The Health Foundation
Inspiring Improvement

Managing the risks of commencing insulin therapy for patients with type 2 diabetes

Laila King

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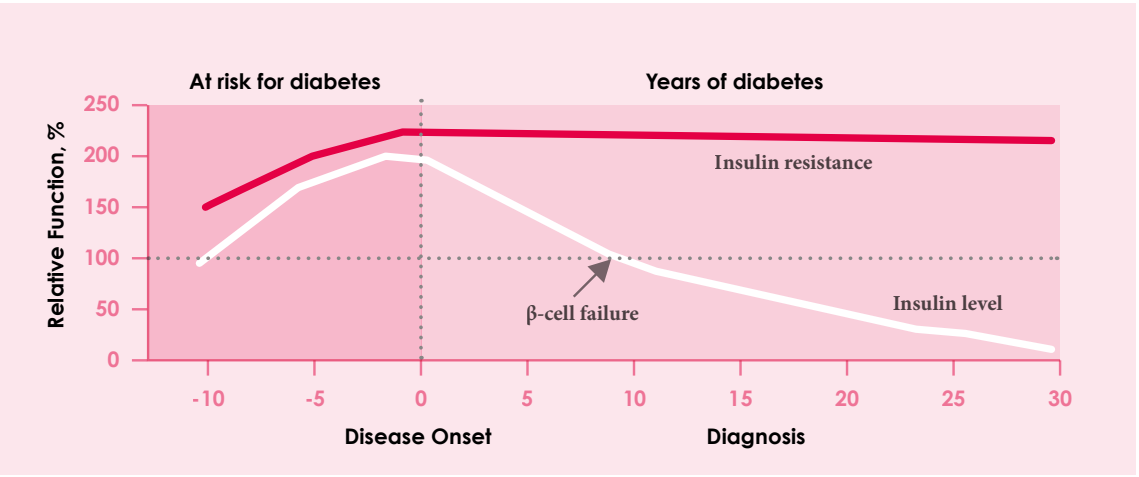
Insulin is a remedy primarily for the wise, and not for the foolish, whether they be patients or doctors. Everyone knows it requires brain to live long with diabetes, but to use insulin successfully requires more than brains.

Elliott Joslin, 1923

Whether or not it is due to these words written by Dr Joslin, 90 years ago, the idea of starting insulin therapy continues to provoke great fear in the hearts and minds of many primary care clinicians in the UK. Yet insulin is the oldest of all glucose-lowering therapies and the only one that occurs naturally in humans and theoretically has no upper dose limit.

Figure 1 illustrates the essential deficit of insulin at the time of diagnosis – otherwise, hyperglycaemia above the range of current diagnostic levels would not occur. This figure, therefore, highlights the rational, logical use of insulin as early as at diagnosis to rest the exhausted, decompensated beta cells. In several trials this has been shown to allow many people to put their dysglycaemia into drug-free remission for a considerable length of time, hence delaying or preventing vascular complications.

Figure 1. Progression of type 2 diabetes mellitus.[1]



The known risks associated with insulin therapy include weight gain and hypoglycaemia. Healthcare professionals have concerns for their patients' safety, acknowledging their own lack of expertise and the time taken to educate each patient and titrate their changing dose requirements.

Conventional guidelines for type 2 diabetes (including NICE 2009[2]) recommend insulin initiation for patients for whom oral anti-diabetic drugs have failed to maintain near normal glucose control. Accordingly, management of patients with type 2 diabetes remains woefully inadequate with ~60% of patients spending over 10 years at HbA1c levels above 7% (53 mmol/mol). Consequently, nearly 80% of NHS annual diabetes care spending (total £12 billion in 2012) goes into treatment of diabetes complications.

In contrast to such guidelines that relegate insulin use in type 2 diabetes to the last resort, new data is accumulating to recommend insulin therapy much earlier in the hyperglycaemic continuum, even at diagnosis of type 2 diabetes. This evidence suggests that short term, 2–3 week insulin therapy on diagnosis, while the patient still has functioning beta cells and intact counter regulatory mechanism (glucagon and adrenaline), can halt the disease progress and, in many patients, restore normoglycaemia for several years. In these patients, hypoglycaemia and weight gain simply do not occur with insulin.

In contemporary clinical practice, insulin therapy is often delayed until the patient with type 2 diabetes is highly vulnerable to the risks of and from hypoglycaemia due to:

- longer duration of diabetes (loss of beta cells and connectivity to alpha cells)
- increasing age and frailty
- deteriorating renal and cognitive function
- autonomic neuropathy resulting in hypoglycaemic unawareness (lack of warning symptoms)
- advanced micro- and macro-vascular complications.

