UNIT NO. 5

STARTING AND MAINTAINING INSULIN THERAPY FOR A PATIENT

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ABSTRACT

Type 2 diabetes is a disease of dual pathology: namely, insulin resistance and beta-cell secretory dysfunction. Insulin resistance occurs many years before the onset of diabetes with a tendency to worsen and then stabilise. Later on in the disease, the beta cell secretory ability starts to fail and the glucose level therefore rises. Hence, the majority of patients with type 2 diabetes require insulin at some stage. Insulin should be considered at the time of diagnosis if patients are very symptomatic, have significant weight loss, present with an acute complication (such as diabetic ketoacidosis or hyperosmotic nonketotic coma) or are pregnant. Insulin should also be added in patients on oral antidiabetic agents who are not achieving therapeutic goals. Both the doctor and the patient need to overcome the barriers to insulin therapy which is the greatest hurdle to better glycaemic control. The simplest way to commence insulin is to start with a basal bolus regimen and intensify with prandial insulin if required. Many of the available insulins can be used for basal insulins; Insulatard, Humulin N, Glargine or Detemir. Weight gain may occur with insulin therapy that is associated with improved metabolic efficiency, but this can be tackled with better dietary counseling.

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INTRODUCTION

Why should we treat patients to goal?

The goals of treating hyperglycaemia are to reduce any acute decompensation and more importantly, to prevent the long-term complications that plague patients with diabetes, which are the commonest causes of significant morbidity and mortality in patients with this disease. The evidence that long-term complications are due either directly or indirectly to the degree of hyperglycaemia, and to the duration of that hyperglycaemia, is clear. The proof of this has come from the Diabetes Control and Complications Trial (DCCT)[1] and the United Kingdom Prospective Diabetes Study (UKPDS)[2]. The relationship between HbA1c levels and the development of retinopathy, nephropathy, and neuropathy clearly shows that with higher HbA1c levels, there is an increased risk of the development of these complications, and any reduction in HbA1c results in a decrease in the risk for these complications. The follow-up data shows that this also holds true for macrovascular disease.

After the DCCT was completed, the patients were followed up in an observational study called the Epidemiology of Diabetes Interventions and Complications study (EDIC)[3]. In this study patients were encouraged to do intensive insulin therapy. Patients previously assigned to the conventional group reduced their HbA1c to about 8%, but the HbA1c increased in the intensive group, also to 8%, so in the end both groups had similar HbA1c levels. Nevertheless, the complications of retinopathy, nephropathy, and neuropathy continued to increase in the patients who had been in the prior conventional-therapy group compared with those who were in the intensive-therapy group. This proved that intensive glycaemic control with near-normalisation of blood glucose levels as early as possible with diabetes has consequences with respect to progression of these complications in the long term.

Why do patients with type 2 Diabetes need insulin?

Type 2 diabetes is a disease of dual pathology 1) insulin resistance and 2) beta-cell secretory dysfunction. For the majority of patients who develop this disease, insulin resistance occurs many years before the onset of diabetes with a tendency to worsen and then stabilise[4,5,6].

Initially the beta cell compensates for this increasing insulin resistance by increasing insulin secretion and thereby, maintaining glucose in the normal range.

But later on in the disease, the beta cell secretory ability starts to fail and the glucose level therefore rises. By the time diabetes is diagnosed, patients have lost almost 50% of their beta-cell secretory function.

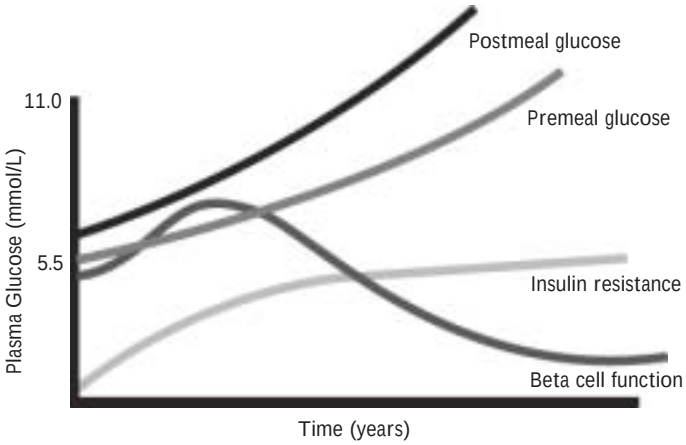

Fig 1. Natural History of Type 2 Diabetes

We know from UKPDS data, that regardless of what medication (including insulin) the patient received, more and more medications were required with time to maintain hemoglobin HbA1c concentrations at goal. So ultimately, the majority of patients end up requiring insulin therapy.

