a GLP-1 mimetic resistant to degradation by DPPIV or designing a drug that could inhibit DPPIV, thereby prolonging the incretin effect.[13,14]

Exenatide (synthetic version of exendin-4, a peptide isolated from the saliva of the Gila monster lizard found in the Arizona desert) is the first GLP-1 mimetic to be approved for adjunctive therapy in patients with type 2 diabetes. It is resistant to degradation by DPPIV, and requires subcutaneous injection twice daily. When added to regimens containing oral hypoglycaemics, exenatide has shown preferable effects for the treatment of type 2 diabetes when compared with placebo – 1.0% (95% CI, 0.8 - 1.2%) reduction in HbA_{1c}, 1.5 mmol/l decrease in fasting plasma glucose, 1.4 kg decrease in body weight and a 4.2 risk ratio for achieving a HbA_{1c} <7%. Although there are currently no long-term studies to evaluate the safety and efficacy of exenatide, an open-label extension of one of the above-mentioned studies in a highly selected subgroup of the main study showed a sustained reduction in HbA_{1c} of 1% and a significant weight reduction of 5.3 kg at 3 years. Studies comparing exenatide to insulin glargine or bi-daily insulin aspart did not reveal significant differences in lowering of HbA_{1c} or episodes of hypoglycaemia. Treatment with insulin resulted in a greater decrease in fasting plasma glucose, while treatment with exenatide resulted in lower postprandial glucose values. In addition, there was a significant weight reduction in the exenatide group whereas there was weight gain in the insulin group. The weight reduction in all studies was more significant in patients with a BMI >30 kg/m^2.

Mild to moderate nausea is the most common side-effect associated with exenatide. Hypoglycaemic episodes are uncommon. The development of anti-exenatide antibodies occurs in 41 - 67% of patients but is usually not of any clinical significance.

Liraglutide (long-acting GLP-1 agonist resistant to degradation by DPPIV) has a longer half-life than exenatide and can therefore be given once daily subcutaneously. Phase 2 studies are yielding results and adverse events tending to be similar to those with exenatide, but phase 3 clinical trial results are awaited.

DPPIV inhibitors

Sitagliptin is the first DPPIV inhibitor to be approved by the FDA for use as monotherapy or together with metformin or thiozolidinediones. Vildagliptin, another DPPIV inhibitor, has been approved for use in Europe. These agents can be taken orally, are weight neutral and relatively well tolerated, and lower HbA_{1c} by 0.6 - 0.9%. When used as monotherapy they do not cause hypoglycaemia.

Role in treating patients with type 2 diabetes

These agents will soon be available in South Africa but their place in the treatment of type 2 diabetes remains to be established. These newer agents are more expensive than sulphonylureas and metformin and are, at best, equivalent in glucose lowering. Their main advantage is weight neutrality or weight loss, particularly in obese patients. They may also have favourable effects on β-cell function, although this remains to be proven. In the USA and Europe, exenatide is indicated for the treatment of patients with type 2 diabetes who are unable to reach a target HbA_{1c} <7% with metformin or metformin plus a sulphonylurea.[10] The National Institute for Health and Clinical Excellence (NICE) has suggested that exenatide should not be used as routine treatment in type 2 diabetes. Rather, it should be reserved for patients with type 2 diabetes who have one of the following: a BMI >35; psychological, biochemical or physical problems arising from a high BMI; HbA_{1c} ≥7.5% on conventional oral hypoglycaemic agents; another high-cost medication such as a thiazolidinedione or insulin is going to be started. They also suggest that exenatide should only be continued if an HbA_{1c} reduction of 1% is seen at 6 months and if weight loss of at least 5% is seen at 1 year.

Self-monitoring of blood glucose

International guidelines recommend self-monitoring of blood glucose (SMBG) as an essential component of daily management to improve glycaemic control in people with type 1 diabetes and insulin-treated type 2 diabetes. In addition to permitting adjustment of insulin doses, SMBG is useful in uncovering specific patterns of hyperglycaemia, identifying and preventing hypoglycaemia and revealing the impact of different behaviours and actions on blood glucose levels. The recommended frequency of SMBG varies from three or more times a day for patients on basal bolus insulin regimens to once to twice daily for those on fewer daily doses.

