HOW TO START AND OPTIMISE INSULIN THERAPY

Starting insulin therapy in type 2 diabetes can be challenging.

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Initiating insulin therapy in type 2 diabetes mellitus is often intimidating, as understanding how and when to use insulin is vital to diabetes management and has repercussions if not done correctly. Patient reluctance as well as health care provider reluctance often plays a role in delaying therapy initiation.

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Type 2 diabetes mellitus (T2DM) is a steadily progressive disease. It is characterised by two defects, namely insulin insensitivity, which tends to plateau during the course of the disease, and declining beta cell function.[1] Beta cell function, during the course of the disease, declines to levels where insulin levels are no longer sufficient to compensate for the insulin resistance. In the United Kingdom Prospective Diabetes Study (UKPDS), islet cell function was shown to deteriorate even before T2DM is diagnosed and loss of beta cell function is associated with rising HbA_{1c} (A_{1c}) levels and disease progression.[2] Thus early diagnosis and management of diabetes is paramount to prevent and delay complications. Early tight glycaemic control has also been shown to have a 'legacy effect', with patients who have better control early after diagnosis having a lower risk of future complications.[3] The progressive nature of this disease and the limited ability of oral anti-diabetic drugs (OAD) to reduce A_{1c}, coupled with the pressing need to obtain euglycaemia as safely and quickly as possible to prevent long-term complications, means most patients will eventually require insulin.

What is the rationale for tight glycaemic control?

Results from landmark studies, viz. the UKPDS, have demonstrated that better glycaemic control with intensive therapy in subjects with T2DM decreased the risk of microvascular complications and showed a 16% risk reduction in myocardial infarction.[4] The Steno 2 study also showed relative risk reduction with multi-targeted intensive therapy.[5] Thus early good control has been proven to have long-term salutary effects and insulin undoubtedly plays a role in achieving good glycaemic control.

The practical reality of glucose control

Most patients will require more than lifestyle modifications and OAD to control their diabetes. The UKPDS showed that 53% of T2DM patients using only sulphonylureas required insulin after 6 years and 80% after 9 years. In the National Health and Nutrition Examination Survey (NHANES 1988 - 1994), i.e. before the results of studies such as the UKPDS confirming the beneficial effect of targeted glycaemic targets, 44% of patients with diabetes were classified as having inadequately controlled DM due to A_{1c} levels above the ADA targets for glycaemic control (Table I). However, in a subsequent analysis of the NHANES (1999 - 2004) and after targeted glycaemic control became part of standard treatment guidelines, only 52.2% met glycaemic targets.[6] Unfortunately the proportion of subjects with HbA_{1c} >7% increases with the duration of the disease due to the underlying progressive nature of the disease.

Table I. Glycaemic targets

	ADA	AACE	SEMDSA
HbA_{1c} (A_{1c}) (%)	<7	≤6.5	<7
Fasting/pre-prandial glucose (mmol/l)	5 - 7.2	<6.1	4 - 7
Postprandial glucose (mmol/l)	<10	<7.8	5 - 8

ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists; SEMDSA = Society for Endocrinology, Metabolism and Diabetes of South Africa.

Current treatment of T2DM

The current recommended treatment for patients is the initiation, at diagnosis, of a combination of lifestyle modifications and metformin (step 1) (Fig. 1). If A_{1c} <7% is not achieved within 2 - 3 months, the second step of adding a basal bedtime insulin or a sulphonylurea to the treatment regimen is advised. The third step for validated therapies is to start or intensify insulin. Unfortunately treatment inertia remains a problem and patients remain on monotherapy for more than a year following an initial HbA_{1c} of 8%.[7]

Early diagnosis and management of diabetes is paramount to prevent and delay complications.

It is important to understand that the beneficial effects of treatment on complications are based purely on the level of glycaemic control rather than any specific characteristic of the intervention used. Unlike other therapies, which lower A_{1c} by 1 - 2%, insulin can decrease any level of elevated A_{1c} to, or close to, therapeutic goal. There is no maximal dose beyond which a therapeutic effect will not occur. It effects are limited only by its hypoglycaemic potential (Table II).

