Optimal glucose control in type 2 diabetes mellitus – a guide for the family practitioner

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Abstract

Type 2 diabetes contributes to significant risk of cardiovascular and micro-vascular complications. The family practitioner plays a significant role in the management of glycaemic control and thereby reducing the related morbidity and mortality. Monitoring of blood glucose control has become an integral part of disease management that can empower patients and physicians to optimal blood glucose management.
Numerous drugs are currently available to treat type 2 diabetic patients. The role of the currently available drugs is discussed as well as the use of insulin. A suggested protocol for the initiation and adjustment of treatment is provided.

SA Fam Pract 2006;48(10): 22-29

INTRODUCTION

The family practitioner plays a crucial role in the management of type 2 diabetes patients, not only in the prevention and early diagnosis of diabetes but also in the long-term follow-up and repeated adjustments necessary. The family practitioner is in the ideal position to maintain close patient contact, since he/she is the entry point for most patients into the health system, and have the most frequent patient contact. This also makes the family physician the ideal person to do patient education and monitoring of progress of glycaemic control as well as management of other cardiovascular risk factors which contribute to a significantly higher risk in diabetic patients.

All patients with type 2 diabetes should understand that the disease is progressive and that blood glucose treatment should frequently be reassessed and adjusted. A clear understanding of this fact is also important for the caring physician who might become disheartened if treatment seems only temporarily effective and glycaemic control frequently elusive. Both the patient and the physician should know and understand that all type 2 diabetic patients might deteriorate to a stage where insulin therapy is essential to control blood glucose. This fact also makes it essential that insulin injections should never, at any stage of diabetes management, be used to threaten patients to improve compliance.[1]

This article will focus on the following challenges/dilemmas of glucose control in family practice:

- The progressive nature of type 2 diabetes leading to deteriorating blood glucose control
- The value and limitations of glucose monitoring, and how to interpret measurements
- How to initiate/adjust therapy

GLYCAEMIC TARGETS FOR TYPE 2 DIABETES MELLITUS (DM)

Glucose control is essential in type 2 DM, as was clearly demonstrated in the United Kingdom Prospective Diabetes study (UKPDS), where improved glucose control decreased the frequency of microvascular complications (nephropathy and neuropathy).[2,3] The UKPDS showed that glucose control improved macrovascular outcomes although not statistically significant, but a recent meta-analysis of 10 prospective cohort studies showed that the relative risk is 1.18 for each 1 percent increase in the HbA1c.[4] In other words, for every 1 % increase in HbA1c the risk of cardiovascular disease increases by 18%). The American Diabetes Association (ADA) recommends the lowering of HbA1c to less than 7% in general and less than 6% (normal) in individual patients, provided that significant hypoglycaemic episodes can be avoided.[5] It makes sense that both the pre- and post-prandial blood glucose should be optimally controlled (< 8 mmol/L fasting, and < 10 post-prandial), since both fasting and prandial blood glucose contribute to the HbA1c. There is insufficient proof that optimal control of prandial blood glucose is associated with less micro- and macro-vascular complications.[6]

The South African national guidelines set optimal glycaemic control targets at 4 to 6 mmol/L fasting, and 5 to 8 mmol/L 2 hours post-prandial, as well as an HbA1c of less than 7%.[7] These targets are essentially the same as those of the Society for Endocrinology Metabolism and Diabetes of South Africa (SEMDSA).[8]

GLUCOSE HOME MONITORING IN PATIENTS WITH TYPE 2 DIABETES

Self-monitoring of blood glucose (SMBG) is an essential component of diabetes care. There are a variety of options regarding the optimal testing schedule for patients.
In a large US-based cohort study (24 312 patients with type 1 and type 2 diabetes), HbA1c was lower in patients who regularly did SMBG. For type 2 patients on oral treatment alone and on diet alone, the difference was 0.6 and 0.4% respectively.[9] The most recent systematic review concluded that SMBG was associated with an improvement of HbA1c of 0.39%. Some of the trials on which this conclusion was based seem to be of poor quality, which makes interpretation difficult.[10]
The American Diabetes Association (ADA) states that the optimal timing and frequency of SMBG in patients on oral agents or diet only is not known, but that it should be individualised for each patient in order to achieve blood glucose goals.[5] Patients with type 2 diabetes on insulin need to perform SMBG more often. Patients should also do SMBG more often after their treatment has been adjusted.