Starting exogenous insulin therapy at such an advanced stage of the disease inevitably means having to use large doses of insulin. Subcutaneously injected insulin results in non-physiological hyperinsulinaemia in the peripheral tissues and causes enhanced storage of fat (= weight gain). In normal physiology, the insulin secreted from the pancreas goes straight to the liver where up to 80% is metabolised or used. The ratio of portal-vein-to-peripheral artery insulin is ~2:1. When insulin is given subcutaneously, it is necessary to create hyperinsulinaemia in the peripheral circulation to regulate the hepatic glucose production (portal-to-peripheral insulin ratio ~1:2).

In my experience, the risk of hypoglycaemia can be minimised by starting insulin therapy in type 2 diabetes in the following circumstances:

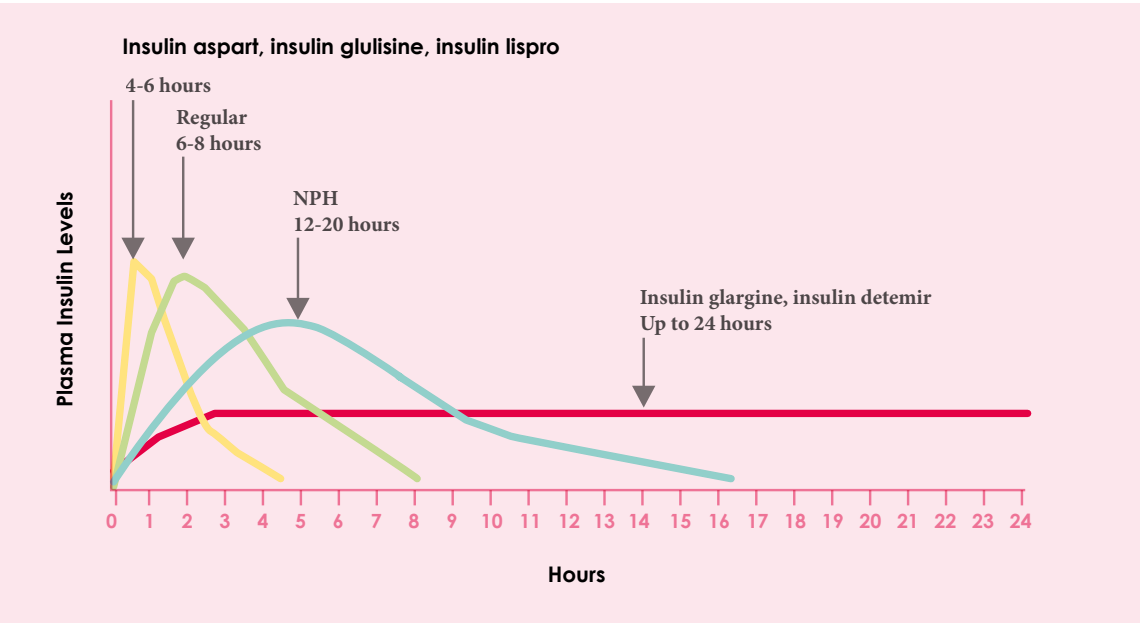
- at any point when glycaemic control is inadequate with HbA1c >7% (≥53 mmol/mol)
- as initial therapy in newly-diagnosed diabetes presenting with HbA1c ≥9% (≥75 mmol/mol)
- in a person with signs of metabolic decompensation (polydipsia, polyuria, blurred vision, paresthaesia, or unintentional weight loss)
- in young females planning pregnancy.

Here are some suggestions for how to start insulin simply and safely:

- starting once daily basal insulin 10 units or 0.2 units/kg/day (in lean individuals and the elderly) – 0.5 units/kg/day (in overweight persons) before bed
- checking renal function, especially in the elderly and frail (eGFR <30 – use caution in titration of dose)
- teaching the patient to check and record fasting blood glucose (FBG) every day, and to self-titrate the basal insulin dose until FBG level 5–7 mmol/l is reached
- self-titration can be achieved by increasing the dose by 2 units every 3 days OR by 1 unit every day
- avoiding excessive basal insulin dosing: the basal dose should not exceed >60 units/day, as absorption from a large pool of insulin becomes less predictable
- splitting the once daily basal insulin dose into twice daily dosing to avoid the risk of nocturnal hypoglycaemia, especially if the patient is also taking a sulphonylurea tablet before the evening meal: the sulphonylurea (such as gliclazide) peaks in ~5–6 hours and hence coincides with the peak action of human NPH insulin and analogue insulin glargine if taken before the evening meal (see figure 3)
- choosing analogue basal insulin (glargine, detemir, degludec) instead of human NPH insulin (eg Insulatard, Humulin I).

Figure 2 may help the reader to visualise both the peak action and the duration of action of the different insulin types which are referred to in the text: for example analogue basal long-acting insulin in contrast to human NPH insulin, which has a pronounced peak – increasing the risk of hypoglycaemia around 4–6 hours into its action. Also, fear of this risk increases the risk of weight gain, as patients may resort to protective snacking.

