Insulin therapy in Type 2 diabetes

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Type 2 diabetes: a disorder of insulin deficiency

The current medical literature is heavily focused on insulin resistance in Type 2 diabetes, in part due to the recent introduction and promotion of the thiazolidenedione class of drugs as insulin sensitisers. It is important to keep in mind, however, that the primary abnormality is a loss of insulin secretion and that a major contributor to insulin resistance is hyperglycaemia secondary to insulin deficit. Type 2 patients are found at autopsy to have lost approximately 50% of beta cell mass secondary to accelerated apoptosis,[1] (obese Type 2 – 63%, lean Type 2 – 41%), and in prospective studies such as the UKPDS[2] a progressive loss of insulin and deterioration in glucose control is noted with increasing duration of disease. In observational studies about 4% of Type 2 patients per year require insulin therapy,[3] the 'secondary failure rate'. It is hoped that newer therapeutic agents such as thiazolidinediones (TZDs) or incretins will preserve beta cell mass and insulin secretion[4] and trials to assess this are in progress but, for the moment, in theory all patients with Type 2 diabetes will progress to severe insulin deficiency given an adequate duration of the disease.

When to start insulin?

Movement to insulin therapy occurs when treatment with lifestyle modification, exercise, weight loss and oral hypoglycaemic agents are no longer adequately effective and benefit is perceived for the patient in achieving tighter glucose control.

What are the benefits of tight glucose regulation?

There is now extensive evidence from prospective intervention studies that low blood glucose values are associated with a lower incidence and progression of microvascular damage. In the UKPDS the incidence of retinopathy and nephropathy was reduced by 37% for each percentage point reduction in HbA1c.[5]

The situation is not so clear for macrovascular events, the more common cause of morbidity and mortality in Type 2. To date, prospective interventional studies of glucose reduction have not produced a significant reduction in macrovascular event rates. This is not to say that macrovascular events are not linked with hyperglycaemia. In the Epic Norfolk study, a prospective population based study; HbA1c was an independent predictor for macrovascular events.[6] In the UKPDS[7] for each 1% reduction in HbA1c% there was a reduction of 14% for myocardial infarction, 12% for stroke and 16% for heart failure. Furthermore in the MRFIT study,[8] for any given combination of conventional macrovascular risk factors in a large group of males followed prospectively, the presence of diabetes multiplied the risk of a macrovascular event approximately threefold. The likelihood is that past intervention trials of glucose reduction in Type 2 have not been able to produce an adequate reduction in glucose values and sufficient separation between control and treatment groups. Nevertheless the consensus of expert groups such as the EASD, AACE, IDF, ADA and the NZ Guidelines Group is to advocate tight glucose control in addition to aggressive management of lipids and blood pressure.

The NZ Guidelines Group advocates an HbA1c% less than 7% for all patients, with a lower target where this may be achieved with safety for patients on metformin or TZDs alone.[9]

Is the HbA1c an adequate glucose control measure?

Whilst HbA1c % values provide simplicity and convenience in determining adequacy of glucose control, it is possible that post-prandial glucose values will be of greater importance to macrovascular events. HbA1c% measures are not sensitive to lesser degrees of glucose intolerance such as impaired glucose tolerance,[9] yet post load glucose values as seen in impaired glucose tolerance are pre-

dictive for macrovascular events.[10] Therefore reliance on the HbA1c alone without reference to pre- and post-meal glucose measures may be too insensitive.

There is a further concept to consider regarding glucose control in Type 2, namely that of glucotoxicity. There is evidence that accelerated glucose oxidation within the beta cell due to hyperglycaemia causes increased free radical formation which increases beta-cell apoptosis and insulin loss.[11] This raises the possibility that tight glucose regulation may preserve beta-cell function by reducing intracellular free radical release.

These considerations form the basis for the decision of the Waikato Diabetes Service to adopt a tighter glucose control target than HbA1c <7% alone for Type 2 diabetes, namely to achieve pre-prandial capillary glucose values less than 6.5mmol/L and two hour post-prandial capillary glucose values less than eight.

Should patients starting on insulin therapy be referred to a specialist centre?

Implementation of insulin therapy in Type 2 diabetes is desirably provided in primary care. A trained and experienced educator is necessary. This may be a visiting diabetes nurse specialist or alternatively a staff member, who has been trained and certificated by a diabetes specialist group to carry this out.

