

Global Guideline

for Type 2 Diabetes

Chapter 10: Glucose control: insulin therapy

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Recommendations

■ Standard care

- IN1 Begin insulin therapy when optimized oral glucose-lowering drugs and lifestyle interventions are unable to maintain blood glucose control at target levels (see *Glucose control levels*).
- Maintain support for lifestyle measures after introduction of insulin.
- Consider every initiation or dose increase of insulin as a trial, monitoring the response.
- IN2 Explain to the person with diabetes from the time of diagnosis that insulin is one of the options available to aid management of their diabetes, and that it may turn out to be the best, and eventually necessary, way of maintaining blood glucose control, especially in the longer term.
- IN3 Provide education, including on continuing lifestyle management (see *Education, Lifestyle management*), and appropriate self-monitoring (see *Self-monitoring*).
- Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 50-100 units/day.
- Initiate insulin therapy before poor glucose control develops, generally when DCCT-aligned HbA_{1c} has deteriorated to >7.5 % (confirmed) on maximal oral agents.
- Continue metformin. Additionally continue sulfonylureas when starting basal insulin therapy. α -Glucosidase inhibitors may also be continued.
- IN4 Use:
- a basal insulin once daily such as insulin detemir, insulin glargine, or NPH insulin (risk of hypoglycaemia is higher with the last), or
 - twice daily premix insulin (biphasic insulin) particularly with higher HbA_{1c}, or
 - multiple daily injections (meal-time and basal insulin) where blood glucose control is sub-optimal on other regimens, or meal-time flexibility is desired.
- IN5 Initiate insulin using a self-titration regimen (dose increases of 2 units every 3 days) or by weekly or more frequent contact with a health-care professional (using a scaled algorithm).

Aim for pre-breakfast and pre-main-evening-meal glucose levels of <6.0 mmol/l (<110 mg/dl); where these seem not to be achievable use monitoring at other times to identify the profile of poor glucose control.

- IN6 Continue health-care professional support by telephone until target levels (see *Glucose control levels*) are achieved.
- IN7 Use pen-injectors (prefilled or re-usable) or syringes/vials according to choice of the person using them.
- IN8 Encourage subcutaneous insulin injection into the abdominal area (most rapid absorption) or thigh (slowest), with the gluteal area (or the arm) as other possible injection sites. Bear in mind that reluctance to use the abdominal region may relate to cultural background.

■ Comprehensive care

- IN_c1 The principles of insulin use are as for *Standard care*.
- IN_c2 Insulin analogues would generally be used.
- IN_c3 Where permitted and appropriate, combination use of insulin and a PPAR- γ agonist is an option, with cautions over cardiac failure.
- IN_c4 Insulin pump therapy may be an additional option.

■ Minimal care

- IN_m1 The principles of insulin use, including professional support, are as for *Standard care*. Self-monitoring may be limited to pre-breakfast and pre-evening-meal.
- IN_m2 Use a combination of an oral glucose-lowering drug (usually metformin) with NPH insulin twice daily (or once daily if initiated early), or twice-daily insulin mixes.
- IN_m3 The supplied insulin should be of assured and consistent quality and type.
- IN_m4 Use insulin syringes and vials.

Rationale

The rationale for the use of glucose-lowering therapy titrated to blood glucose targets is given in the section on oral agents. The natural history of Type 2 diabetes is of progression of islet B-cell failure – insulin remains the only glucose-lowering therapy which can maintain blood glucose control despite such progression.

