

Insulin therapy: Indication and initiation

At a recent lunch symposium, Dr Norman Chan highlighted the importance of controlling diabetes to prevent complications. He also discussed the role of insulin in the management of patients with diabetes.



Dr Norman Chan
Specialist in Endocrinology
Clinical Director of Qualigenics Diabetes Centre
GenRx of HKR International, Hong Kong

Targeting well-controlled diabetes

Uncontrolled diabetes can lead to microvascular and cardiovascular complications resulting in significant morbidity and mortality. The United Kingdom Prospective Diabetes Study (UKPDS) showed that controlling glycosylated haemoglobin (HbA_{1c}) at 7.0% compared with 7.9% reduced the risk of complications during 10 years of follow-up.¹ The main benefits were for microvascular complications, particularly nephropathy and neuropathy. Overall, the microvascular complication rate was decreased by 25% (p=0.009).

In 2006, the American Diabetes Association and the European Association for the Study of Diabetes published a consensus statement, in which they provided an algorithm for the management of hyperglycaemia in type 2 diabetes.² After diagnosis, the algorithm recommended lifestyle interventions and first-line treatment with metformin. If metformin failed to control HbA_{1c} at 7%, then the algorithm provided three different ways to manage the patient: adding sulfonylurea, initiating basal insulin or adding glitazone. If HbA_{1c} levels remained uncontrolled, third-line treatment options involved adding drugs that had not already been added. Dr Chan commented that insulin may be considered for many of these patients.

Other classes of diabetes treatments are now available, making the 2006 algorithm out of date. A revision of the consensus statement was published in early 2009.³ The new algorithm takes into consideration the growing clinical experience and evolving efficacy and safety data with novel classes of medications. The algorithm is divided into two panels depending on the level of evidence available to support their use. Tier 1 includes well-validated therapies and is almost entirely based on results from the UKPDS. As before, lifestyle and metformin are recommended as first-line treatment. If first-line treatment is not successful, then sulfonylurea or basal insulin should be added. Intensive insulin is needed if basal insulin plus sulfonylurea fails.

Tier 2 is not as well validated as there appears to be a lack of robust, well-powered clinical studies to support it. This pathway includes glitazone or glucagon-like peptide-1 (GLP-1) agonists as second-line treatment options. If diabetes remains uncontrolled, then other drugs that have not been added can be used. Ultimately, if the patient still does not achieve an HbA_{1c} level of 7%, insulin therapy is indicated.

Insulin: A therapeutic option for many patients

Traditionally, type 2 diabetes has been managed in a step-wise fashion with insulin reserved as a last resort after failure of combination oral therapy. However, Dr Chan suggested that not all patients should follow this path. Every patient has a slightly different presentation, and there are some circumstances under which patients should be given insulin earlier.

The question remains as to which patients require insulin therapy. The two obvious groups of patients are those with type 1 diabetes and those with an acute metabolic complication, such as diabetic ketoacidosis or hyperosmolar nonketotic coma (HONK). In patients with type 2 diabetes, insulin is required after failure of oral hypoglycaemic agents or when oral agents are contraindicated (eg, in renal failure). Short-term insulin therapy may also be required in patients whose diabetes is normally well controlled with oral treatment, but suffer from acute hyperglycaemia due to an acute severe illness. It may also be required peri-operatively in patients who have less-than-ideal control with oral agents. These patients can be switched to insulin before the operation, and then converted back to oral agents afterwards.

Oral hypoglycaemic agents are not recommended for pregnant women because blood glucose levels are generally not tightly controlled in these patients. It may also be logical to use insulin beforehand in women who are trying to become pregnant since they will need to be switched to insulin once they conceive.

Some studies suggest that insulin treatment after myocardial infarction can reduce the mortality rate in these patients. Insulin should be used acutely after the event when blood glucose is unstable. After that, patients should be re-evaluated to assess whether they should be switched to oral agents or continue with long-term insulin therapy.