Insulin is the most effective of diabetes medications in lowering blood glucose. Unlike the other blood glucose–lowering medications, there is no maximum dose of insulin

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beyond which a therapeutic effect will not occur. Relatively large doses of insulin (≥1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower HbA1c to goal.

INDICATIONS FOR INSULIN IN TYPE 2 PATIENTS

Insulin should be considered at the time of diagnosis if patients are very symptomatic, have significant weight loss, present with an acute complication (such as diabetic ketoacidosis or hyperosmotic nonketotic coma) or are pregnant.

Insulin should also be added in patients on oral antidiabetic agents who are not achieving therapeutic goals. This could include the use of a basal insulin to patients sub-optimally controlled on 2 or possibly 3 oral hypoglycaemic agents (and in future maybe 4), but would extend to include prandial insulin if postprandial glucose concentrations are not adequately controlled on oral insulin secretagogues.

BARRIERS TO INITIATING INSULIN THERAPY

For patients with type 2 diabetes, adding insulin to an oral agent regimen will almost always lead to some improvements in glycaemic control. But there are many reasons why insulin is not initiated. Often it is not an absolute contraindication, rather there is significant resistance both from the patient as well as the doctor.

Doctors may worry that insulin might cause a worsening of insulin resistance, but clearly in patients who are hyperglycaemic, a reduction of glucose toxicity will actually improve that insulin resistance. Some doctors may be concerned that insulin will worsen cardiovascular risk. But we know from the DCCT and the UKPDS data, that reduction in glucose levels actually improves cardiovascular risk. Weight gain may occur with insulin therapy that is associated with improved metabolic efficiency, but this can be tackled with better dietary counseling. Hypoglycaemia is always a concern amongst doctors, especially the fear of an unhappy patient who encounters a severe hypoglycaemic event.

Certainly significant events can occur in patients with type 1 diabetes as they approach the optimum glycaemic goal, but it is far less common in patients with type 2 diabetes. Regardless, it should not stop us from achieving good glucose control as the benefit clearly outweighs the risk. Doctors may also engage in some wishful thinking that patients may lose weight and intensify their lifestyle treatments, but we know from practice that this is the exception rather than the rule. Doctors also worry about alienating and angering the patient by suggesting that they start on insulin therapy.

Understandably most patients oppose the notion of starting insulin therapy. The patient may deny the need to go on insulin, and keep wishing they will lose weight or that some other thing will happen to allow them to avoid starting insulin. They may default on their clinic appointments, knowing that insulin therapy is the next step. They worry that insulin use is time-consuming and involves adjusting some doses, and certainly are concerned about discomfort that may be associated with an injection. They may also be concerned about developing hypoglycaemic reactions to insulin. There are common misconceptions in our society, that being on insulin means their disease is now 'very serious' or that once on insulin therapy they will 'never get off it'. Patients in our culture also feel that they will be ostracised and look like a 'drug addict' needing to inject themselves all the time. But with adequate counseling and patient explanation, many of these fears can be addressed and overcome.

Once both the doctor and the patient overcome these barriers to insulin, the greatest hurdle to better glycaemic control will have been removed.

PHYSIOLOGICAL INSULIN SECRETION

Reviewing the physiological secretion of insulin allows us to better understand why we do the things we do when we are instituting insulin therapy.

There is continual basal glucose production by the liver even in the fasting state. The extent of that basal glucose production is controlled by a certain amount of basal insulin secreted by the islet cells. Once food is consumed, glucose is absorbed from the intestine so that glucose levels rise; almost immediately, there is a rise in islet cell insulin secretion, and this will then peak as the glucose levels peak. Once the absorption of glucose from the intestine starts to fall and glucose exits out of the bloodstream into the tissues as a result of adequate insulinisation, then so does insulin secretion decrease from the pancreas, and levels come back down to baseline between meals.

So insulin should be considered in 2 parts 1) basal insulin secretion that suppresses glucose production overnight and between meals, which is relatively constant throughout the day, and 2) mealtime or prandial insulin, which is insulin released with the meals by the pancreas.

Patients with type 2 Diabetes have an elevated basal glucose level and also an exaggerated rise in glucose post meals. Both these issues may need to be addressed.

BEGIN BY REPLACING BASAL INSULIN

This is the easiest and most effective way to bring down a patient's HbA1c with insulin. Many of the available insulins can be used for basal insulins; Insulatard, Humulin N, Glargine or Detemir. The ideal basal insulin is one that is relatively constant throughout the day. Glargine best fulfils this criteria. Detemir has a slight peak effect and does not last for the full 24 hours, whilst Insulatard and Humulin N have a significant peak at 4 hours and last for about 8 hours duration. However, the latter drugs are far cheaper than Glargine in our local market.

