Taking the stress out of insulin initiation in type 2 diabetes mellitus

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For many family physicians, initiating insulin therapy in people with type 2 diabetes mellitus (DM) can be anxiety-provoking and time-consuming. Often it is physicians' lack of confidence in starting insulin, not patients' fear of insulin injections, that delays optimizing glycemic control. Accessing resources such as diabetes treatment guidelines,[1-3] *RxFiles Drug Comparison Charts,* and the services of pharmacists or diabetes educators can help take the stress out of this important aspect of diabetes care. The current debate over the uncertain benefits and risks of tight glucose control is beyond the scope of this article, but is discussed in the RxFiles "Diabetes—Glucose Control: Landmark Outcome Trials—Summary," available on **CFPlus.***

Case

Tom is a 72-year-old man who has type 2 DM, hypertension, hyperlipidemia, and stable angina. He has had type 2 DM for about 14 years; until recently, his blood glucose (BG) levels were well controlled with combinations of oral hypoglycemic agents (OHAs), diet, and regular exercise. Over the past year his glycosylated hemoglobin A_{1c} (HbA_{1c}) levels have climbed; last month they were measured at 9.2%. This translates to an estimated average glucose (eAG) level of 12.1 mmol/L.[4] Recent self-monitored BG readings include the following: fasting 8.9 to 11.2 mmol/L; before lunch 7.8 to 9.2 mmol/L; 1 hour after lunch 10.9 to 13.4 mmol/L; before supper 9.9 to 10 mmol/L.

Current diabetes medications include 1000 mg of metformin twice daily, 30 mg of pioglitazone daily, and 60 mg of gliclazide daily. He is taking optimal therapy for cardiovascular protection, including blood pressure control and statin therapy, which have proven outcome benefits.

In the clinic, you review Tom's recent HbA_{1c} and BG values; he informs you that he is following the diet guidelines recommended by the dietitian 6 months ago and is exercising for 30 to 60 minutes most days. A recent 2-kg weight loss confirms Tom's lifestyle management progress. Tom asks you, "What else can I do to improve my blood sugars?"

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*The "Diabetes—Glucose Control: Landmark Outcome Trials—Summary," the insulin pen delivery devices chart, an approach to management of type 2 diabetes in adults chart, an insulin comparison chart, and "Insulin Management: Evidence, Tips & Pearls" are available at **www.cfp.ca**. Go to the full text of the article on-line, then click on **CFPlus** in the menu at the top right of the page.

While it is tempting to avoid the "inconvenience" of initiating insulin therapy at this clinic visit, it might be the preferred option for pursuing glycemic control. Tom is already taking adequate doses of 3 classes of OHAs.[5] Further dose increases are unlikely to result in substantial reduction in glucose levels and might increase his risk of side effects. Sitagliptin could be considered, given its postprandial effect and minimal weight gain; however, it lacks outcome evidence and long-term safety data and reduces HbA_{1c} by only about 0.7%.[6] There is no evidence supporting its role as an add-on therapy to 3 other classes of OHAs.

Type 2 diabetes is characterized by insulin resistance and progressive decline in pancreatic β-cell function and endogenous insulin production.[1] Physicians and patients need to acknowledge the progressive nature of type 2 DM and make appropriate advances in diabetic therapy (diet and lifestyle → OHAs → insulin). Because he has had type 2 DM for 14 years, Tom's pancreas might not be able to produce adequate amounts of insulin even with additional OHA therapy. Thus insulin is an appropriate step-up therapy.

