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EDUCATIONAL SERIES

Guidance on the Use of Insulin in the Management of Type 2 Diabetes in Primary Care

About the Commentator

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Dr. Brandon Orr-Walker is an Endocrinologist working at Middlemore. Initially employed in general endocrinology, he was invited to lead an already well-established and innovative clinical diabetes team in 2004, and from 2005 provided clinical leadership for the Counties Manukau DHB "Let's Beat Diabetes Program", and subsequently was the Minister of Health's Clinical advisor on Diabetes (2010-2012). He is has the current President of The New Zealand Society for the Study of Diabetes (NZSSD).

Brandon has served on numerous local, regional, and national advisories including the NZ Guidelines Group, and provided clinical advice leading to the development of the Diabetes Care Improvement Packages (DCIP) when the long-established annual "Get Checked" program was scrapped. He remains committed to the promotion and provision of excellent diabetes care regardless of clinical venue, and for the differing needs, of patients.

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Abbreviations used in this issue
BID = twice daily
BGL = blood glucose level
FPG = fasting plasma glucose
FBG = fasting blood glucose
OD = once daily

This review is intended as an educational resource for primary healthcare professionals involved in managing patients with type 2 diabetes. It discusses the use of insulin in this patient group, with emphasis on the use of premix insulin and the concept of patient-centred therapy.

Introduction

Primary care providers are well positioned to manage diabetes as a long-term condition and to support complex patients who require specialist diabetes services as part of a multidisciplinary team approach.[1] However, New Zealand primary care guidelines for the management of type 2 diabetes, which were published in 2012,[2] have not been updated since new insulin products have become available. Moreover, recent local and international guidance advocates a patient-centred approach to treatment rather than fixing glycaemic targets for all patients.[3-5]

Overview of insulin therapy

In managing type 2 diabetes, it is essential to target both fasting plasma glucose and postprandial glucose to achieve optimal glycaemic control, with glycaemic targets set individually according to specific patient factors.[5] It is also essential to escalate therapy in a timely manner to compensate for the progressive nature of the disease. Indeed, the normal progression of type 2 diabetes means that most patients will eventually require insulin therapy.[6,7]

Insulin therapy in the management of type 2 diabetes, including the different types of insulin, dosing and titration, patient characteristics, and concurrent non-insulin glucose-lowering drugs, is summarised in **Table 1**.[5,6,8,9]

With regard to the initiation and intensification of insulin therapy, clinical trial evidence indicates that no single insulin or insulin regimen is superior on all treatment endpoints, and that improved glycaemic control can be expected irrespective the regimen used.[5] Against this background, individual patient factors and preferences assume greater importance, i.e. selection of the regimen that is best for a particular patient should be the primary consideration.

Initiating insulin therapy

There are three general types of insulin regimens: basal insulin, premix (biphasic) insulin, and basal-bolus insulin. The former two are usually utilised to initiate insulin therapy in type 2 diabetes and the latter to initiate insulin therapy in type 1 diabetes (but is also used "when all else fails" in type 2 diabetes).

Basal and premix insulin regimens may be intensified by higher dosing or more frequent dosing (e.g. twice daily). The basal regimen may be intensified by the addition of rapid-acting prandial insulin, referred to as the basal plus or basal-bolus regimens.

Basal insulins are either long acting or intermediate acting and may be administered once or twice daily. Although there is little difference in efficacy between long- and intermediate-acting forms, long-acting insulins may be appropriate if hypoglycaemia is a concern.[10] NovoMix 30 and Humalog Mix 25 are becoming the preferred premix insulins as they are rapid acting and are "inject and eat", which is easier for patients. Premix insulin can be administered once- or twice-daily.

Specific patient characteristics that may help decide which of the two main regimens (basal or premix insulin) may be most appropriate for an individual patient initiating insulin therapy are outlined in **Table 2**.[5] Note the value of both the pre- and post-prandial self-monitored blood glucose levels to determine the increase in blood glucose after a meal (postprandial increment). Given the likely need for intensification, patient characteristics regarding future intensification (basal-bolus or premix insulin) also require consideration.