The ROSSO study investigated the outcome of type 2 diabetic patients who do SMBG.[11] It demonstrated that morbidity and mortality were significantly lower in patients doing SMBG (adjusted hazard ratios 0.68 and 0.49 respectively). In other words morbidity and mortality was respectively 32% and 51% lower in patients who do SMBG. This improvement was independent of whether the patients were on oral, insulin or a combination of oral and insulin therapy.

The national guidelines of the South African Department of Health suggest that patients with type 2 diabetes should test blood glucose fasting and two hours post-prandially once or twice a week until glucose levels are normal.[7] Once blood glucose is normal, fasting blood glucose should be checked once a month if the patient is ***on diet and oral agents***. This is in general not achievable in the South African public health system since most patients do not have access to home monitoring due to the inability of public health care facilities to supply the necessary glucometers and strips.

Patients ***on insulin*** should do SMBG as in type 1 diabetes patients: four times daily during an intensive effort to improve glycaemic control (before each meal and at bedtime). This can be reduced to twice daily before meals and at bedtime, choosing a different meal each day once control is achieved. The alternative is a four times a day profile done twice weekly, once on a working day and once during the weekend. Blood glucose should also be tested between 3 am and 4 am once or twice a month.[12] Blood glucose monitoring is a useful tool to motivate patients to change their behaviour and to comply with treatment schedules. The author is also of the opinion that keeping record of blood glucose measurements is important to detect patterns of poor glucose control and to implement appropriate interventions.

Day profiles (the measurement of blood glucose seven to eight times a day, before meals, two hours after meals, at bedtime and, if necessary, between 2 am and 4 am) can be extremely useful in identifying hyperglycaemic episodes in patients in whom there are discrepancies between capillary blood glucose recorded and HbA1c levels. This can be done if poor control is present, as indicated by the HbA1c, and should be done for two to three days, usually including a weekend day.

HbA1c

HbA1c is a reflection of blood glucose control during the preceding two to three months. This test should be done two to four times a year and, if possible, at the time of patient contact. This opens an opportunity for patient education and motivation, as well as an opportunity to change therapy if needed. The patient cannot manipulate the result, as may happen with a random glucose measurement.[5,13]

The HbA1c should always be correlated with the patient's SMBG and the results must be discussed with the patient in order to make well-informed decisions. Be aware that even frequently done SMBG can miss significant hyperglycaemic episodes, which can have an influence on the HbA1c. If such a discrepancy occurs, the patient should be requested to test more regularly or to do a glucose day profile. These discrepancies frequently occur in patients who are measuring capillary blood glucose fewer than two times a day, especially if it is only done pre-prandially.[14,15]

Take note that inaccurate HbA1c values occur in conditions with rapid red blood cell turnover, in patients with HIV and in renal failure.[16,17,18]

OFFICE AND FASTING PLASMA GLUCOSE MEASUREMENTS

Fasting plasma glucose correlates with HbA1c in type 2 diabetic patients, since the fluctuations in blood glucose are not as severe as in type 1 diabetic patients. It thus can give an indication of glycaemic control, but does not replace the HbA1c as a measure of blood glucose control.[19]

Non-fasting blood glucose monitoring can be a good indicator of blood glucose control, but caregivers should be cautious to use a single office blood glucose measurement to adjust treatment.[20]

The author is of the opinion that patients frequently behave differently on days that they visit the diabetic clinic. They tend to skip meals or inject more insulin a few days before they visit clinics. It is for this reason that office capillary blood glucose measurements should not be used as the only measure to assess blood glucose control to adjust treatment. Home monitoring or HbA1c should rather be used to adjust therapy instead of a single office blood glucose value to adjust therapy.