Rationale behind insulin therapy

Insulin in normoglycaemic individuals is produced at a basal rate even in the fasting state to limit lipolysis and hepatic glucose output.

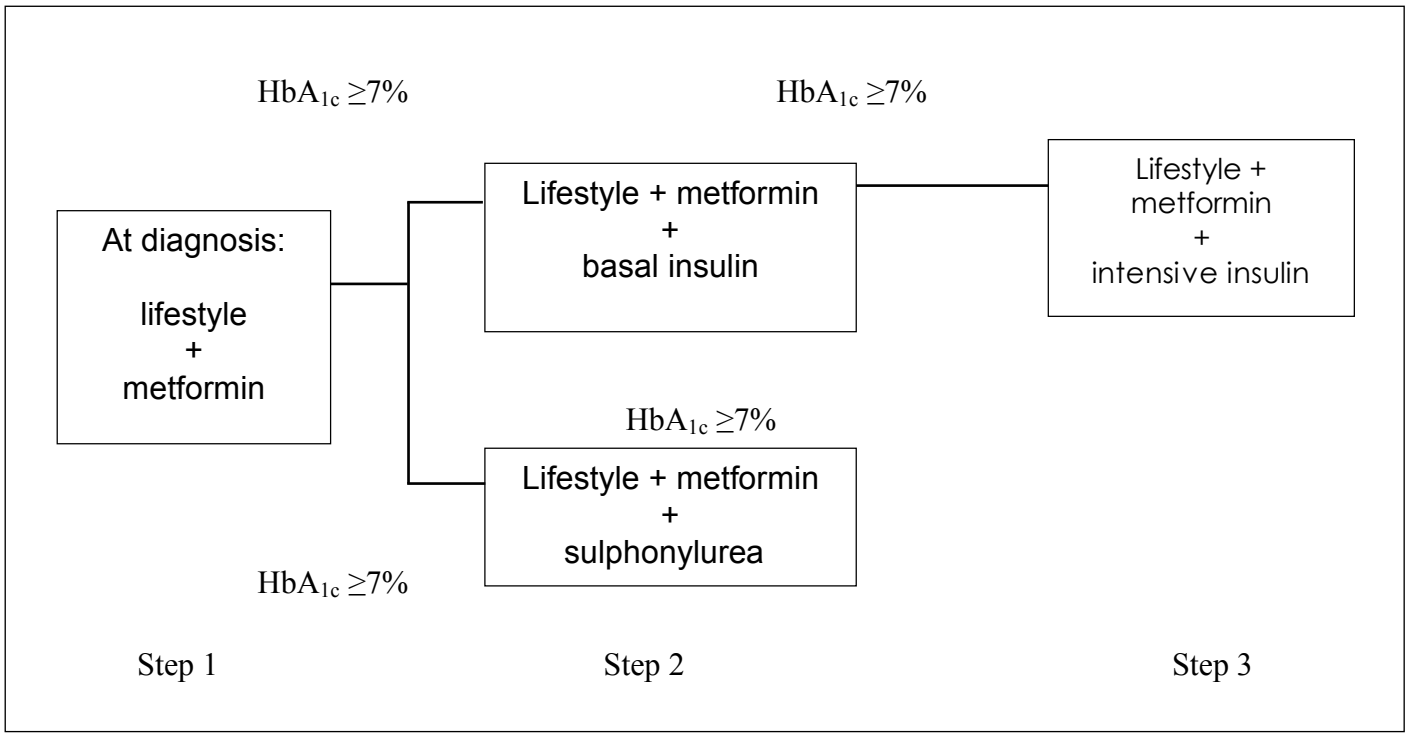

Fig. 1. Algorithm for the metabolic management of type 2 diabetes. Adapted from Nathan D et al. Diabetes Care *2009;32:1-11.*