Preparing patients for insulin therapy can be a complex process, including allaying patient concerns about insulin therapy and blood glucose monitoring and selecting the optimal HbA1C target for an individual patient.[5] Some DHBs provide funding to support the time and effort required to initiate treatment with a patient. Check with your Primary Health Organisation.

Insulin type	Patient characteristics	Insulin	Insulin dosing and adjustment	Metformin	Sulphonylurea	Monitoring
Basal	Obese High nocturnal and morning BGL but lower levels during the day when active Require assistance with injections Desire a simple, OD regimen Lower risk of hypoglycaemia	Basal insulin – long-acting (**glargine**, **detemir**) or intermediate-acting (**protaphane**, **isophane**)	Starting dose: 10 U OD or 0.1-0.2 U/kg/day Bedtime dosing if FBG high pre-breakfast Morning dosing if pre-breakfast FBG on target but pre-dinner BGL high Titrate dose until agreed glycaemic level reached or hypoglycaemia limits further increases If there are episodes of nocturnal or early morning hypoglycaemia, reduce dose of intermediate-acting insulin or switch to long-acting insulin (morning or night) If HbA1c is >64 mmol/mol at 3 months, there is significant hyperglycaemia after meals, or insulin doses >50 U are required, consider switching to a BID premix regimen	Continue at current dose	Continue at current dose	Monitor pre-breakfast and pre-evening BGL Monitor 2-hr post evening meal At 3 months, aim for HbA1c ≤64 mmol/mol or individual target Once stable, self-monitor 3-4 times/day, 2-3 days/week
OD premix (biphasic insulin)	Main high glucose readings after dinner and through to the morning	NovoMix 30 and Humalog Mix 25 are the preferred options and are given just before meals. If needed, use Penmix 30, Mixtard 30 or Humulin 30/70, which are given 30 minutes before meals	10 U before evening meal Titrate the evening premix insulin dose once or twice a week (see **Box 1**). If a morning dose is given, adjust insulin dose according to evening pre-prandial BGL The timing of meals is important as too is consistency of carbohydrate intake	Continue at current dose	Usually stopped, but consider tapering as glycaemic control improves	Monitor before breakfast or 2-hr post-prandial BGL
BID premix (biphasic insulin)	Significant hyperglycaemia after meals Once FBG is at target, if evening pre-prandial BGL > FBG or if evening pre-prandial BGL is high After 3 months if HBA1c > target despite FBG and evening pre-prandial BGL at target	Humalog Mix 25, NovoMix 30 are the preferred options and are given just before meals. If needed, use Penmix 30, Mixtard 30 or Humulin 30/70, which are given 30 minutes before meals	12 U before breakfast and 8 U before evening meal if obese, or 10 U before breakfast and 6 U before the evening meal if slim The timing of meals is important as too is consistency of carbohydrate intake Once a week adjust both insulin doses independently (according to the 'Dose adjustment' protocol in **Box 1**). Pre-breakfast insulin is adjusted according to pre-dinner BGL and pre-dinner insulin is adjusted according to FBG In some cases of poor glycaemic control, the use of premix insulin thrice daily may be required	Continue at current dose	Usually stopped, but consider tapering as glycaemic control improves	Monitor BGL pre-breakfast, pre-evening meal, and 2-hrs post evening meal

Table 1. Guide to insulin therapy in the management of type 2 diabetes.[5,6,8,9]

Considerations at initiation		
Favours premix		**Favours basal**
>3 mmol/L	What is the postprandial increment?	<1 mmol/L
No	Is the patient likely to manage basal-bolus therapy when intensifaction is needed?	Yes
Yes	Is there a large carbohydrate intake at one or two meals?	No
Yes	Is the patient's lifestyle predictable (e.g., eating pattern, working hours)?	No
Considerations for future intensification		
Favours premix		**Favours basal-bolus**
Prefers fewer injections	Patient preference regarding number of injections	Comfortable with more frequent injections
Prefers less frequent monitoring	Patient preference regarding self-monitoring of blood glucose	Comfortable with more frequent monitoring
Poor	Patient ability to inject (e.g., cognitive ability, manual dexterity, need for carer)	Good

Table 2. Patient factors for consideration when choosing whether to initiate therapy with premix insulin or basal insulin.[5]

Titrating when initiating therapy with premix insulin

Guidance on dose and titration when initiating insulin therapy with premix insulin is summarised in **Box 1**. The lowest of the three most recent self-monitored blood glucose values should be used to determine whether dose adjustment is necessary.