When a patient's HbA1c is not at target, get the patient to check their fasting glucose levels on several occasions. If the fasting glucose is elevated, it makes sense to lower this glucose, since lowering the fasting glucose towards the normal range will automatically lower the postprandial glucose excursions. In this situation, addition of basal insulin, usually given at night to lower the fasting glucose, would be appropriate. After the institution of this basal insulin, glucose levels need to be checked again and the dose of insulin adjusted to ensure the fasting glucose level goals are met.

A rough guide would be to add a single evening dose of NPH or glargine or detemir at bedtime, starting with 10 units or 0.1 U/kg, and adjust the dose according to the fasting glucose concentration using a simple algorithm with insulin adjustments being made every 3 to 5 days. If the fasting glucose exceeds 6.7 mmol/L (120 mg/dL), increase the dose of basal insulin by 2 units. If it exceeds 7.8 mmol/L (140 mg/dL), increase by 4 units, and if it exceeds 8.9 mmol/L (160 mg/dL), increase by 6 units.

Once the fasting glucose level is at target, continue the treatment for the next 6-8 weeks and then repeat the HbA1c. You may well find that this simple addition of once a day insulin will bring the patient back to goal in terms of their HbA1c. In fact in the Treat-to-Target study (which utilised either NPH or Glargine) approximately 60% of patients achieved target HbA1c concentrations of less than 7%, just by the addition of basal insulin alone[7].

The oral agents should be continued at the same dosage if only basal insulin is instituted.

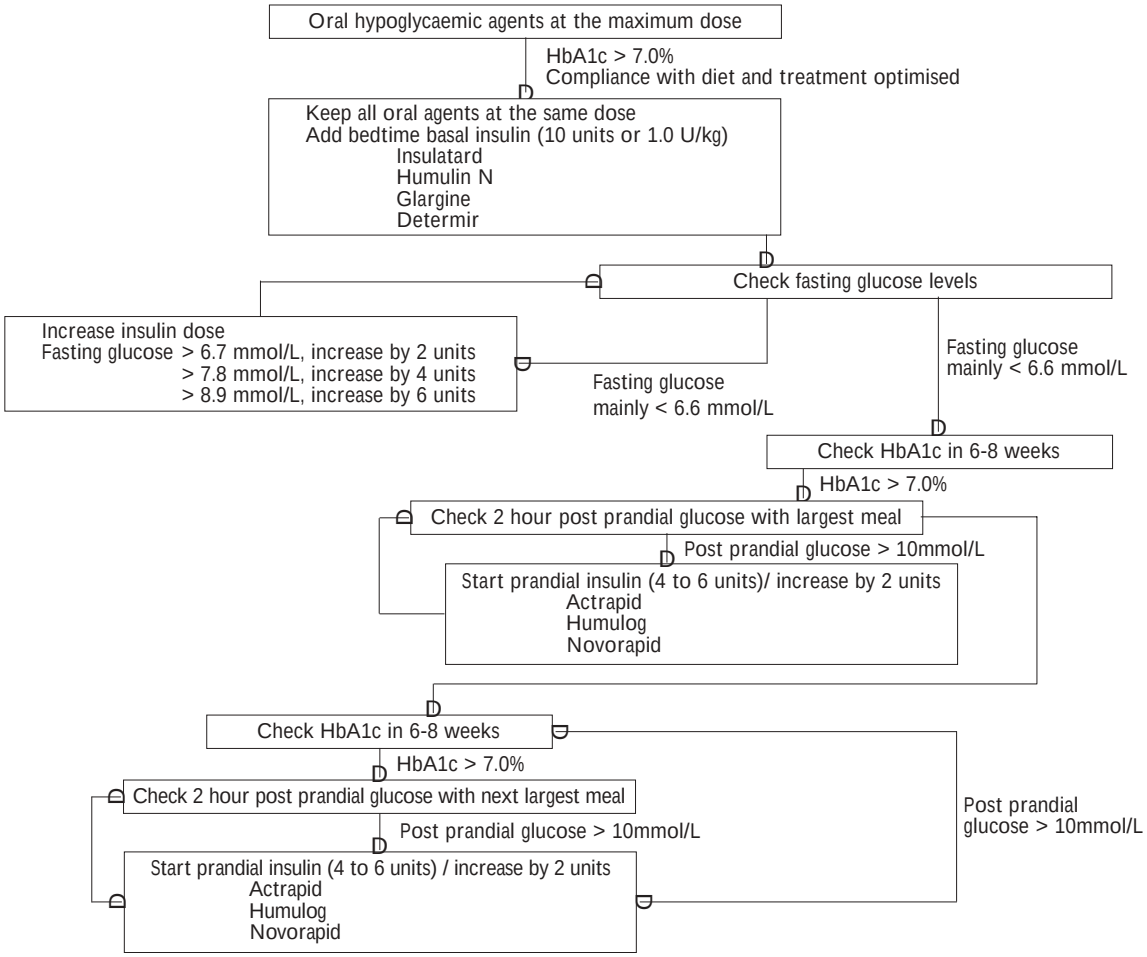
STEP UP TREATMENT BY INTRODUCING PRANDIAL INSULIN

