Insulin – myths and facts

Statement 1

Insulin is the last resort for patients with Type 2 diabetes

After initial metformin and sulfonylurea therapy, NICE and SIGN suggest a number of options in the progressive treatment of hyperglycaemia in Type 2 diabetes. Glitazones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon like peptide (GLP)-1 analogues and sodium-glucose co-transporter-2 (SGLT2) inhibitors may all be appropriate if insulin is considered unacceptable.

Since Type 2 diabetes is a disease heterogeneous in pathogenesis and clinical manifestation, choice of therapy should be individualised to the patient and take into account numerous factors including patient choice, co-morbidities, baseline and personalised target level HbA1c.

As beta cell function declines over time, the need for replacement insulin will increase in order to normalise hyperglycaemia. Beta cell decline can occur due to a number of factors and the rate of beta cell decline and the degree of insulin resistance will be different for each individual. Therefore the right time to commence insulin will differ in each individual. Insulin should not be seen as the last resort in optimising glycaemic control or as failure by the patient to control their diabetes. Insulin should be seen as an option in care to optimise glycaemic control to prevent longer term complications.

National studies have shown that there is an average delay of between six to seven years before starting insulin in those with uncontrolled Type 2 diabetes. Optimal control in Type 2 diabetes reduces, in the long term, the risk of microvascular complications. Evidence shows that if we optimise glycaemic control earlier in the pathway, we can also protect beta cells for longer.

Insulin is an important part of the treatment package and currently, there are so many different types of insulins and regimens, that actually it’s not the last resort, it’s the beginning of a wide range of further options.

In clinical practice, insulin may be the most appropriate choice in the following circumstances:

1. Patients who have symptomatic hyperglycaemia e.g weight loss, polydipsia, polyuria, blurred vision, recurrent infections or tiredness, or marked hyperglycaemia.
2. Patients unable to control blood glucose levels despite dual therapy, who are markedly hyperglycaemic and the patient agrees to start insulin.
3. Patients who are unable to adequately control blood glucose levels despite triple therapy with oral glucose lowering drugs.
4. When other hypoglycaemic agents will not reduce baseline HbA1c to personalised HbA1c levels.
5. Patients who cannot tolerate/have allergies with non-insulin hypoglycaemic medication.
6. Patients who are limited with other hypoglycaemic medication due to renal or hepatic function decline.
7. Patients who have progressive microvascular complications.
8. When concomitant therapies that cause hyperglycaemia such as steroids are prescribed (depends on type of steroid please discuss with diabetes team).
9. Women who are pregnant or planning pregnancy.
10. Where the patient preference is to start insulin.
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Statement 2
NPH insulin is not as effective as analogue insulin in HbA1c reduction, causes more frequent and severe hypoglycaemia, and causes more weight gain in those diagnosed with Type 2 diabetes.

Glycaemic control
A systematic review found no difference in HbA1c level between insulin glargine and NPH insulin, and only a small non-significant difference in trials of insulin detemir versus NPH insulin (HbA1c level was higher with insulin detemir by 0.08%; 95% CI –0.03 to 0.19). Overall, the systematic review concluded that “insulin glargine and insulin detemir are equivalent to NPH in terms of glycaemic control as reflected in HbA1c level”\(^\text{13}\).

Hypoglycaemia
No differences in the frequency of severe hypoglycaemia between the insulin analogues and NPH insulin were found, but, overall hypoglycaemia was less frequent with both insulin glargine (OR 0.74, 95% CI 0.63 to 0.89) and insulin detemir (OR 0.51, 95% CI 0.35 to 0.76). The systematic review concluded that insulin analogues have modest advantages in terms of hypoglycaemia, especially nocturnal\(^\text{13}\).

Weight
Insulin therapy is likely to increase body weight by 2-4kg on average and usually greatest during early stages of insulin use\(^\text{14}\). Strategies to minimise weight gain should be discussed at insulin initiation and periodically throughout therapy to minimise weight gain. Weight gain in patients on insulin glargine was slightly less than in patients on NPH insulin (0.28 kg; 95% CI –0.72 to 0.15) but this was neither clinically nor statistically significant. On insulin detemir, the difference was a little greater (1.2 kg; 95% CI –1.6 to –0.8) but again unlikely to be clinically significant\(^\text{13}\).

Summary
The systematic review did not identify any robust data on the effect of long-acting analogues on outcomes such as mortality, morbidity or quality of life\(^\text{13}\).

In the absence of evidence to suggest the superiority of insulin analogues over NPH insulin with respect to improved safety, glycaemic control or reduction of long-term diabetic complications, a cautious approach to their prescribing is advised\(^\text{15}\).

Statement 3
NPH insulin is not as effective as insulin degludec in HbA1c reduction, causes more frequent and severe hypoglycaemia, and causes more weight gain in those diagnosed with Type 2 diabetes.

No published studies were identified comparing insulin degludec (long-acting insulin analogue) with NPH insulin and no studies were identified that measured patient orientated efficacy outcomes\(^\text{16}\).

Statement 4
Analogue insulin works better than NPH insulin in certain ethnic backgrounds.

No published studies were identified that evaluated the efficacy or safety of insulins on the basis of ethnicity.
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Statement 5
GLP-1 analogues (exenatide, liraglutide, lixisenatide) can take the place of insulin in Type 2 diabetes.

