UNIT NO. 4

INSULIN THERAPY

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ABSTRACT

Besides impaired insulin action, insulin secretory dysfunction is usually present at diagnosis of type 2 diabetes. Insulin secretory dysfunction often worsens over time and many people with long-standing type 2 diabetes require chronic insulin therapy in addition to oral antidiabetic agents. The focus of this article would be on the initiation and chronic use of insulin in patients with type 2 diabetes, either as monotherapy or more commonly in combination with oral antidiabetic agents.

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INDICATIONS FOR USE

People with type 1 diabetes have substantial absolute deficiency in insulin secretion and insulin therapy is generally considered essential. Adult patients diagnosed with latent autoimmune diabetes (LADA) are also often treated chronically with insulin.

On the other hand, both impaired insulin action and relative insulin deficiency are recognised as key pathogenetic factors in the causation of type 2 diabetes[1]. Even at diagnosis of type 2 diabetes, besides insulin resistance, there is concurrent relative insulin secretory dysfunction[2]. Although increasing age, increasing weight, physical inactivity (and other factors) may increase insulin resistance in the lifetime of a patient with type 2 diabetes, it is deterioration in insulin secretion which is often the dominant factor responsible for the ever increasing hyperglycaemia[3] and the ever increasing need for more oral antidiabetic agents[4]. Hence, it is not surprising that many patients with longstanding type 2 diabetes require insulin therapy to help achieve metabolic control. In addition, insulin therapy is often also needed in patients with type 2 diabetes for acute intercurrent illnesses as well as in the peri-operative period; and in female patients with type 2 diabetes as they plan conception and go through pregnancy.

As the majority of patients with diabetes seen at primary care would belong to the type 2 category, the focus of this article would be on the initiation and chronic use of insulin in patients with type 2 diabetes, either as monotherapy or more commonly in combination with oral antidiabetic agents.

INSULIN PREPARATIONS

Physiologic insulin secretion from beta cells consists of a basal component, as well as a rapid prandial insulin response which subsides quickly soon after completion of a meal. Current insulin therapy, although less than physiological on account of its subcutaneous (and thence systemic) rather than portal delivery, is aimed at mimicking this as closely as possible. Besides recombinant human insulin, many insulin analogues are now available. There are many ways to categorise insulin preparations[5] but perhaps the most clinically useful way might be to categorise them into preparations which fulfill a role of either basal or prandial insulin. Table 1 adapted from the MOH CPG[6] summarises the characteristics of these prandial (short and rapid acting), basal (intermediate and long acting), and mixed basal-prandial (pre-mixed, biphasic) insulin formulations.

The rapid-acting insulin analogues (insulin lispro, aspart, glulisine) have shorter time to onset of action after injection, as well as shorter duration of action when compared to regular human insulin. Hence, the patient can inject a rapid-acting analogue just a few minutes before meals. There is also no necessity to take a snack 3-4 hours after injection usually, as may be the case with regular insulin. The basal insulin analogues are relatively 'peakless' and generally have longer duration of action than NPH insulin. This reduces the risk of hypoglycaemia (especially nocturnal hypoglycaemia when compared to NPH insulin injected in the evening). At the same time, the longer duration of action allows for a single injection of basal insulin in many patients with type 2 diabetes.

INITIATION OF INSULIN THERAPY AND SELECTING AN INSULIN REGIMEN IN PEOPLE WITH TYPE 2 DIABETES PREVIOUSLY TREATED WITH ORAL ANTIDIABETIC AGENTS

Both the MOH CPG[6] as well as the ADA/EASD consensus guidelines on management of hyperglycaemia in type 2 diabetes[7] provide recommendations on an appropriate time to add insulin on to other pharmacological agents. Patients who are adhering to healthful lifestyle habits, but are not able to attain their customised HbA1c targets while on moderately high doses of oral antidiabetic agents, should be considered for insulin therapy. When seeing patients with hyperglycaemia for the first time, the possibility that intercurrent illnesses (including urinary tract infection, tuberculosis, thyrotoxicosis, etc.) may have contributed to elevation of blood glucose would have to be considered. For patients who are being followed up on an ongoing basis, discussion on the need for insulin therapy should begin early as it often requires more than one consultation visit to persuade the patient to begin insulin therapy (Table 1).