Table II. Efficacy of glucose-lowering therapies*

Class	Reduction in HbA_{1c}	Agents
Biguanides	1.0 - 2.0	Metformin
Sulphonylureas	1.0 - 2.0	Glibenclamide, gliclazide
Insulin	1.5 - 3.5	
Thiazolidinedione	0.5 - 1.4	Pioglitazone
GLP-1 agonist	0.5 - 1.0	Exenatide
DPP4-inhibitor	0.5 - 0.8	Sitagliptin, vildagliptin
Glinide	0.5 - 1.5	Repaglinide
Amylin analogue	0.5 - 1.0	Pramlintide

*Adapted from Nathan D *et al. Diabetes Care* 2009;32:1-11.

During meals, a bolus of insulin is secreted in two phases. The first phase inhibits hepatic glucose production and the second phase stimulates peripheral glucose uptake. Patients with type 2 diabetes mellitus often have first-phase secretory defects. The goal of insulin therapy is to provide near-physiological control that can simulate this basal-bolus insulin secretion.

Indications for insulin therapy

The current ADA and EASD (European Association for the Study of Diabetes) guidelines recommend the following indications:

- Basal insulin can be added when A_{1c} ≥7% with lifestyle intervention and metformin.
- If a combination of oral hypoglycaemic agents (OAD) does not lower A_{1c} to <7%.
- Patients with uncontrolled diabetes mellitus with catabolism defined as
  - fasting plasma glucose >13.9 mmol/l
  - random glucose levels consistently above 16.7 mmol/l
  - A_{1c} above 10%
  - presence of ketonuria or symptomatic diabetes with polyuria, polydipsia and weight loss.
- Patients with specific conditions, e.g. severe renal disease.

Types of insulin preparations

There are insulins for basal and prandial cover. All insulins are available as regular human insulins or analogues. Analogue insulin preparations were developed to mimic endogenous insulin secretion. They are different from human insulins in their structure, onset, peak and duration of action and are thought to be more physiological. The use of analogue preparations is more flexible than regular human insulin due to these properties.

Basal insulins

These include NPH (neutral protamine Hagedorn) or long-acting insulin analogues (insulin glargine (Lantus), insulin detemir (Levemir)). The pharmokinetic profiles of both differ, as seen in Table III.

The analogue insulins tend to have flatter profiles while NPH peaks at 4 hours. This tends to affect dosing and efficacy. The pharmacokinetics of NPH also demonstrate more within-patient variability. This is due to the protamine added to the insulin to extend its action. This often tends to ionise the insulin molecule, which forms a complex with itself to remain in a hexameric structure at the injection site (which is responsible for its extended action). The poor solubility, however, also increases the variability in pharmacokinetics, which is not seen with the analogues.

The goal of insulin therapy is to provide near-physiological control that can simulate this basal-bolus insulin secretion.

Compared with NPH, glargine and detemir have a longer duration of action, less within-patient variability and less potential for hypoglycaemia. In the INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) trial adding once daily glargine provided better glucose control than optimised oral therapy.[8] Studies comparing NPH versus glargine or detemir showed a decreased risk of hypoglycaemia with the analogue insulins but similar glycaemic control.[13,14] In another study, when glargine was added to OHA and compared with detemir with OHA, similar A_{1c} lowering was seen. There was also a similar low rate of hypoglycaemic events, although weight gain with detemir was less when used once daily.[9]