THE EFFECT OF NON-PHARMACOLOGICAL AND PHARMACOLOGICAL INTERVENTIONS ON GLUCOSE LEVELS

Diet, weight reduction and exercise

All patients should receive individualised nutritional advice by a registered dietician or a family physician who is knowledgeable in diabetes nutritional care.[5] Carbohydrate counting, carbohydrate exchanging, glycaemic index and glycaemia load are all important concepts and, when implemented, could improve glycaemia control.[21]

Dietary intervention can improve various aspects of type 2 diabetes, including improvement of insulin sensitivity and secretion. For overweight and obese patients, significant benefit can be gained with regard to lowering the blood glucose if body mass is reduced. In the UKPDS study a patient with mildly elevated fasting blood glucose of 6 to 8 mmol/L a 10 kg weight loss (16% of initial body weight) was needed to achieve a persistent fasting blood glucose below 6 mmol/L. If fasting blood glucose was above 14 mmol/L patients needed to lose on average 26 kg of body weight (41% of initial weight) in order to achieve the same effect. [22,23] A slow but progressive weight loss strategy with a moderately reduced caloric diet in conjunction with lifestyle changes, including an increase in physical activity, should be advised.[24] The majority of diabetic patients are unable to maintain weight loss. This is most likely due to a lowering of the metabolic rate, which retards further weight loss.[25]

PHARMACOLOGICAL INTERVENTIONS

Principles of pharmacological treatment of type 2 diabetes

- Insulin should be started whenever the fasting blood glucose exceeds 15 mmol/l, or if significant unexplained weight loss has occurred, or if the patient is ketotic.[26]
- Combining drugs is usually more effective than stopping one agent and introducing another.
- Adding a second agent is usually better than increasing the dose of one that is already near maximum dosage.
- Secondary failure of two drug combinations can eventually be expected.
- Three drug combinations may be useful, but evidence of added efficacy is lacking.
- Failure of two oral drug combinations usually calls for the use of insulin, alone or in combination with oral agents.

Oral agents

Currently, five classes of oral hypoglycaemic agents are available in South Africa, of which only the biguanides and sulphonylureas are listed in the essen-

Table I: Oral hypoglycaemic agents and their effects[27,34]

Oral hypoglycaemic class	↓Fasting glucose (mmol/l)	↓HbA1c (%)	Lipids	Body weight	Major side effects	Available on EDL
Sulfonylureas(SU) Glibenclamide[1] Gliclazide[2] Glimeperide	3.3-3.9	0.8-2.0	No effect	↑	Hypoglycaemia	Yes[1, 2]
Meglitinidees Repalglanide Netaglanide	3.6-4.2	0.5-2.0	No effect	↑	Hypoglycaemia	No
Biguanide Metformin	2.8-3.9	1.5-2.0	TG ↓LDL ↑HDL	↓	GI Disturbances; Lactic acidosis (rare)	Yes
Thiazolidinediones (TZD) Pioglitasone Rosiglitazone	3.3-4.3	1.4-2.6	↓TG -LDL ↑HDL -TG ↑LDL ↑HDL	↑	Fluid retention; decreased Hb	No
α-Glucosidase Inhibitors Acarbose	1.9-2.2	0.7-1.7	No effect	No effect	GI Disturbances	No

Abbreviations: HbA1c: glycosylated haemoglobin A1c; TG: triglycerides; LDL: low density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol

tial drug list (EDL).[27] All the oral agents used as single therapy can be expected to lower the HbA1c by between 0.5 and 2% (absolute). Combination therapy will achieve additive reductions in the HbA1c (see Table I).

There are three basic mechanisms of action of oral hypoglycaemic agents for reducing blood glucose.