Box 1. Practical guidance for dosing and titration when initiating insulin therapy with premix insulin once daily (OD).[5]

- When choosing an insulin dose, and for dose titration, err on the side of safety and convenience.
- Initiate with premix insulin analog OD, immediately before or soon after the start of the meal with the highest prandial load (usually the evening meal).
- Initiate with a dose of 10–12 units and titrate.[a]
- Increase by 2 units once or twice a week until the patient reaches target [aim for <7 mmol/L, but no values <4 mmol/L based on the lowest premeal glucose level] or experiences hypoglycaemia (see dose adjustment table below). Dose titration can be halted when self-monitored blood glucose levels consistently fall within the target.
- If blood glucose <4 mmol/L or hypoglycaemia occurs, down-titrate by 2 units. If hypoglycaemia persists, the patient should review with their doctor or nurse.

a If HbA1c is above a certain value [suggested ≥8.5% (≥70 mmol/mol)], it is also possible to initiate therapy with 6 units twice daily.

Dose adjustment	
Lowest pre-meal blood glucose level:	**Adjustment for the next dose:**
≥7.0 mmol/L	+2 units
4.1–6.9 mmol/L	0 units
≤4.0 mmol/L	-2 units

Intensifying insulin therapy

Intensification of insulin therapy is as important as initiation.[5] For some patients initiated on basal insulin, a switch to premix insulin may be necessary (**Figure 1**). For some patients initiated on premix insulin once daily, a switch to premix insulin twice daily may be necessary (**Figure 2**). The units at which to start the premix insulin are detailed in **Box 1**. Practical guidance for switching from basal insulin, or from premix insulin once daily, to premix insulin twice daily is summarised in **Box 2**.

If control is not satisfactory with a twice-daily regimen consider specialist referral.[5] In some cases of poor glycaemic control, the use of premix insulin thrice daily may be required.

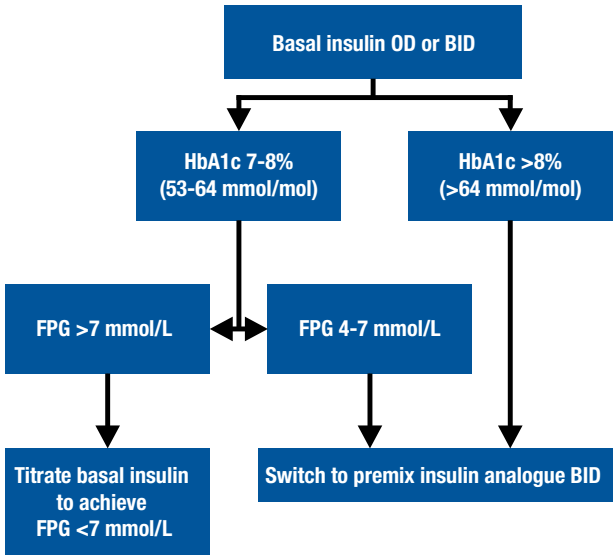

Figure 1. Algorithm for switching from basal insulin once- or twice-daily to twice-daily premix insulin.[5]

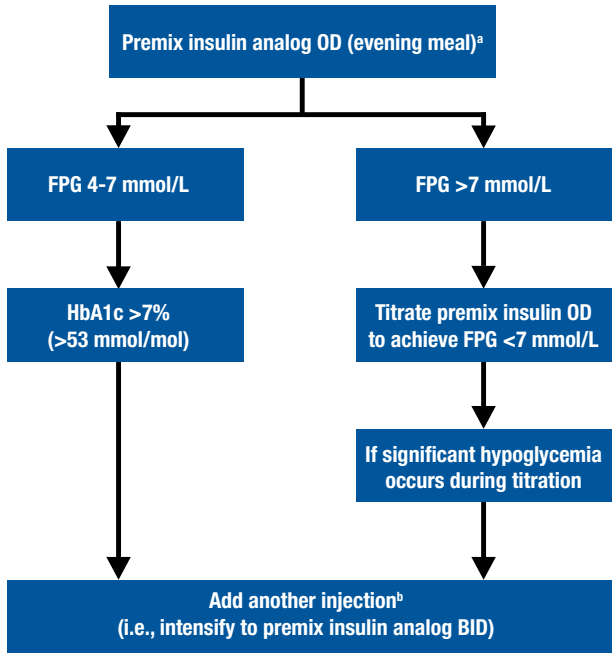

Figure 2. Algorithm for intensifying premix insulin therapy from once daily to twice daily.[5]
a The evening meal is given as an example.
b Split the once-daily dose 50/50 breakfast and dinner.