Successful initiation of insulin might be facilitated by the following considerations[7,8]:

- Explain the rationale for starting insulin, emphasizing the progressive nature of type 2 DM and not blaming the patient. A demonstration of how insulin injections can be easily administered with a pen device allays many fears and misconceptions that people have about insulin, needles, and syringes (**Box 1**[9]).
- To avoid large drops in BG levels and ensure patient adherence, start with a low dose of basal insulin (eg, intermediate-acting insulin) at 5 to 10 units or 0.1 to 0.2 units/kg total body weight at bedtime. Give the patient written instructions on titrating the dose (eg, increase by 2 units every 3 days until fasting glucose <7 mmol/L).[1] Avoid dosage increases if the patient experiences nocturnal hypoglycemia or 2 or more episodes of BG levels below 4 mmol/L.
- Contact the patient's pharmacist or diabetes educator and ask him or her to provide instruction on use of the insulin delivery device and dosage adjustment if you are not able to do this in your practice.
- Metformin therapy should generally be continued when initiating insulin if it is not contraindicated (eg, in acute heart failure). Metformin has outcome evidence for reduced mortality, results in less weight gain from

Box 1. Starting insulin in type 2 diabetes mellitus: *Tips for patient buy-in.*

- Discuss insulin early to change negative perceptions about insulin
- Provide information about insulin benefits
- Consider suggesting a "trial" for 1 month
- Discuss the relative ease of using the newer insulin devices (eg, insulin pens, smaller needle) compared with syringes and vials (see also RxFiles Insulin Pen Delivery Devices chart at **www.RxFiles.ca***)
- Link patient to community support, such as a certified diabetes educator, for education on injections and monitoring
- Ensure patient has time to get comfortable with loading and working a pen (or syringe)
- Refer patient for nutrition and physical activity counseling

Adapted from *Starting Insulin*.[9]

insulin, and might decrease the required insulin dose.[10,11] Thus metformin can be continued even with multiple daily insulin injection regimens. Caution and dose reduction are required in patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min).[1,2]

- Sulfonylureas (eg, gliclazide) might contribute to glycemic control when once-daily basal insulin is used, but should usually be discontinued if mealtime short-acting or rapid insulin is added. Thiazolidinediones (eg, pioglitazone, rosiglitazone) are not approved for use with insulin and are usually discontinued owing to the increased risks of edema, heart failure, and weight gain.[12,13]
- Hypoglycemia is rare in patients with type 2 DM taking combinations of metformin and basal intermediate- or long-acting insulin. However, all patients using insulin should learn the risks, symptoms, and treatment of hypoglycemia.[1,7]
- Self-monitoring of BG needs to be individualized.[1,7] Type 2 DM patients taking insulin will need to monitor BG more frequently. Preprandial and postprandial BG levels are required to decide if and when to start mealtime insulin therapy.
- Individualize treatment goals balancing uncertain benefits with potential risks and difficulties of tighter glucose control.[1,14]

Most patients with type 2 DM have few problems with insulin therapy when it is started once daily in addition to metformin. Once comfortable with basal insulin therapy, they are more willing to accept the introduction of bolus (short-acting or rapid) insulin (**Table 1**[8]) before meals for better postprandial glycemic control.[1,2]

There is some debate about the role of long-acting insulin analogues (LAIAs) in the initiation of basal

Table 1. Insulin available in Canada

INSULIN TYPE AND PRODUCT	FORM	COST/15 ML, $*	ONSET	PEAK	DURATION
Rapid acting			10-15 min	1-1.5 h	3.5-6 h
• Insulin lispro (Humalog)	v,c,p	52-67			
• Insulin aspart (NovoRapid)	v,c	54-70			
• Glulisine (Apidra)	v,c,p	48-62			
Short acting			0.5-1 h	2-3 h	5-10 h
• Humulin R	v,c	40-52			
• Novolin ge Toronto	v,c	41-52			
Intermediate acting or NPH			2-4 h	4-10 h	12-18 h
• Humulin N	v,c,p	40-50			
• Novolin ge NPH	v,c	41-52			
Premixed, regular or rapid/intermediate			0.5-1 h	2-12 h	14-18 h
• Humulin 30/70	v,c,	40-51			
• Novolin ge 30/70;	v,c	41-52			
40/60, 50/50	c				
• Humalog: Mix25, Mix50	c,p	64			
• NovoMix 30	c	61			
Long acting					
• Detemir (Levemir)	c	135	1 h	6-8 h	16-24 h
• Glargine (Lantus)	v,c,p	105	>2-4 h	none	20-24 h

c—cartridge, NPH—neutral protamine Hagedorn, p—pen, v—vial.
*Reflects cost to patient; includes markup and dispensing fee.
Data from Regier et al.[8]

