UNMET NEEDS IN CLINICAL PRACTICE: INSULIN IN TYPE 2 DIABETES

Introduction

Type 2 diabetes mellitus is currently a worldwide pandemic, affecting close to 500 million people.¹ In South Africa, government clinics are overwhelmed by almost 15 000 new diabetic patients per month. No health care professional, especially the general practitioner, can ignore diabetes, as primary care will encounter these patients several times per day. This update is essential for achieving best practice in everyday primary care.

A very concerning modern trend is that type 2 diabetic patients now present at a younger and younger age, some even before the age of 10 years. This will result in a loss of productivity and a loss to society as a person who is diagnosed with type 2 diabetes in their late teens or early twenties is unlikely to survive to retirement age and will develop many complications over time, adding to escalating health care costs. A focused prevention strategy is urgently required, because health systems will not be able to cope. A further worrying fact is that diabetes control all over the world is suboptimal and in South Africa often just plain poor; this applies to both public and private sectors.²⁻³

We have to ask ourselves if there really are any unmet needs in diabetes care today, because we have at least seven different classes of drugs, including many insulins. There is no excuse not to control diabetes with our current armamentarium. The main reasons for poor control are poor lifestyle, poor compliance with therapy and a poor treatment regimen, probably in that order.

Diabetes control

This review will deal mainly with those patients who have been diabetics for a while and are poorly controlled on oral therapy. Clinical experience has shown that, on average, a patient will fail oral therapy after about seven years and therefore require insulin. There will therefore soon be a tidal wave of diabetics who require insulin; this will require primary care practitioners to be confident about insulin therapy, including insulin initiation and titration.

Worldwide there is a delay in initiating insulin,⁴ which contributes to poor control, poor outcomes and increased complications. This delay is even more pronounced in developing countries, including South Africa.⁵ There are multiple reasons for this delay, including barriers resulting from patient resistance, doctor resistance (and sometimes incompetence) and cost.
New South African primary care guidelines for type 2 diabetes management

South Africa recently updated its guidelines and lowered insulin’s status as therapy in the treatment algorithm for type 2 diabetes. Reasons for this change are many, including problems experienced with insulin (Table 1). There has also been an increase in alternative therapies that have other beneficial effects, including weight loss and even renal and cardiovascular protection; these can be used before insulin.

Insulin is still the most potent weapon in the fight against high blood glucose levels. Even if all the novel agents are used, patients will eventually require insulin therapy as a consequence of beta-cell failure. The clinician must, however, keep in mind that insulin offers no additional benefits over and above glucose control and currently has no cardiovascular outcome benefits.

<table>
<thead>
<tr>
<th>Problems with insulin therapy</th>
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<tbody>
<tr>
<td>High hypoglycaemia risk</td>
</tr>
<tr>
<td>Weight gain, nearly universal in all patients</td>
</tr>
<tr>
<td>An expensive therapy</td>
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<tr>
<td>No cardiovascular outcome data</td>
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<tr>
<td>Injections are required</td>
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<td>Glucose testing is essential</td>
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<tr>
<td>Resistance from patient and doctor</td>
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</tbody>
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Table 1. Problems with insulin therapy

When should insulin be considered?

A practical approach is to consider insulin therapy whenever a patient’s HbA1c is more than 1% higher than the patient-specific target on active therapy with two oral agents at maximum dose. These patients should also have made optimal lifestyle changes.

It is good clinical practice that all diabetic patients should have individualised targets for fasting plasma glucose (FPG), post-prandial glucose (PPG) and HbA1c as part of an overall management plan. Figure 1 from the 2017 SEMDSA guidelines illustrates the selection of HbA1c targets according to risk.

It is important not to use lifestyle as an excuse not to start insulin. It should also be noted that increasing the dose of metformin or gliclazide MR is unlikely to bring about sufficient improvement when HbA1c is off target and requires a reduction of 1% or more.