Table III. Onset, peak, and duration of action of insulin therapies

	Onset action (hrs)	Peak (hrs)	Duration
Ultra-rapid acting*			
Lispro (Humalog®)	0.2 - 0.5	0.5 - 2	<5 hours
Aspart (Novorapid®)	0.2 - 0.5	0.5 - 2	<5 hours
Glulisine (Apidra®)	0.2 - 0.5	0.5 - 2	5 hours
Short-acting			
Regular (Actrapid®, HumulinR®)†	0.5 - 1	2 - 3	5 - 8 hours
Intermediate/long-acting			
NPH (Protaphane®, Humulin N®)†	1.5 - 4	4 - 10	10 - 16 hours
Glargine (Lantus®)*	1 - 3		up to 24 hours
Detemir (Levemir®)*	1 - 3	-	up to 24 hours
Mixes			
Human 30/70 (Actraphane®, Humulin®)†	0.5 - 1	3 - 12	10 - 16 hours
Lispro (Humalog Mix25®)*	0.2 - 0.5	1 - 4	10 - 16 hours
Aspart (NovoMix30®)*	0.2 - 0.5	1 - 4	10 - 16 hours

*Analogue insulin.
†Human insulin.

Prandial insulins

Regular human insulin has a slow absorption and needs to be injected 30 - 45 minutes before meals. Rapid-acting analogues (aspart, glulisine, lispro) have a shorter duration of action, quicker onset and less variability. They can be injected within 15 minutes of starting a meal, including during, or even after, a meal. Although they are more flexible, they are more expensive. There is little difference in glycaemic control between the two in medium- to long-term studies.

Premixed insulins

These contain intermediate protaminated insulin for basal cover with rapid-acting insulin for prandial cover. Peak concentrations of analogues occur more rapidly than human insulin. The incidence of hypoglycaemia is less with premixed analogues compared with human insulin. The ACTION trial showed that twice daily Bi Asp 30 added to metformin and pioglitazone provided better glucose control than oral therapy alone.[10] Interestingly, when premixed insulin analogue Novomix 30 twice daily added to OAD (metformin) was compared with Lantus with OHA, lower A_{1c} levels were seen with the premixed insulin combination although it was associated with more weight gain.[11] On the other hand, in the recent 4T study, the addition of a basal or prandial insulin-based regimen to oral therapy resulted in better glycated haemoglobin control than the addition of a biphasic insulin-based regimen. However, in the premix group fewer patients had intensification of therapy with a second insulin during the 3-year period. Fewer hypoglycaemic episodes and less weight gain occurred in patients adding basal insulin.[12]

How should insulin be initiated?

Initial insulin therapy needs to be individualised to optimise target goals while avoiding hypoglycaemia. Patients need to measure their blood glucose at least twice a day (3 times if taking multiple injections) and have self-monitoring data available so dosage changes can be made.

Insulin should not be delayed if the patient is a candidate for therapy or is not meeting targets for control. Basal insulin can be started at 10 units or 0.2 units/kg at night if control is not achieved with OAD or if they fall into the group of patients where insulin is indicated. If cost is a factor, NPH can be used. An analogue may be preferred if this is not the case. Insulin analogues, however, have equivalent glycaemic control, when compared with regular human insulin and there are few data in medium- to long-term studies that show that analogues have better glycaemic control. They are also more expensive. A simple patient-led dose titration algorithm may be provided (an example in Table IV) to allow patients to make dose changes while avoiding hypoglycaemia.

Alternatively it has been suggested that the fasting glucose be checked daily and the dose increased by 2 units every 3 days until fasting levels are in the range of 3.9 - 7.2. Fasting plasma glucose contributes to A_{1c} when there is poor glycaemic control, but once control