The benefit of SMBG on glycaemic control in type 2 diabetics treated with oral agents and/or diet but not insulin, on the other hand, has been the subject of considerable debate for some years. The recent publication of two randomised clinical trials (RCTs) and a meta-analysis of 9 RCTs addressing this question provide robust evidence that the routine use of SMBG does NOT impact on glycaemic control in this group of patients.[15-17] The four trials in the meta-analysis that extended to at least 1 year yielded a pooled decrease in mean HBA_{1c} of -0.21% in patients using SMBG – a minimal decline does not have clinical importance. A brief description of the two recently reported trials may be helpful. The one trial (ESMON) was conducted in newly diagnosed patients with a mean HBA_{1c} ~8.7% who were randomised to SMBG or not. Both groups received identical education programmes and treatment algorithms. The SMBG group additionally received advice on appropriate responses to high and low readings. Although the trial was adequately powered, SMBG had no impact on glycaemic control after 12 months and was associated with reduced wellbeing. The DIGEM trial of non-insulin-treated type 2 diabetics, with a mean diabetes duration of 3 years and better glycaemic control than the ESMON trial (mean HBA_{1C} ~7.5%) also failed to demonstrate that either of two SMBG strategies, one incorporating appropriate advice for abnormal readings, had any significant impact on glycaemic control after 1 year and once again was associated with a decline in quality of life. Finally, SMBG has been found to be non-cost-effective in these patients.

At present SMBG does not have a place in the routine management of patients with type 2 diabetes who are on diet or oral glucose-lowering agents alone. When it is prescribed for patients on insulin, it is critical to ensure that they are given the opportunity to develop the skills not only to perform the tests accurately, but also to interpret the data and appropriately adjust medication, food intake and/or exercise in order to achieve the agreed-upon glycaemic targets. This should ensure that the commonly encountered situation of doctor and patient reviewing pages/records of multiple SMBG results outside target range without any action ensuing on the part of the patient would become part of history.

This brief update has focused on a few recent developments regarding type 2 diabetes. Importantly though, we need

to diagnose diabetes early such that the individual's exposure to the consequences of hyperglycaemia is reduced. The achievement and maintenance of individualised glycaemic targets which do not place the person at increased risk for hypoglycaemia, remains central to the care of people with diabetes. So too does maintaining blood pressure and lipid targets, screening for and appropriate management of the well-recognised complications of diabetes. Finally, people with diabetes should be equipped with all that is needed to actively self-manage their diabetes.

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In a nutshell

- The 10-year follow-up of the UKPDS showed that in the group originally treated with sulphonylureas and/or insulin, significant risk reductions appeared over time for death from any cause and myocardial infarction, while the risk reduction (24%) in microvascular outcomes persisted.
- The persistent and delayed beneficial impacts of intensive glycaemic control in the UKPDS were not replicated for blood pressure control.
- Once the difference in blood pressure between groups disappeared, the early benefit of tight blood pressure control on micro- and macrovascular endpoints was lost.
- Early intensive management of glycaemia should become the norm in patients with type 2 diabetes.
- An entirely glucocentric approach is not desirable, and a multi-pronged strategy which also includes aggressive blood pressure and lipid lowering is imperative.
- Current guidelines are that the target for glycaemic control in people with type 2 diabetes is an HBA_{1c}<7% and that a level of ≥7% should be a call to action.
- Glycaemic targets need to be individualised. In people with limited life expectancy, severe hypoglycaemic episodes, hypoglycaemic unawareness, severe co-morbidity and advanced complications of diabetes, less stringent goals should be sought.
- International and local societies advocate the initiation of treatment in newly diagnosed type 2 diabetic patients with lifestyle modification plus metformin.
- Lifestyle modification is superior to treatment with any drug in preventing or delaying progression to type 2 diabetes in the pre-diabetes phase. However, lifestyle modification alone is no longer regarded as sufficient treatment once a person is diabetic.
- Self-monitoring of blood glucose has no effect on outcomes in type 2 diabetics who are not treated with insulin.

Erratum

In the article by Mervyn Mer (*CME* Nov/Dec 2008; 26 (11): 540-544) his qualifications were printed incorrectly. The correct qualifications are: MB BCh, Dip Pec (SA), FCP (SA), MMed (Int Med), FRCP (Lond), FCCP.