Box 2. Practical guidance for switching from basal insulin once daily (OD) or twice daily (BID), or from premix insulin OD, to premix insulin BID.[5]

- From basal: 1:1 total dose switch to premix insulin. Split the dose 50/50 breakfast and dinner.
- From premix insulin OD: split the OD dose 50/50 breakfast and dinner.
- Administer premix insulin immediately before or soon after the start of a meal.
- Titrate the dose preferably once or twice a week (see **Box 1**).
- Adjust the evening meal dose first, followed by the breakfast dose.

Key messages

- **Individualised glycaemic targets should be set.[10]**
- **The management of type 2 diabetes requires regular review and timely intensification of treatment, including insulin initiation and intensification when appropriate.[10]**
- **Adopt a patient-centred approach when initiating and intensifying insulin therapy.[5]**
- **Premix insulin and basal insulin are both suitable for the initiation of insulin therapy.[5]**
- **Pre- and post-prandial self-monitored blood glucose levels must be recorded.[5]**
- **Premix insulin should be considered for initiation when the post-prandial increment is >3 mmol/L.[5]**

Expert's concluding comments

Glycaemic management in type 2 diabetes requires an incremental management approach utilising lifestyle and pharmacotherapies due to the complex nature of diabetes and declining beta cell function with time.

If all of the people with type 2 diabetes currently in New Zealand lived in one city it would be the fourth largest equal with Hamilton, and so it is nonsensical to think of a "single one-size-fits-all" approach. But a consistent approach after diagnosis, to proactively manage glycaemia (and CVD and renal risk and proactive assessment of renal, retinal, and foot complications) is needed. This is where primary care has a pivotally important and enduring role.

Effective intensification of treatment, i.e. targeting goals, has been shown to reduce complications including microvascular events (retinopathy, nephropathy) and, in the longer term, cardiovascular and other "macrovascular" complications. Earlier attainment of excellent glycaemic control pays long-term benefits, which cannot be "made up" later, and a late "throw everything at it" approach has been shown to have hazards (especially hypoglycaemia in a now older and more vulnerable group of patients).

There is a plethora of guidelines about treatment initiation and intensification. Many describe "what to do" but do not really offer practical guidance on how to achieve it effectively and safely. International guidelines (in environments with a substantially larger armamentarium of funded pharmaceutical options) are tending to suggest a range of possibilities beyond first-line therapy ("diet and metformin"), emphasising the pros and cons of each, and promoting and tailoring these to each patient. This approach respects the wide phenotype, needs, and circumstances of people with type 2 diabetes.

In New Zealand, our treatment options are much more limited (and have been lagging behind for a decade). Therefore, expert management of insulin is even more important in our environment. By "expert" I mean to consistently be able to safely and effectively initiate and titrate insulin.

Insulin comes in many forms with particular theoretical (e.g. pharmacokinetics) and practical (e.g. mixing of "cloudy" insulin, injection techniques, pen use etc.) expertise to optimise its use. It is the ability to manipulate the intensity and duration of insulin (by means of dose and preparation) to modify glucose levels that is a key strength of insulin as a therapy in type 2 diabetes. This complexity and efficacy is also a reason people (patients and clinicians) are put off it, aware that its powerful glucose-lowering effect can be "too much of a good thing" if not managed with care.

The guidance referred to in this article summarises safe approaches to titration and initiation that in published studies have been shown to be "patient proof" in achieving consistent results with modest clinician input. Clinician familiarity and expertise will provide confidence with treatment and achieve good results. This is, after all, why we make diagnoses, i.e. to help reduce complications and to allow us to move from a discussion about complications, e.g. "if you don't get your HBA1c down…." to "look how much better we have this under control to keep you well".

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