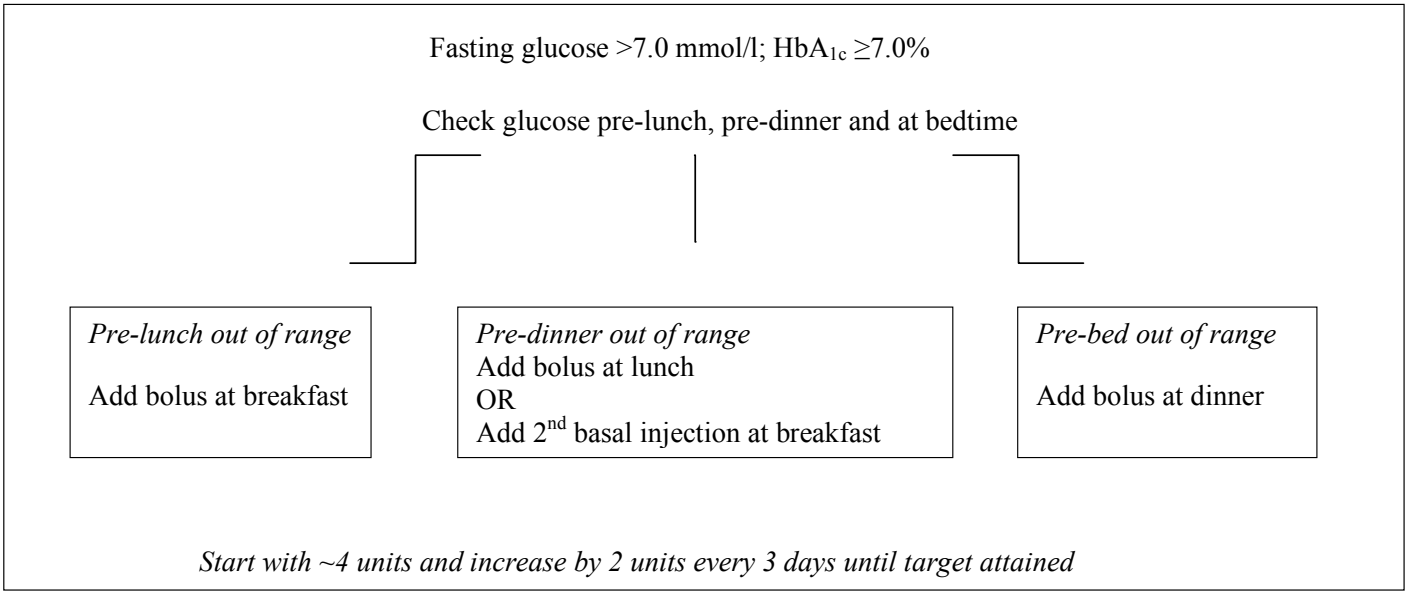

Fig. 2. ADA and EASD algorithm: Addition of bolus injection to optimised basal insulin. Adapted from: Nathan D et al. Diabetes Care *2009;32:1-11 .*

Table IV. Basal insulin titration algorithm

Fasting glucose (mmol/l)*	Adjustment (U)
≥9.9	+ 8
8.8 - 9.9	+ 6
7.7 - 8.7	+ 4
6.6 - 7.6	+ 2
5.5 - 6.5	+ 1
4.4 - 5.4	No change
3.3 - 4.3	- 2
<3.3	- 4

*Average over 3 days.
Mooradian AD *et al. Ann Intern Med* 2006;145:125-134.

improves, post-prandial glucose is the major contributor. Patients should be reviewed regularly on a 1 - 3-month basis. If after 2 - 3 months, A_{1c} levels are still >7%, prandial rapid-acting insulin can be added, depending on blood glucose levels before lunch, supper and bedtime or the regimen can be changed to twice a day premix insulin to target post-prandial hyperglycaemia.

For premix insulins

The decision to choose between premix and adding prandial doses should be individualised. Patients' lifestyle, eating habits and how convenient it is to inject on multiple occasions versus twice daily will influence the decision, e.g. patients with consistent mealtimes and inability to incorporate multiple injections into lifestyle will be more suitable for premix insulin therapy.

Patients need to be educated from the outset that diabetes is a progressive disease.