GLP-1 analogues work on different pathways within the body. They can reduce appetite, regulate gastric emptying and enhance glucose dependent insulin secretion\(^{10}\). When combined with diet and exercise interventions, reductions in HbA\(_{1c}\) and weight can be achieved however in practice we do not see this in all patients\(^{5}\). Insulin on the other hand is effective at reducing HbA\(_{1c}\) levels irrespective of the level beta cell function\(^{7}\). Studies have shown that after nine years of diagnosis, a substantial number, possibly the majority of patients will need the addition of insulin therapy\(^{17}\).

No published studies were identified that compared liraglutide/lixisenatide with NPH insulin. The comparative data below are for exenatide and insulins:

**Glycaemic control**
When glycaemic control with exenatide is compared with various insulin regimens, the results are similar, suggesting non-inferiority, although very few studies evaluated NPH insulin and the issue of non-optimisation of the insulin treatment remains a concern. Furthermore, long term data are not available\(^{13}\).

**Weight**
Most studies have reported weight loss with exanatide compared with insulin although in routine care, this has not always been demonstrated\(^{13}\).

**Other outcome data**
No studies evaluating other mortality or cardiovascular data were identified\(^{13}\).

**Hypoglycaemia**
Hypoglycaemia is perceived to be less of a problem with exanatide, but the differences in the trials were not marked\(^{13}\).

Both insulin and GLP-1 analogues have their individual place in the pathway of the management of hyperglycaemia and choice of agent should be directed by patient factors\(^{5}\).

In the right patient at the right time, GLP-1 analogues are important adjuncts to other oral hypoglycaemic agents (and insulin in some patients), and can support both weight loss and HbA\(_{1c}\) reduction\(^{8}\).

However, GLP-1 analogues cannot be used instead of insulin in those patients that require insulin. Thinking about the principles of the right time and the right patient, it is incredibly important that we identify the right diabetes treatment to be given to the patient and review on a frequent basis in order to ensure optimal outcomes\(^{7}\). SIGN guidance emphasises the need to apply careful clinical judgement in those people with a long duration of Type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years) as these individuals are poorly represented in published studies, and to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 analogues\(^{7}\).
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Common patient barriers and perceptions regarding insulin therapy and suggestions of how to address:

Common barriers

• Needle phobia
  Concern or fear about injecting insulin is common but true needle phobia is rare. Advise patients that insulin injections are not considered painful and are usually less uncomfortable than the finger-pricking performed for blood glucose monitoring.[9]

• Weight gain
  This is a common adverse effect of insulin treatment and can increase the person’s body weight by 2–4 kg. Weight gain can be minimised by appropriate lifestyle and dietary changes and continuing with metformin (if tolerated).[6] A number of studies have shown there is less weight gain when started on a basal insulin regimen than on a biphasic or basal bolus regimens.[9][20].

• Fear of hypoglycaemia
  Offer reassurance that most episodes of hypoglycaemia can be self-managed. Additionally hypoglycaemia is minimised as patients are initiated on a low dose of insulin, with gradual dose titration. An education package provided to individuals who start insulin may also go through management and prevention of hypoglycaemia.[9].

• Driving guidelines
  The Driver and Vehicle Licensing Agency (DVLA) highlight the regulations in place for those people with Type 2 diabetes and who use insulin. Using insulin does not automatically mean people with Type 2 diabetes won’t be able to drive. A number of factors are taken into consideration including the type of licence held, frequency and severity of hypoglycaemia and presence or absence of any eye complications.[5]. The healthcare professional initiating the insulin will discuss current driving needs and provide individual advice on DVLA requirements. A guide for healthcare professionals can be downloaded from here.

Common perceptions and discussion points

Perception 1
Diabetes has become worse, or is a more serious disease if you are started on insulin

Perception 2
Insulin treatment is a sign of personal failure to manage the condition

Discussion points:

• Type 2 diabetes is a progressive disease and over time the body produces less insulin. As less insulin is produced by the body, more medication and lifestyle changes will need to be made to control HbA1c levels.

• There are many effective therapies for the management of Type 2 diabetes, including insulin.

• Insulin treatment is the next logical step in treatment when other diabetes therapies are not controlling glucose levels or where we think insulin would be the best option for the patient. Therefore the right time for insulin will differ in each individual.

• Insulin should not be seen as the last resort in optimising glycaemic control or as failure by the patient to control their diabetes. Insulin should be seen as an option in care to optimise glycaemic control to prevent longer term complications.
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Perception 3
Insulin treatment will adversely impact on their lifestyle and will be inconvenient

Discussion points:
• There are lots of different insulin preparations and regimens available.
• The healthcare professional starting insulin will look at appropriate insulin regimens for the individual, taking into account their lifestyle, driving requirements and occupation.
• It is possible that insulin will be started as a once-daily insulin at night time with minimal need for blood glucose testing.

Perception 4
Insulin treatment leads to complications such as leg amputations and blindness. When my “Dad started insulin, he then went to hospital and lost his foot”

Discussion points:
• Complications are caused by high blood glucose levels over a long period of time.
• Insulin, along with other medications used to reduce HbA1c levels help to reduce the complications by controlling blood glucose levels.
• If we can control blood glucose levels effectively over time, we can reduce complications.

Perception 5
Family and friends treat you differently if you are on insulin

Discussion points:
With consent from the person with Type 2 diabetes, carers and family members would be welcome to attend appointments and education sessions to learn more about Type 2 diabetes and how to support family members/people they care for.


5. Health Innovation Network Clinician Opinion