The first mechanism is augmentation of the release of insulin from pancreatic β-cells (potentiate glucose-mediated insulin secretion). This is achieved via the binding of sulphonylureas to the sulphonylurea receptor (SUR) unit, which, with a second subunit (Kir), triggers closure of the ATP-sensitive potassium channels, opening voltage sensitive calcium channels, with an influx of calcium that stimulates translocation of insulin-containing granules to the plasma membrane and the release of insulin. The meglitinides have a similar, but not exactly the same, mechanism of action: they bind to a different site on the SUR subunit of the ATP-dependent potassium channel. This explains why suphonylurias and meglitinides should not be used in combination.[28]

The second mechanism is the increase in insulin sensitivity. Metformin achieves this by the suppression of hepatic glucose production, increased insulin-mediated muscle glucose uptake, decreased fatty acid oxidation and increased intestinal glucose utilisation. The exact molecular mechanisms for Metformin action is not yet clearly understood, but activation of the AMP-activated protein kinase seems to play a major role.[29] The thiazolidinediones exert their effects by activation of the peroxisome proliferator-activated nuclear receptor (PPAR). When this receptor is activated, glucose transporter gene transcription is mediated, with increased glucose transport across cell membranes. Since thiazolidinediones (TZD) action is mediated via gene transcription, its maximal effect is only achieved after three to six weeks.[30]

The third mechanism whereby oral anti-diabetic agents exert their effect is delaying the absorption of carbohydrates from the intestines. The α-glucosidase inhibitors are competitive suppressants of the small intestine's brush border enzymes, which are needed to hydrolyse oligosaccharides and polysaccharides to monosaccharides.[31]

WHEN TO USE WHICH DRUG

In most patients the first line of treatment is either sulphonylurea (SU) or Metformin. Metformin has the advantage of moderate weight loss or stabilisation of body weight. This makes it the ideal choice for overweight and obese patients with diabetes.[32]

SU and meglitinides are more or less equally effective in blood glucose lowering; the meglitinides have the advantage of increasing early prandial insulin secretion, which makes it ideal for patients with high prandial blood glucose peaks. In contrast to sulphonylureas, the meglitinides have little effect on insulin secretion between meals and during the night. The major advantage of sulphonylureas is their ability to lower blood glucose on a once daily dosing schedule with the newer drugs, and their reasonable price.[33]

The thiazolinediones (TZD) are useful in patients with significant insulin resistance. Although they can be used as monotherapy, they are more frequently used as second line therapy in combination with other agents or insulin. TZDs are more expensive than Metformin, and cause more weight gain.[28]

The α-glucosidase inhibitor (Acarbose) is effective for a reduction in post-prandial glucose peaks, and is mostly used in combination with other oral antidiabetic drugs or insulin. Due to its mechanism of action, Acarbose tends to cause abdominal distension, flatulence and diarrhoea.[31]Due to the progression of β-cell depletion in type 2 diabetic patients, a significant proportion of patients will develop insufficient glycaemic control on oral agents alone or will need insulin after initial control on diet and oral treatment.[35]

Beta-cell exposure to prolonged hyperglycaemia leads to a loss of responsiveness to glucose. This reversible β-cell exhaustion is also called glucose toxicity and is characterised by a fasting plasma glucose level higher than 13.9 mmol/L. The β-cell function may recover after a few weeks of intensive glycaemic control, which is attained by temporary insulin therapy.[36,37]

If diabetic patients are started on insulin treatment, it is preferable to continue with oral therapy, especially Metformin, since this has a limiting effect on weight gain due to insulin.[38,39]

Traditionally, insulin was used in type 2 diabetic patients when hyperglycaemia persisted despite diet and maximum oral therapy.[40] Currently, there is more and more evidence to suggest earlier exogenous insulin administration.[26,41] Due to the decline of beta cell function (loss of first phase and delayed and inadequate second phase insulin secretion) mealtime insulin administration may be needed earlier than what was traditionally given in an attempt to delay β-cell depletion and allow for β-cell recovery.[42] The threshold fasting blood glucose level where the initiation of insulin therapy should be considered as the initial treatment of type 2 diabetes varies from 13.9 mmol/L to 16.7 mmol/L.[12,33,36,37]