Pre-insulin patient assessment

Prior to moving to insulin therapy it is important to re-assess the patients management carefully. In particular it is important to assess physical exercise, knowledge and adherence to dietary targets, and compliance with medications.

Dietetic review

All patients should be reviewed by a dietitian with an expert knowledge of diabetes management, and where possible be tutored in carbohydrate counting. Concepts of glycaemic index can be included. Many patients will have little knowledge of carbohydrates beyond simple identification, and may be eating uncontrolled amounts in the belief that this is acceptable. Restriction of carbohydrate amounts to less than 80 to 90 grams at any one meal, and sourcing these from foods with a low glycaemic index may restore adequate glucose control. For those patients who are not able or do not wish to learn carbohydrate counting, it is possible for the dietitian to provide sample menus based on a modification of the meals the patient commonly prepares. The critical point is that dietetic review is essential if insulin therapy is to be implemented successfully with avoidance of excessive weight increase.

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How to choose an insulin regimen

Insulin therapy is selected to correct the two major abnormalities seen in poorly controlled Type 2 diabetes, namely increased overnight hepatic glucose output, as reflected in an elevation of the pre-breakfast glucose, and impaired nutrient dispersal after meals, as seen in an elevation of the post-prandial glucose values.[12]

Combined oral hypoglycaemic therapy with overnight long acting insulin

There is not a universal consensus on insulin treatment regimens in Type 2 diabetes, but a meta analysis of available studies[13] identifies a modest superiority of insulin plus oral hypoglycaemic agents over monotherapy with insulin, and a lesser weight gain when metformin is included in the regimen. This forms the basis for the commonly adopted practice advocated here to add insulin therapy overnight to correct fasting hyperglycaemia with continued oral hypoglycaemic therapy during the day. Where the post meal values continue to be elevated, pre-meal rapidly absorbed insulin is introduced.

Controlling overnight hyperglycaemia

A long acting insulin such as Protaphane (NovoNordisk) or Humulin N (Eli Lilly) is started at a dose of 0.3 units per kg of body weight. If and when funded in New Zealand, very long acting analogue insulins such as Lantus (Aventis) should be used as they provide a more consistently absorbed and constant diurnal basal insulin platform with a lesser frequency of hypoglycaemia.[14]

The insulin dose may be increased weekly in increments of 10% until the pre-breakfast capillary glucose is less than 6.5mmol/L or at least under 7mmol/L. The patient should carry out a 2am glucose measurement prior to any dosage increment to assess the safety of any further increment. If the 2am value is less than 5–6mmol/L then no further increment should be made.

If nocturnal low glucose values prevent adequate pre-breakfast control, then referral should be made to a specialist center.

Controlling post-prandial glucose values

Where the post-prandial two hour values exceed 8mmol/L (and certainly 9mmol/L) despite restoration of normoglycaemia pre-breakfast, our local practice is to add pre-prandial doses of rapidly absorbed analogue insulins such as Novorapid (NovoNordisk) or Humalog (Eli Lilly). These are commenced in a dose of one unit per 10 grams of carbohydrate in the meal, and adjusted based on the ensuing test results. Sulphonylureas are discontinued to simplify the patient's regimen but metformin is continued.

Twice daily pre-mixed insulin regimens

A number of patients will not want to take multiple doses of insulin, others will find it too complex, and yet others will be at a stage in their health where the primary goal of treatment is symptom relief alone. For these patients it is possible to implement a very simple insulin regimen of a twice daily dose of a premixed insulin (e.g. Penmix 20 – NovoNordisk). It can be started in a dose of 0.2 units/kg body weight pre-breakfast and 0.1 units/kg pre-dinner. The doses are then adjusted to achieve satisfactory capillary glucose values pre-breakfast and pre-dinner.

Education considerations

Some key issues should be covered in the patient's education, preferably with a family member present to help with understanding, safety, support and compliance.