Figure 1. The physiological insulin profile⁴

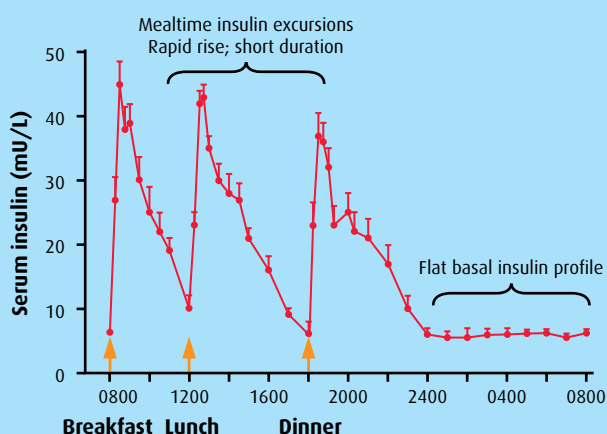
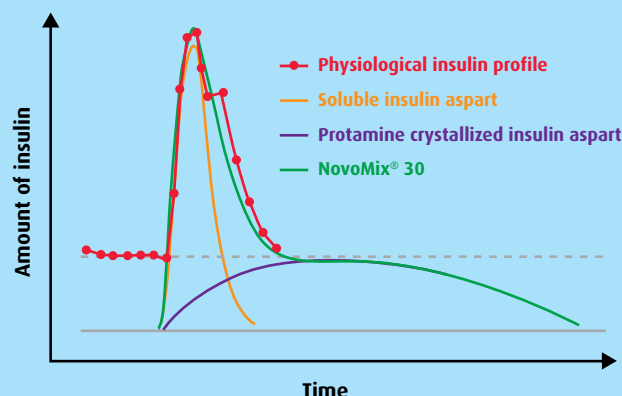


Figure 2. The dual-release insulin concept



Using insulin to mimic a physiological response

Insulin therapies are divided into three categories depending on their time-activity profile: short-acting, intermediate-acting or long-acting. When treating patients with diabetes, the goal is to mimic the normal physiology of insulin production (Figure 1). Normally, a small amount of insulin is produced, even in the fasting state. This is referred to as the basal insulin level. After meals, there are three peaks each for breakfast, lunch and dinner. These peaks correspond to the pancreas producing insulin to reduce the postprandial blood glucose level. This physiological insulin profile can be simulated using a basal bolus insulin regimen. Long-acting insulin gives 24-hour cover and fast-acting insulin provides a bolus dose for postprandial control.

Intermediate-acting insulin has a peak effect around 6 to 8 hours, which can cause hypoglycaemia in some patients. Insulin detemir (Levemir®, Novo Nordisk) is a long-acting insulin with a smooth time-activity profile and causes less hypoglycaemia when compared to traditional neutral protamine Hagedorn (NPH) insulin.

NovoRapid® (Novo Nordisk) is a newer insulin analogue (insulin aspart) that begins working immediately after injection. The advantage is that patients can inject at the start of the meal. By comparison, other fast-acting products, such as Actrapid® (Novo Nordisk), need to be injected 20 or 30 minutes prior to eating, which can sometimes be difficult for patients to predict. NovoRapid® reaches peak effect at about 1 hour and then its effects fade quickly over the next few hours so that its levels are very low at the time of the next injection or the next meal. As a result, NovoRapid® lowers postprandial plasma glucose and are associated with few hypoglycaemic episodes. It also reduces HbA_{1c} levels in type 2 diabetic patients treated with a sulfonylurea.

NovoMix 30® (Novo Nordisk) is a dual-release insulin, with both a basal component and a rapid-acting component. It is made

from insulin aspart, with 70% as crystallized protamine. The dual-release insulin provides control on both postprandial and fasting glucose (Figure 2). According to Dr Chan, this formulation is a good choice for patients who want to minimize the number of injections, particularly if they have relatively good fasting glucose levels.

The dose of insulin is usually between 0.4 and 0.7 units per kilogram per day. Insulin should be injected in areas with adipose tissue such as the abdomen, thighs or buttocks. Some patients prefer to inject it into their arms. It should be noted that absorption is slower when the injection is given lower down the body. For this reason, Dr Chan prefers for long-acting agents to be injected in the thighs or buttocks and fast-acting agents in the arms or abdomen. Injection sites should be rotated within each region.

Insulin therapy should be used with caution in elderly patients, obese type 2 diabetic patients, visually impaired patients and patients who do not monitor their blood glucose at home.

Conclusion

Patients with well-controlled diabetes (HbA_{1c} ≤7.0%) suffer less microvascular and cardiovascular complications. For many patients, insulin therapy is required to achieve adequate blood glucose control. The goal is to mimic the physiological insulin response. Basal insulin can be achieved with once-daily injections with long-acting insulin products such as Levemir®. Bolus injections at meal times with fast-acting products such as NovoRapid® simulate the pancreatic response to postprandial blood glucose levels. The availability of good-quality insulin products with a low risk of hypoglycaemia allows patients to be treated to target.

References

1. UK Prospective Diabetes Study Group. *Lancet* 1998;352:837-53.
2. Nathan DM, Buse JB, Davidson MB, et al. *Diabetes Care* 2006;29:1963-72.
3. Nathan DM, Buse JB, Davidson MB, et al. *Diabetes Care* 2009;32:193-203.
4. Kruszynska YT, Home PD, Hanning I, et al. *Diabetologia* 1987;30:16-21.