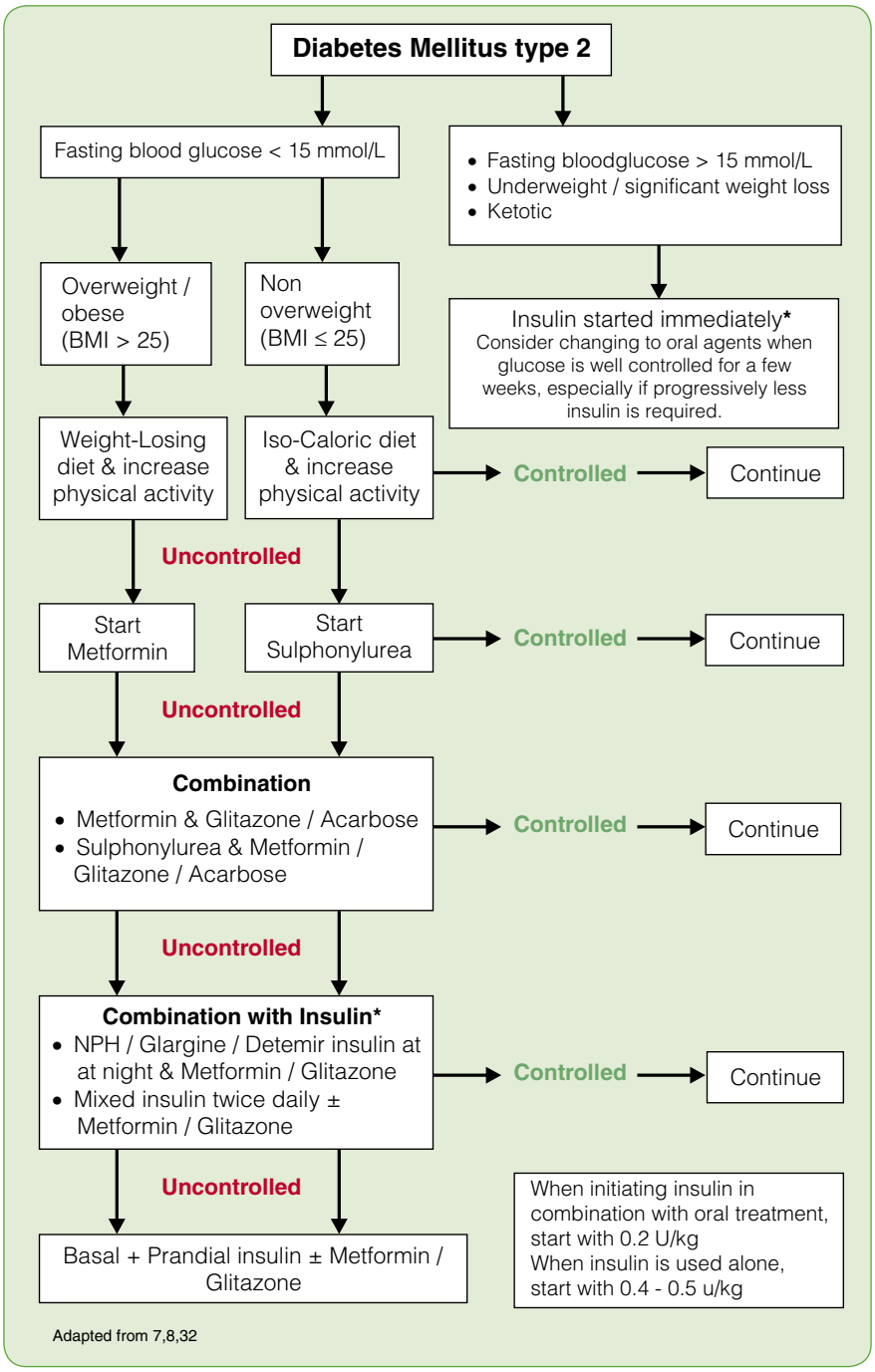
Insulin therapy should also be initiated if unintended, unexplained weight loss or ketonuria is present. Temporary insulin therapy may also be needed during episodes of acute illness.[43] With insulin, glycaemic control can always be achieved and it can be initiated at any stage in type 2 diabetic patients.

Insulin therapy can be implemented in numerous ways and a wide variety of insulins are available. Healthcare providers need to consider each patient's ability and individual circumstances to select the optimal way to control blood glucose.[44]

Three aspects of insulin therapy need to be considered in patients receiving insulin: basal insulin requirements, prandial (bolus) insulin requirements and, lastly, adjustments of insulin. In type 2 diabetic patients, not all three aspects should initially be replaced, since residual β-cell function may still be present. As the disease progresses to total depletion of β-cell function, all three aspects should be addressed.