Evidence-base

The evidence-based guidelines addressing insulin use in Type 2 diabetes [1-3] draw on the evidence from UKPDS that insulin was among the glucose-lowering therapies which, considered together, reduced vascular complications compared with 'conventional' therapy [4]. The options for insulin therapy (preparations, delivery) have expanded

considerably since the UKPDS. The NICE evidence review found that studies on older preparations tended to be less highly rated for quality, while evidence for the newer insulin analogues was still emerging [1]. The more recent Canadian guidelines found indications for use of analogues in relation to postprandial glucose excursions, risk of hypoglycaemia, and weight gain [2]. A recent meta-analysis found good evidence of less hypoglycaemia with insulin glargine compared with NPH insulin [5]. Insulin glargine was the subject of specific guidance from NICE [6] including a recommendation for use where once-daily injections would suffice or NPH insulin gave troublesome hypoglycaemia. Other studies with insulin analogues or comparing basal analogues and analogue premixes have since appeared [7,8]. These suggest that basal analogues have advantage over NPH insulin for combined endpoints (HbA_{1c} + hypoglycaemia), while there is a balance of advantage between biphasic analogues and basal analogues when HbA_{1c}, hypoglycaemia and weight gain are considered together. Risk, and hence fear, of hypoglycaemia is greater with insulin than with any of the insulin secretagogues.

There is supporting evidence for insulin use in combination with metformin, insulin secretagogues (sulfonylureas), metformin plus sulfonylurea (no meta-analysis), α -glucosidase inhibitors, thiazolidinediones [2,9]. The NICE review found that for people on insulin therapy, glucose control was improved and body weight and hypoglycaemia risk reduced when metformin was used in combination; the evidence that blood glucose control was improved when sulfonylureas were taken concomitantly with insulin was not conclusive [1]. Uncontrolled observations since that review support the hypothesis, notably in combination with basal insulin therapy [10]. Major outcome studies are not yet available for the combination of insulin with rapid-acting insulin secretagogues or thiazolidinediones.

A 2005 Cochrane review including 45 RCTs with 2156 participants found no differences in metabolic control or hypoglycaemic episodes between human insulin and animal insulin [11], although patient-oriented outcomes like quality of life, diabetes complications and mortality were not suitably addressed by high-quality RCTs. Although cost-effectiveness currently favours non-human insulin, this situation is changing.

Rapid-acting insulin analogues were the subject of a recent Cochrane review, which had some methodological weaknesses [12]. Modest benefits were found for the analogues, which might be considered for patients using rather more intensified regimens or with more advanced insulin deficiency.

Intensified insulin therapy in Type 2 diabetes has been shown to improve metabolic control, improve clinical

outcomes [13], and increase flexibility. Evidence on pump therapy in Type 2 diabetes is still insufficient to support a recommendation for use in general, although it is a potential option in highly selected patients or in very individual settings [14].

Consideration

The evidence shows that a DCCT-aligned HbA_{1c} level of around 7.0 % (population mean) is achievable with insulin therapy in combination with oral glucose-lowering drugs, provided insulin deficiency has not progressed too far. This suggests it is worthwhile starting when control has deteriorated to >7.5 %. Active titration of dosage by self-monitoring and continued educational support is needed to achieve this. It is well recognized that personal preferences have a major role to play in the use of insulin. Long-acting analogue studies show less hypoglycaemia compared with NPH insulin. However, the evidence suggests that active use of combination oral agents is necessary in many people to maintain glucose control throughout the day, and that meal-time insulin (as biphasic preparations or with meal-time supplements) becomes necessary with time.

Insulin analogues can be expensive. Where this is an issue, NPH insulin and human insulin mixes are still very useful alternatives. However, consistency of supply (quality, availability, insulin type) requires careful organization.

Implementation

Contracts should be in place for uninterrupted availability of insulin and supporting materials (including for self-monitoring and education).

Availability of an HbA_{1c} assay (except in *Minimal care*), and of health-care professionals for education and advice at high intensity when titrating doses, needs to be assured.

Avoiding delay in starting insulin therapy has been problematic in nearly all diabetes services. Structured guidelines and protocols and audit of glucose control of people on oral drugs appear to be an integral part of dealing with this problem.

Evaluation

Evaluation should be of achieved blood glucose control of people on oral drugs and those started on insulin therapy, with reference to the documented use of those therapies once insulin has been started. Local protocols and resources should be identifiable.

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