A recent study suggested that in the setting of maximal combination sulphonylurea-metformin therapy, the improvement in HbA1c with the addition of rosiglitazone as a third oral antidiabetic agent was comparable to that attained

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Table 1: Insulin Preparations[6]

Insulin Types		Onset	Peak	Duration
Rapid-acting insulins	Human insulin ananlogues:			
	1) Insulin lispro (Humanlog)	5-15 mins	1-2 hours	3-5 hours
	2) Insulin aspart (NovoRapid)	10-20 mins	1-3 hours	3-5 hours
Short-acting insulins	Recombinant human regular insulin:			
	1) (Humulin R)	30-60 mins	2-4 hours	6-8 hours
	2) (Actrapid)			
Intermediate-acting insulins	NPH (Humulin N or Insulatard	1-4 hours	8-12 hours	12-20 hours
	Lente (Humulin L or Monotard)			
Long-acting insulins	1) (Humulin U)	3-5 hours	10-16 hours	18-24 hours
	2) (Ultratard)	3-5 hours	10-16 hours	18-24 hours
	3) Insulin glargine (Lantus)	1-4 hours	peakless	24 hours
	4) Insulin detemir (Lemevir)	1-4 hours	peakless	18-24 hours
Premixed Insulins	1) (Mixtard 30 or Humulin 30/70): premixed 30% regular insulin + 70% intermediate-acting insulin	30-60 mins	2-8 hours	24 hours
	2) (Mixtard 50 or Humulin 50/50): premixed 50% regular insulin + 50% intermediate-acting insulin	30-60 mins	2-8 hours	24 hours
	3) Biphasic insulin analogue - (NovoMix 30): premixed 30% insulin aspart + 70% protaminated insulin aspart	10-20 mins	1-3 hours	24 hours
	- (Humalog Mix 25/75): premixed 25% insulin lispro + 75% protaminated insulin lispro	10-20 mins	1-3 hours	24 hours

when adding on subcutaneous basal insulin. However, in patients whose baseline HbA1c was more than 9.5% while on maximal sulphonylurea and metformin, adding on subcutaneous insulin glargine gave better HbA1c improvement than adding on rosiglitazone[8]. With the recent concern about increased risk for cardiovascular events in people with type 2 diabetes on rosiglitazone, the use of insulin in such a setting may gain wider acceptance[7, 9].

When it has been decided that insulin be used as part of the clinical solution to the management of glycaemia in type 2 diabetes, it is necessary to obtain an intimate understanding of patient's biological characteristics (e.g. age, body mass); patient's disease characteristics (e.g. duration of diabetes, HbA1c and glucose excursion profile, presence of symptomatic hyperglycaemia, renal function, and other co-morbidities); patient's lifestyle preferences and requirements (e.g. activity status, dietary habits including regularity of meals); and patient's social support. These factors should then be matched with the time course of action of the different insulin preparations to select an appropriate insulin regimen.

Although all of these factors are of importance, the degree of elevation of HbA1c and the daily glucose excursion profile are still the essential considerations in the selection of an appropriate insulin regimen. Hence, self blood glucose monitoring, if not already being performed, is a skill which needs to be taught to the patient and/or his caregiver. Even if the patient expresses inability to perform this in the long term, having available some data on daily blood glucose excursion pattern – prior to selection of an appropriate insulin regimen, and having daily blood glucose readings – during the first few weeks of insulin initiation and adjustment – would facilitate this process to a major extent. Prevention and appropriate response to hypoglycaemia should also be reinforced.

There is some evidence that patients with higher HbA1c are better treated by adding on both prandial and basal components of insulin from the onset[10]. Hence, in patients with type 2 diabetes who have HbA1c of greater than 10-11% and who often have 'round the clock' hyperglycaemia, use of insulin regimens with both components of insulin (e.g. regular insulin with NPH insulin, premixed human insulin, or biphasic insulin analogues) twice daily before breakfast and dinner (while continuing with metformin, but discontinuing oral insulin secretagogues) may result in lower HbA1c than adding a basal insulin analogue on to all existing oral antidiabetic agents. As a rule of thumb, when replacing both prandial and basal components of insulin secretion, an initial

total daily dose of 0.5 units per kg body weight –divided into morning and evening doses each with basal and prandial components– can be used. Thereafter, the doses of insulin can be adjusted based on patient's self monitored blood glucose readings. Of course, other circumstances, e.g. unavailability of care-giver to give injections in a patient who is unable to do so himself, may preclude the initial use of such a regimen in which case initiating therapy with a single daily injection of NPH insulin or a basal insulin analogue may still provide much meaningful reduction in HbA1c.