The traditional way to start insulin in type 2 diabetic patients is to initiate basal insulin with NPH or isophane insulin once daily, usually at bedtime, when oral agents alone are insufficient to control

Fig 1: Insulin in type 2 diabetic patients



blood glucose.[45] Newer, peak-less analogue insulin glargine or detemir seem to be very effective for this purpose, and also pose a smaller risk of hypoglycaemia.[46,47] Basal insulin should be adjusted according to fasting morning blood glucose levels. The usual starting dose is 0.1 to 0.2 U/kg per day. This strategy should be seen as an augmentation of β-cell function and should be used in conjunction with oral agents, especially sulphonylureas or meglitinides.

Beta-cell function can also be augmented by the addition of meal-related regular or short-acting analogue insulin (Aspart/Lispro/Glulisine).[48,49,50] Postprandial glucose should be monitored and the insulin dose adjusted to these measurements, with the aim of keeping it below 10 mmol/L. This strategy makes good sense because insulin deficiency is usually most pronounced during meals and shortly afterwards in diabetic patients. This strategy is not frequently followed, because numerous injections are required unless total replacement of insulin is indicated, in which case basal insulin and an adjustment plan according to pre-meal glucose are added.

Both basal and prandial insulin re-

quirements can be satisfied by giving combination insulin (premixed Regular and NPH / Isophane insulin or newer biphasic insulin Aspart and Lispro) twice daily.[51,52,53] The disadvantage of this strategy is that a fixed meal schedule needs to be followed. The two advantages of the newer analogue insulin mixtures is that a much less pronounced insulin peak is present in the basal component of the dosage[54] and the second is that only two injections need to be given daily. The newer insulin analogue mixed insulins seem, however, to give even better results if given three times per day immediately before meals.[55]

Glycaemic control can also be achieved by the administration of basal insulin (NPH / Isophane / Glargine / Detemir[56]) with mealtime boluses (Aspart/ Glulisine), which allows the greatest flexibility with regard to eating habits. This is also known as the basal bolus regimen.[57] This strategy, especially if applied with new analogue insulins, allows for insulin administration immediately before meals (Aspart/Lispro/Glulisine) and provides a constant supply of basal requirements (Glargine / Detemir) without the need to take snacks between meals.[58] This strategy is usually applied in patients with very little remaining β-cell function.

It is important that initiating insulin should never be seen as failure on the part of the patient to comply with oral therapy; it should rather be seen and explained as the normal progression of disease. Secondly, patients should be prepared for the possibility that insulin might be needed at some stage in the future as part of disease management. However the patient should never see insulin treatment as a punishment for poor diet and oral treatment compliance.[59]

In community health centres in Cape Town, unsatisfactory glycaemic control in type 2 diabetic patients was found to be due to barriers against the initiation of insulin. The reasons related to the doctors were: a lack of knowledge, lack of experience with and the use of guidelines related to insulin therapy, language barriers between doctors and patients, and the fear of hypoglycaemia. Patient barriers included: wrong beliefs about insulin, non-compliance, lack of understanding of diabetes, use of traditional herbs, fear of injections and poor socio-economic conditions. System barriers included inadequate time, lack of continuity of care and financial constraints.[60] The author believes that these barriers are not only present in Cape Town, but are prevalent in the whole country. It therefore is every healthcare provider's responsibility to gain sufficient knowledge and to educate patients regarding the progressive nature of type 2 diabetes and not to delay the initiation of insulin when needed.

CONCLUSION

The management of type 2 diabetes is complex, with numerous options. The appropriate option for each patient will be determined by the patient's ability to cope with a regimen, patient preferences and, frequently, by the patient's ability to afford the medication. Independent of what treatment regimen is prescribed, all patients should be educated on the importance of glycaemic control and how to use treatment optimally. Due to the chronic nature of diabetes it is essential that all patients should be kept motivated, which calls for a motivated, tenacious, supportive health caregiver.

See CPD Questionnaire, page 48

This article has been peer reviewed

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