- All topics covered should be recorded in the patient's file and signed and dated by the staff member who provides them.
- During the implementation period the patient should test and record their capillary glucose values pre-breakfast and two hours post meals.
- Clear instructions should be provided on insulin injection techniques whether with a syringe or pen injector. The patient should demonstrate practically their ability to draw up and administer a dose of insulin, and demonstrate their ability to alter the dose if directed.
- The patient should be aware of the storage conditions for insulin, the sites of administration, the need for site rotation, the action time characteristics of their insulins and their ideal relationship to food.
- The initiation doses should be provided to the patient in written form, preferably in their glucose record book, together with their glucose targets, agreed glucose test times and frequency of testing.
- Patients on a basal bolus regimen with both overnight and pre-meal insulin doses should be provided with an action plan for management of high values and be provided with an approximate insulin sensitivity ratio. All patients should be given written advice on dosage change limits for self initiated dosage changes.
- The patient must understand how to recognise hypoglycaemia, and how to treat it. The patient should be able to describe hypoglycaemia, when it is likely, how variation in insulin, food and exercise may contribute to this, and what effects it may have on their ability to comprehend instructions, drive a motor vehicle or operate potentially dangerous equipment.
- All patients who drive or use potentially dangerous machinery should be warned to be particularly careful when first moving to insulin therapy, and at times of dosage change.
- The interaction of alcohol and insulin should be covered, and the patient must be aware of the dangers the combination of alcohol and insulin poses for driving.
- The patient's driving licence categories should be reviewed by a staff member conversant with the guidelines issued by the Lands Transport Safety Authority, and the patient advised if the LTSA may impose restrictions on these. Ideally the patient should be provided with a copy of the relevant section of the LTSA guidelines. The need for capillary glucose testing prior to driving, the need to record glucose values, and the need to carry a rapidly absorbed form of glucose to correct hypoglycaemia must be emphasised. The capillary glucose test meter should have a memory to enable retrieval of date, time and value of glucose measurements.
- A family member should be taught how to draw up and administer glucagon and a prescription for this provided.
- All patients should be advised to procure a Medic Alert bracelet.

Follow-up

The person starting on insulin needs to have ready access to support and information on a daily basis in the first two to three weeks when implementing therapy.

Weekly review in the practice is needed until stable control is reached. The weekly review should include a measurement of weight. A total weight increase of three to five kg with insulin therapy may be expected, but more than this indicates a lack of dietary restraint and requires further dietetic review prior to any additional increment in insulin doses.

Capillary glucose testing frequency

There are no standards for capillary glucose testing frequency once stable control has been reached. This therefore needs to be agreed on an individual basis. Driving a vehicle really mandates a glucose test prior to any lengthy drive, and at subsequent two to three hourly intervals. For many Type 2 patients glucose values are quite reproducible from day to day, and testing pre-breakfast and two hours post-meals on three days per week is appropriate but should be increased to daily when unwell, when driving as mentioned, when unstable or during pursuits that might be expected to pose a risk for hypoglycaemia. This should be matched with a treatment action plan for the patient to implement in these circumstances.

Summary targets

Measurement	Target
HbA1c	<7%
Pre-breakfast capillary glucose	<6.5mmol/l
Post-meal capillary glucose	<8mmol/l

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Cochrane Conclusions

'The question whether insulin therapy in type 2 diabetes should be applied as monotherapy, or in addition to oral agents (combination therapy) is still a subject for debate. Guidelines on type 2 diabetes are conflicting about indications, regimen, and dosages of the possible treatment regimens, and most recommendations are not based on clear evidence. Overall, the results of this review are in accordance with the findings of other reviews. We found no evidence that insulin monotherapy (applied as a two or more injection scheme) is superior to a single bedtime injection of NPH insulin in addition to a common oral agent regimen over the duration of the trials studied. Therefore, insulin-OHA combination therapy should be considered a suitable simple starting point for most insulin-requiring type 2 diabetes patients. Since both physicians and patients are often inclined to delay the start with insulin, such a strategy might encourage the timely use of insulin. Presently, due to lack of studies it remains unclear whether such regimens with metformin alone are superior to the combination with a sulphonylurea.'

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'Stigma is still associated with depression. This was shown most clearly in these surveys by the ambivalence in consulting a family doctor. The respondents may be projecting their feelings on to their general practitioner when they say that doctors think that depressed patients are unbalanced or neurotic and therefore irritating or annoying...Doctors need to ensure that they do not stigmatise colleagues who suffer from depression or other forms of mental illness. Articles bringing this uncomfortable angle into the open are bound to help, but sadly not all people with depression feel confident enough to put their names to their experiences.'

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