<table>
<thead>
<tr>
<th>Patient features</th>
<th>&lt; 6.5%</th>
<th>&lt; 7%</th>
<th>7–8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks of hypoglycaemia/drug interactions</td>
<td>Low</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td></td>
<td>Short</td>
</tr>
<tr>
<td>Major comorbidities</td>
<td>Absent</td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Established macrovascular disease</td>
<td>Absent</td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Patient attitude</td>
<td>Highly motivated</td>
<td>Non-motivated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adherent</td>
<td>Non-adherent</td>
<td></td>
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<tr>
<td></td>
<td>Good self-care capability</td>
<td>Poor self-care capability</td>
<td></td>
</tr>
<tr>
<td>Resources and support</td>
<td>Readily available</td>
<td></td>
<td>Limited</td>
</tr>
</tbody>
</table>

Figure 1. Selection of HbA1c targets according to risk

“Insulin is still the most potent weapon in the fight against high blood glucose.”
Selecting insulin therapy – what criteria define an ideal basal insulin?

Table 2 shows some of these essential characteristics. Although clinical medicine may never reach perfection, we are approaching it and with the imminent launch of insulin degludec and U-300 insulin glargine, South African clinicians will have basal insulins that are probably very close to ideal.

The biggest limitation of current basal and short-acting insulin is the subcutaneous route of administration. The subcutaneous route causes a delay in the onset of action and contributes to variability and unpredictability, which we cannot currently overcome.

The clinician must know how to initiate and up-titrate/intensify insulin therapy and do this with confidence. Until recently, the most affordable option was starting basal insulin in the form of NPH insulin. Comparative studies have shown that NPH insulin can achieve the same HbA1c-lowering as the newer long-acting insulin analogues like insulin glargine and detemir, but at the price of a marked increased risk of hypoglycaemia. This hypoglycaemia risk has been largely ignored in the past, but recent data show that hypoglycaemia translates into increased morbidity and even mortality. There is no doubt that the newer, long-acting analogues are much safer and easier to use; in my view, they should be the clinician’s first choice. This view is further supported by marked price reduction (up to 40% in the past year), which has made analogue insulin much more cost-effective and even matches NPH insulin pricing in private practice. There is no reason for medical schemes not to fund these newer and safer analogues.

Hypoglycaemia is the biggest and most dangerous drawback of insulin and is usually a consistent feature of insulin therapy. An insulin that does not cause hypoglycaemia will probably never exist. Insulin therapy has to be judged not only on price and efficacy, but also on safety, especially its hypoglycaemic risk. Using the safest insulin will save funders’ financial resources, with fewer hospital admissions for hypoglycaemia and other complications; it will probably save a significant number of lives too.

Confident insulin use

Reluctance to initiate insulin is largely contributing to poor control and the development of complications. We need to make sure that the reluctance to initiate insulin therapy is not on the part of the clinician!

Practical tips to better insulin prescribing

The easiest way to initiate insulin is with basal insulin on top of the patient’s current therapy. Insulin can be added to every available combination without changing therapy, making it very simple for both doctor and patient. Start with a fixed insulin dose of 10 or 12 units and escalate the dose by two units twice weekly until a set FPG is reached. Give insulin at a fixed time in the evening between 19h00 and 22h00 (I prefer 21h00). Keep in mind that all glucose targets must be individualised and should appear in the patient’s notes. The patient should clearly know and understand his/her personal targets for FPG, pre-meal glucose values and HbA1c. Table 3 shows some suggested targets, also discussed in the SEMDSA guidelines.
I would recommend starting with insulin glargine or detemir and titrating up. If you expect that only a low dose is needed, insulin glargine will have a longer duration of action and more easily provide 24-hour control. If higher doses are required, both insulins will last for 24 hours and insulin detemir might offer a small weight advantage. Both insulins have a significantly reduced risk of hypoglycaemia relative to NPH insulin. This insulin should be uptitrated until the set target is reached.