If the fasting glucose levels are at goal but the HbA1c is still not, then the problem most probably lies with the post meal glucose levels. In this case, insulin therapy will need to be intensified by the addition of prandial insulin. These include Novorapid, Humulog, Actrapid and Humulin R. The ideal prandial insulin would have the desired characteristics of having a predictable profile when you inject it, a relatively rapid onset of action, and also a short duration of action, so it doesn't carry over to the next meal. This would allow precise dosing with the reduced risk of hypoglycaemia. Novorapid and Humulog have a fast onset of action and least hang-over to the next meal, however they are also significantly more expensive than Actrapid or Humulin R.

Practically, the best way to do this is to ask the patient to check their blood glucose levels 2 hours after their largest meal. If this is not at goal then prandial insulin before the largest meal should be instituted and adjusted till target glucose levels are achieved. This exercise can be repeated subsequently for all the meals, tackling one meal time at a time. However, not all patients will require postprandial insulins with all meals from the outset. Attacking post dinner hyperglycaemia may also have implications to the basal dose of insulin required at night. If the night time glucose is lowered by pre-dinner insulin, then the amount of basal insulin cover may also need to be lowered.

Once the patient has advanced to 2 or more injections of insulin a day, and if one is using rapid-acting or prandial insulin, then stopping oral insulin secretagogues may be considered. The insulin sensitisers should be continued as this usually helps to lower the effective dose of insulin required.

Fig 2. Algorithm of insulin treatment in Type 2 patients



PREMIXED INSULIN

If both basal and prandial insulin are required, it may be more convenient to prescribe premixed insulin, which already have both prandial and basal insulin in one. The disadvantage of these fixed mixed doses of insulin is that, indeed, they are fixed, and not every patient responds best to these fixed doses. Sometimes, different proportions of NPH and short- acting insulin are required.

ADDRESSING THE PROBLEM OF HYPOGLYCAEMIA

The major consequence of trying to be aggressive at managing glucose levels is the increased risk for hypoglycaemia. The more we aim for euglycaemia the higher the risk of hypoglycaemia.

ACUTE WORSENING OF GLUCOSE CONTROL

From time to time, treatment regimens need to be looked at and modified as patients' life conditions change. In particular acute worsening, which may occur over hours to days, should be investigated. The most common reason is intercurrent illness such as an underlying infection — commonly a urinary tract infection or other systemic infection that may cause a problem. Acute worsening of glycaemic control may be a clue that something else major is happening.

Sometimes acute worsening is due to the fact that the insulin may have degraded before its expiry date. The new modified insulins seem to be a little less stable and should be kept in the refrigerator. Sometimes it will degrade if left out in room temperature (particularly in our warm climate) or in areas where there's a rise in temperature, even before the end of the month.

In patients with poor vision accuracy of technique may be a problem. They may have problems seeing the syringes accurately, or sometimes the needle tip may be above the level of the fluid in the bottle as they are drawing the insulin into the syringe. Therefore it is important to have their technique checked. A pen device may also be very helpful in this setting.

CONCLUSIONS

In summary, therefore, type 2 diabetes is a progressive disease and at this present time in medicine, it seems that insulin therapy is inevitable for the majority of our type 2 patients if we are going to have them at goal with regard to their blood glucose levels. Starting insulin is not complicated and most patients are able to achieve significantly improved glucose control with simple regimens.

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LEARNING POINTS

- **Insulin should be considered at the time of diagnosis if patients are very symptomatic, have significant weight loss, present with an acute complication (such as diabetic ketoacidosis or hyperosmotic nonketotic coma) or are pregnant.**
- **Insulin should also be added in patients on oral antidiabetic agents who are not achieving therapeutic goals. This could include the use of a basal insulin to patients sub-optimally controlled on 2 or possibly 3 oral hypoglycaemic agents (and in future maybe 4), but would extend to include prandial insulin if postprandial glucose concentrations are not adequately controlled on oral insulin secretagogues.**
- **Both the doctor and the patient need to overcome the barriers to insulin therapy.**
- **The simplest way to commence insulin is to start with a basal bolus regimen and intensify with prandial insulin if required.**
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