Figure 2. Time–action profiles of insulin products.[3]



Basal insulin in combination with incretin based therapy

Currently, all DPP-4 inhibitors, as well as exenatide BD, liraglutide, and lixisenatide, are approved for use with basal insulin in type 2 diabetes. Such complementary combination does not increase the risk of hypoglycaemia and would have beneficial effects on weight. Basal insulin controls fasting and pre-prandial glycaemia by suppressing hepatic glucose production, while the incretin based therapy controls post-prandial glucose spikes by stimulating glucose dependent insulin secretion, reducing post-prandial glucagon secretion, slowing gastric emptying, and decreasing food intake.

The tripartite Figure 3 aims to reinforce the logic of fixing fasting hyperglycaemia with a simple, once-daily basal insulin (the 'fix the fasting first' idea) and then adding a GLP-1 agonist to lower post-prandial hyperglycaemia – safely, without hypoglycaemia and without weight gain risks. Conventionally, pre-prandial insulin has been used but with the known issues of demanding dose adjustment and weight gain.

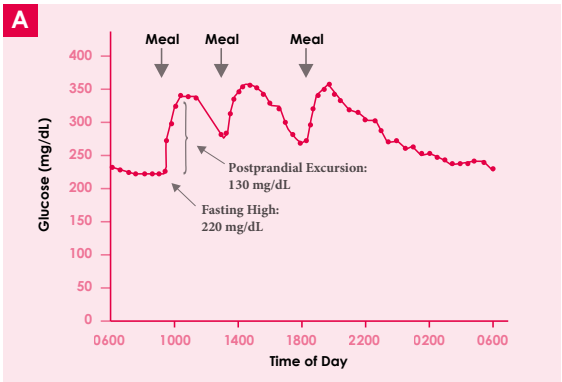
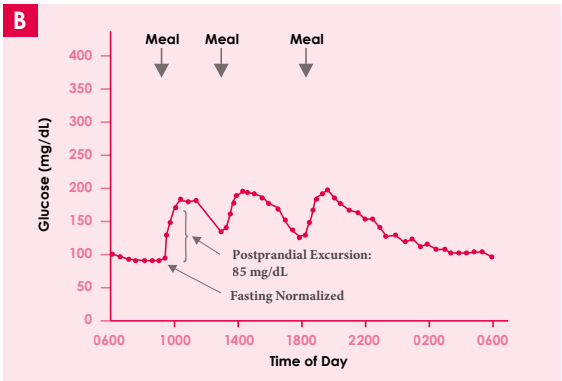
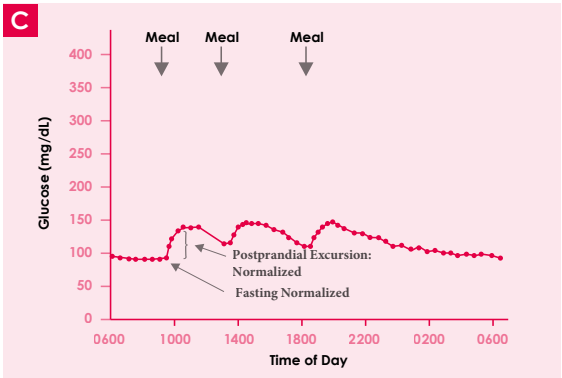


Figure 3. A: Uncontrolled hyperglycaemia in type 2 diabetes.



B: Fasting hyperglycaemia corrected using basal insulin.



C: Fasting hyperglycaemia corrected using basal insulin, and post-prandial hyperglycaemia normalised with bolus insulin OR GLP-1 therapy.[4]

I truly believe in a patient-centred approach. To quote the father of modern medicine, Sir William Osler: "It is much more important to know what sort of a patient has a disease than what sort of disease a patient has." I emphasise to every patient diagnosed with this heterogeneous, complex, progressive disorder that the goal is not to stay off insulin, but to achieve and maintain as near normal glucose levels as possible. Individualised treatment includes consideration of the patient's overall health status, weight issues, glucose patterns, comorbidities, and preferences.

As clinicians, it is time we recognised the unacceptable burden – in human as well as financial cost terms – resulting from not treating glucose toxicity early, effectively, and efficiently in patients with type 2 diabetes, without increasing their morbidity and mortality by detrimental escalation in their BMI and incapacitating surge in episodes of hypoglycaemia.

The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler

Further reading

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3 From Hirsch IB. Insulin analogues. *N Engl J Med* 2005, 352 (2):174–83

4 Adapted from Hirsch IB, Bergenstal RM, Parkin CG, Wright E Jr, Buse JB. A Real-World Approach to Insulin Therapy in Primary Care Practice. *Clinical Diabetes* 2005, 23 (2)

5 Adapted, with permission of the American Diabetes Association, from DeFronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009, 58 (4): 773–95