When the FPG target is reached, the patient has to test pre-lunch and pre-dinner glucose values, which should be below 10mmol/l. HbA1c measurement should be repeated after three months. If the patient is not at target, consider ‘upgrading’ the insulin. The options are either: (1) using a basal plus one regimen, covering the main meal with short-acting analogue insulin or (2) being guided by the biggest glucose excursions after meals. The alternative is to change the basal insulin to a premix analogue with supper, covering both the FPG and the dinner, but this means that the patient will most likely be back on NPH insulin (currently used premixes do contain NPH). You can also combine the added insulin with a DPP-4 inhibitor, GLP-1 receptor analogue or a SGLT-2 inhibitor.

The combination of insulin degludec and insulin aspart can offer a useful alternative and is the only mixed option that does not contain NPH. This regimen (once-daily premix) can easily be upgraded to premixed insulin twice a day, but then the sulphonylureas should be stopped. I would still continue metformin and pioglitazone therapy if they were being used. You can also combine the added insulin with a DPP-4 inhibitor, GLP-1 receptor analogue or a SGLT-2 inhibitor.

Two new ultra-long-acting basal insulins are entering the market soon, U-300 insulin glargine and insulin degludec. They will contribute significantly to improving basal options and will become the insulins of choice if affordable. Both of these excellent insulin’s duration of action is longer than 24 hours, both have an extended flat profile and cause significantly less hypoglycaemia compared to current basal insulins. To improve on them will be very difficult and pricing might influence therapeutic choice. Both will certainly be used to replace current therapy, probably unit-for-unit and will be selected for use in patients currently uncontrolled on their existing insulin and those with recurrent hypoglycaemia or at high risk for hypoglycaemia.

Both have shown significant reduction in hypoglycaemia, especially nocturnal hypoglycaemia relative to U-100 glargine insulin. There is, however, no HbA1c-lowering benefit versus U-100 glargine. In the EDITION trials, U-300 glargine was tested extensively against insulin glargine and showed a 24% reduction in
hypoglycaemia. In the BEGIN trial, insulin degludec was tested against insulin U-100 glargine and showed a 36% lower rate of nocturnal hypoglycaemia. Many other studies were done with both U-300 glargine and insulin degludec showing hypoglycaemic benefit in different patient populations. Degludec was tested against U-100 glargine in respect of cardiovascular safety, but there was no difference.

**Hypoglycaemia and hospitalisation, morbidity and mortality**

There are increasing recent data to show that hypoglycaemia is a major risk factor for hospitalisation, morbidity and cardiovascular mortality. The largest risk is in those patients on insulin therapy and probably contributes significantly to the neutral results of many of the cardiovascular outcome trials in diabetes. Table 4 from SEMDSA guidelines highlights the risk factors. Severe hypoglycaemia in type 2 diabetes patients has been shown to increase major cardiovascular events nearly threefold and death from cardiovascular events 2.7-fold.

Type 2 diabetes is a national and international crisis; let’s all work together to help to manage it by arming ourselves with the knowledge and confidence to initiate and titrate insulin so as to improve the glucose control of our patients and ultimately their outcomes (Table 5).

**Table 4. Independent risk factors for severe hypoglycaemia**

- Insulin or sulphonylurea use
- Intensive glucose control
- Use of two or more oral glucose-lowering drugs
- Older age
- Diabetes duration
- Hypoglycaemia unawareness
- Impaired cognitive function
- Low body mass index
- Renal impairment
- Microvascular complications

**Table 5: Summary of practical tips to use insulin more effectively**

- Start with basal analogue insulin no
c
- Refer to diabetic nurse educator
- Start with low dose and let the patient titrate the dose
- Make sure the patient understands their own target
- Titrate slowly, only twice per week, two units per titration
- Ask patients to test FPG only (initially)
- Warn against hypoglycaemia and educate on self-management
- Optimise diet with dietician; the PMBs permit all diabetics to see a dietician every year.

“New ultra-long-acting basal insulins will contribute significantly to improving basal options.”
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References


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