Table 2. Advantages and disadvantages of insulin: *Evidence for insulin analogues is limited to small, short-term trials, and benefits are modest; anecdotal experience is favourable. Recent systematic and economic reviews rigorously assessed benefits, risks, and incremental cost.*[15-22]

INSULIN		ADVANTAGES	DISADVANTAGES
Bolus	**Short acting** Human regular (Humulin R, Novolin ge Toronto)	• more long-term and safety data • low cost • extensive safety data in pregnancy	• injecting 20-30 min before meals is often impractical (short acting but not rapid acting)
	Rapid acting* Lispro (Humalog) Aspart (NovoRapid) Glulisine (Apidra)†	• inject-and-eat convenience (take just before or within 20 min of starting meals); valuable when diet or activities are unpredictable (eg, adolescents) • some patients might have less hypoglycemia • high patient satisfaction in type 1 DM • safe during pregnancy but less experience	• moderately expensive relative to clinical benefits in type 2 DM‡
Basal	**Intermediate acting** Human NPH Humulin N, Novolin ge NPH	• long-term safety and outcome evidence • low cost • convenient: might avoid need for lunchtime bolus injection (eg, good for children)	• NPH vial must be mixed before withdrawing dose; affects absorption • intermediate action and peak at 4-12 h predispose to hypoglycemia
	Long acting Detemir (Levemir) Glargine (Lantus)	• decreases nocturnal hypoglycemia (subjective, not blinded): type 2 DM estimated NNT ≥6 for 6-12 mo§ • slightly less weight gain vs NPH: in type 2 DM, only detemir had decrease in weight‖ • once-daily dosing (detemir: many will require BID)	• expensive relative to benefit in type 2 DM‡ • limited and inconsistent evidence for any difference in severe hypoglycemia • more injections if not mixed with bolus • caution needed in pregnancy
Mixed	**Premixed**[20,21]	• convenience; decreases HbA_{1c} more than basal only	• limited flexibility with fixed dose; not suitable if tight control desired

BID—twice daily, DM—diabetes mellitus, HbA_{1c}—hemoglobin A_{1c}, NNT—number needed to treat, NPH— neutral protamine Hagedorn.
*Rapid onset might lead to better postprandial control; significance is uncertain.
†Glulisine appears similar to lispro and aspart but is too new to be included in systematic reviews referenced here.
‡There are no clinically significant differences in HbA_{1c} control likely to affect clinical outcomes.
§Most pronounced decreased risk for long-acting insulin analogs is on nocturnal hypoglycemia[16] (long acting vs NPH, NNT ≥6 [95% confidence interval 4-33]).[15]
‖Weight change with long-acting insulin analogs vs NPH: type 1 DM -0.73 to -0.4 kg; type 2 DM -1.27 to -0.8 kg (with detemir; glargine no difference). There are questions about the clinical significance of the minor weight change of <1.3 kg here (or <5% in general).

insulin therapy in patients with type 2 DM. While some authors suggest a prominent role, recent systematic reviews have found that LAIAs offer little advantage over neutral protamine Hagedorn (NPH) for initial therapy.[15-18] The primary advantage of LAIAs is the potential for less nocturnal hypoglycemia in some patients; HbA_{1c} and weight end points are similar to those seen with intermediate-acting insulin[15,16] and outcome evidence is lacking. Newer LAIAs cost more than twice as much as intermediate-acting insulin (**Table 1**[8]). Further advantages and disadvantages of the different types of insulin are outlined in **Table 2**.[15-22]

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