The total insulin dose (0.4 - 0.6 U/kg) should be divided in two, with half given before breakfast and the other half before supper. Adjustments in pre-breakfast dosages are based on pre-supper glucose levels and adjustments in pre-supper dosages are based on pre-breakfast glucose levels. A titration schedule can be provided to patients to prevent hypoglycaemia (Table V). Titration to goal will depend on monitoring and meal history (largest meal will require largest dose of insulin). Hypoglycaemic events should prompt a reduction of the total insulin dose by 20% and more in-depth monitoring should be conducted to assess if further dose titrations would be required. Premix insulin analogues have peak concentrations that occur more rapidly than human insulin and day-to-day absorption variability is reduced. The incidence of hypoglycaemia is less in premixed insulin analogues. There is equivalent glycaemic control between regular human insulin and insulin analogues.

Table V. Titration schedule premix insulin therapy

Fasting glucose (mmol/l)*	Adjustment pre-supper dose (U)	Pre-supper glucose (mmol/l)*	Adjustment pre-breakfast dose (U)
7.7 - 9.9	+ 4	7.7 - 9.9	+ 4
6.1 - 7.6	+ 2	6.1 - 7.6	+ 2
4.4 - 6.0	No change	4.4 - 6.0	No change
3.3 - 4.3	- 2	3.3 - 4.3	- 2
<3.3	- 4	<3.3	- 4

* Average over 3 days. Adapted from Mooradian AD *et al. Ann Intern Med* 2006;145:125-134.

Table VI. Barriers to insulin therapy

Patient barriers	Physician barriers
Lack of awareness or knowledge	Perception of poor clinical efficacy
Anxiety	Perception that it is asking too much of some patients
Fear of hypoglycaemia	Poor confidence in patient's abilities
Negative perceptions of outcome	Fear of inducing hypoglycaemia
Needle phobias	Too demanding for the staff
Social stigma	Lack of experience
Lack of self-efficacy or confidence	

If HbA_{1c} is not ≤7.0% with basal insulin plus OAD, or with premixed insulin, consider implementing a basal-bolus regimen. Total daily insulin dose is calculated at 0.4 - 0.6 U/kg. Basal and bolus requirements are half of the total daily insulin dose each. The bolus dose is then divided into breakfast, lunch and dinner doses while the basal dose is provided at bedtime. Again self-monitoring of blood glucose (SMBG) provides crucial information regarding dose titrations. If fasting glucose readings are within target but A_{1c} remains high, then postprandial SMBG should be initiated.

Barriers to insulin therapy

The crucial problem with initiating insulin is patient resistance to using it. This is due to a number of problems (Table VI).

The best way to address these is by information and education. Patients' reluctance needs to be explored and addressed in a non-judgemental way. Patients need to be educated from the outset that diabetes is a progressive disease and insulin needs to be presented not as a last resort or punishment but as a validated therapy that, when initiated early, can prevent complications. Patients also need to be empowered to make changes in their own insulin doses based on their SMBG. Discussion also needs to focus on recognition of hypoglycaemia associated with insulin use and its precipitants and how to treat episodes. It is important to address weight gain associated with insulin use and ways to minimise this (i.e. use of metformin, use of detemir rather than NPH, and diet and exercise counselling).

Conclusion

A wide variety of insulin preparations are now available that make it easier to simulate the normal insulin secretory pattern. Insulin delivery systems have also improved with easier pen sets and programmable insulin pumps. Insulin, when properly administered at the correct dose, is the most potent drug available to attain glycaemic control and prevent complications. Insulin therapy requires more frequent monitoring as well as increased patient involvement in the treatment regimen. Insulin therapies are nonetheless effective and well tolerated. Treatment should be individualised and incorporate SMBG and insulin dose adjustment based on these readings.

References available at www.cmej.org.za

In a nutshell

- Basal and premix insulins are effective.
- Basal analogue and NPH are equivalent in glucose lowering.
- Basal analogues cause less hypoglycaemia than NPH.
- Detemir causes less weight gain than glargine.
- The superiority of premix insulin to basal insulin is debatable with recent trials, but premixed insulins cause more weight gain.
- Multiple injections are superior to basal insulin but are associated with more hypoglycaemic events.
- Titration to target is crucial.
- The insulin regimen chosen needs to be individualised to the patient.