In patients who have relatively lower HbA1c, e.g. 9%, addition of a single daily injection of NPH insulin or a basal insulin analogue without withdrawing existing oral antidiabetic agents may suffice. If the patient has substantially higher morning blood glucose, the basal insulin dose should be injected at bedtime in an attempt to reduce morning blood glucose. Whereas, if the patient has substantially higher evening blood glucose, the basal insulin injection should be given in the morning[11]. The initial dose of basal insulin is about 0.1-0.2 units per kg body weight. If the basal insulin is injected at bedtime, the dose can be increased by 2-4 units every 3-5 days until the morning blood glucose reaches individualised target set for the patient (e.g. 6 mmol/L), while avoiding nocturnal hypoglycaemia. If morning blood glucose target has been attained, but evening blood glucose readings and the HbA1c remain unacceptably high after 2-3 months, addition of a second dose of basal insulin in the morning may be attempted. Another option in these circumstances is to switch to premixed human insulin or biphasic insulin analogues twice daily before breakfast and dinner, in which case, insulin secretagogues can be discontinued.

SUMMARY

Insulin therapy is essential in people with type 1 diabetes. Besides impaired insulin action, insulin secretory dysfunction is usually present at diagnosis of type 2 diabetes. Insulin secretory dysfunction often worsens over time and many people with long-standing type 2 diabetes require chronic insulin therapy in addition to oral antidiabetic agents.

Insulin preparations can be categorised into either basal or prandial insulin. Newer analogues have some practical clinical advantages over human regular and NPH insulin. Patients who are adhering to healthful lifestyle habits but are not able to attain their customised HbA1c targets, while on moderately high doses of oral antidiabetic agents, should be considered for insulin therapy. However, patients with HbA1c not more than approx. 9% while on moderately high doses of sulphonylurea and metformin may benefit from addition of a third oral antidiabetic agent.

When insulin therapy is decided upon, besides considering a multitude of factors, the patient's HbA1c and glucose excursion profile should be studied before a decision on any particular insulin regimen. For patients with very high HbA1c (e.g. more than 10-11%), who often have 'round the clock' hyperglycaemia, pre-mixed human insulin or a biphasic insulin analogue injected twice daily before breakfast and dinner in addition to metformin may be a useful initial regimen. For patients with moderately elevated HbA1c, and elevated morning blood glucose, a bedtime basal insulin injection in addition to existing oral antidiabetic agents should be considered. On the other hand, for patients with moderately elevated HbA1c, and elevated evening blood glucose, a morning basal insulin injection in addition to existing oral antidiabetic agents should be considered.

Besides the skills required of insulin injection and glucose monitoring, patients and caregivers should have an understanding of how diet, activity, oral antidiabetic agents, and insulin therapy may interact to bring about optimal blood glucose control or otherwise. Only then might they be engaged actively in self-management. Finally, other important facets of diabetes management such as weight, blood pressure and LDL cholesterol optimisation as well as smoking cessation should not be forgotten.

REFERENCES

1. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med. 1990;113(12):909-15.
2. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787-94.
3. Levy J, Atkinson AB, Bell PM, McCance DR, Hadden DR Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. Diabet Med. 1998;15(4):290-6.
4. U.K. Prospective Diabetes Study Group. UKPDS 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes. 1995;44:1249-58.
5. Bell DSH. Insulin therapy in diabetes mellitus: how can the currently available injectable insulins be most prudently and efficaciously utilised? Drugs. 2007;67(13):1813-27.
6. Ministry of Health Singapore. Clinical Practice Guidelines 3/2006 Diabetes Mellitus
7. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes.Diabetes Care. 2008;31(1):173-5
8. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care. 2006;29(3):554-9.
9. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471
10. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A; INITIATE Study Group. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005;28(2):260-5.
11. Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. Ann Intern Med. 2006;145(2):125-34.

LEARNING POINTS

- **Patients who are adhering to healthful lifestyle habits, but are not able to attain their customised HbA1c targets while on moderately high doses of oral antidiabetic agents, should be considered for insulin therapy.**
- **Patients with HbA1c not more than approx. 9% while on moderately high doses of sulphonylurea and metformin may benefit from addition of a third oral antidiabetic agent.**
- **For patients with very high HbA1c (e.g. more than 10-11%), who often have 'round the clock' hyperglycaemia, pre-mixed human insulin or a biphasic insulin analogue injected twice daily before breakfast and dinner in addition to metformin may be a useful initial regimen.**
- **For patients with moderately elevated HbA1c, and elevated morning blood glucose, a bedtime basal insulin injection in addition to existing oral antidiabetic agents should be considered.**
- **For patients with moderately elevated HbA1c, and elevated evening blood glucose, a morning basal insulin injection in addition to existing oral antidiabetic agents should be considered.**