

Insulin Therapy: Taking Care to the Next Level

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WHY BOTHER?

Why bother, indeed. As the decision to intensify management is being made, it must be remembered that diabetes is a progressive disease that can be managed by achieving well-established glucose targets. Recent major clinical trials have emphasized the importance of reaching these targets to help prevent the long-term vascular complications of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) (1) examined the benefit of intensive glucose management from the moment of diagnosis and provided some of the most valuable information we have on the long-term management of type 2 diabetes. Similarly, the Diabetes Control and Complications Trial (DCCT) (2) in type 1 diabetes emphasized the value of reaching glucose targets in preventing vascular complications. The subsequent long-term follow-up of these studies, the UKPDS legacy study (3) and the Epidemiology of Diabetes Interventions and Complications (EDIC) trial (4), both emphasized the benefit of early, aggressive management of both type 1 and type 2 diabetes in preventing or delaying vascular complications.

Subsequent long-term intensive glucose control studies, such as Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) (5), Veterans Affairs Diabetes Trial (VADT) (6), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) (7), all provided additional evidence on the benefits of intensive management of type 2 diabetes.

Despite the strength of the studies, it is apparent that the glucose targets that have been well described and published (8) are not being met. Data from the Diabetes In Canada Evaluation (DICE) study (9) demonstrated that not only are 50% of patients with type 2 diabetes not reaching the stated glycated hemoglobin (A1C) targets, but also that appropriate therapies are being delayed and often not used. These results were further substantiated by the Braga data (10), which also identified that intensive treatment programs were not being used in Canadian patients with type 2 diabetes and that glycemic targets were not being met. A recent study further emphasized the long delays in initiating insulin being observed in Canadian patients with type 2 diabetes. A mean 10.3-year delay was seen between the time of diagnosis and initiating insulin despite a mean A1C value of 9% at the time of commencing the insulin (11).

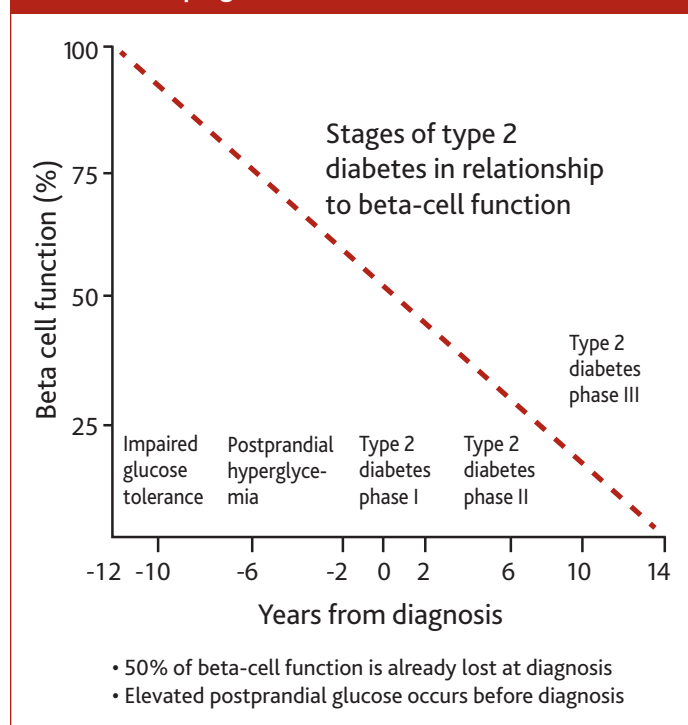
UNDERSTANDING THE CHANGES IN INSULIN SECRETION IN TYPE 2 DIABETES

In the person without diabetes, there is a constant secretion of insulin over a 24-hour period often referred to as basal insulin. This basal release of insulin acts as a platform for the release of bursts of insulin, which are released in response to food intake and help control glucose in the postprandial phase.

Type 2 diabetes, it must be recognized, is a progressive disease (1). It is estimated that when glucose levels rise to the point that diabetes is diagnosed (fasting plasma glucose [FPG] >7 mmol/L or postprandial glucose [PPG] >11.1 mmol/L [4]) that 50% of insulin-producing ability has been lost and this functional impairment continues at a rate of about 5% per year on average. When maximal insulin output has decreased to 15% or 20% of normal (6–8 years after diagnosis), glycemic control can no longer be achieved with oral hypoglycemic agents and metabolic instability occurs with increasing glucose levels. At this point, insulin supplementation is required to achieve control. In her article published in the spring 2011 issue of *Canadian Diabetes*, Dr. Alice Cheng described the initiation of insulin with basal (long-acting) insulin together with oral agents, but as insulin deficiency

continues to progress, a point is reached where glycemic control (A1C $\leq 7\%$) can no longer be maintained using basal insulin and oral agents (12). At this point, the introduction of rapid-acting insulin to meet insulin needs with meals is required. This article is concerned with the addition of rapid-acting insulin to cover meals when basal insulin alone is insufficient to achieve control.

Figure 1. Type 2 diabetes is characterized by insulin resistance and progressive beta-cell failure



Adapted with permission from Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Review*. 1999;7:139-153.

As shown in Figure 1, loss of beta-cell function will continue, and within 10 years of diagnosis of type 2 diabetes, much of the beta-cell response has been lost (13). The physiologically normal basal levels of insulin will fall, and there will be an inadequate response to food ingestion. In addition, the traditional early, first-phase insulin response to food, which helps control PPG, will be lost.

The reduction in basal insulin will lead to a rise in FPG, and the inadequate response of insulin to food will lead to a rise in PPG. It must be remembered that the A1C measurement represents the contribution of both the FPG and the PPG (14). FPG is the major contributor to elevated A1C, but as the A1C value falls below 8%, PPG is the major contributor. Thus, based on the A1C value, we can select therapies that primarily affect either FPG or PPG levels to improve A1C control.

ACHIEVING GLYCEMIC TARGETS

The Canadian Diabetes Association clinical practice guidelines are quite clear as to the targets that should be strived for in diabetes management (8). Appropriate lifestyle changes should be immediately implemented at the time of diagnosis and reinforced at all times. If these measures fail and A1C targets are not met within 3 months of diagnosis, the guidelines recommend early intervention with oral antihyperglycemic agents and/or insulin. If oral antihyperglycemic agents do not achieve the appropriate A1C target, then insulin will be required. As recently reviewed, introduction of a basal insulin regimen can achieve a dramatic decrease in A1C values that may well reach the target of $\leq 7\%$ (12). Recent trials using the early administration of insulin in the disease process have emphasized both the ease of reaching glycemic targets and patient satisfaction with the insulin (15).

The introduction of basal insulin must represent the beginning of a more intensive approach to insulin therapy. With the decreasing beta-cell response, not only will basal insulins be required, but in addition, rapid-acting insulin prior to meals will be necessary to achieve both FPG and PPG control and, thus, a reduction in A1C.

WHY ARE GLUCOSE TARGETS NOT REACHED?

Barriers to commencing insulin or intensifying therapy exist on the part of both the healthcare provider and patient. Several potential barriers tend to dominate: the risk of hypoglycemia; weight gain; difficulty in initiating the insulin regimen; patient embarrassment at the potential need to administer insulin in public; and the concept that intensive management of diabetes is in some way dangerous. And yet, with appropriate education, modern insulins and simple insulin delivery systems, all these barriers can easily be overcome.

For the person with type 2 diabetes, one of the major barriers to reaching glucose targets remains hypoglycemia. Despite the fact that many patients with diabetes would experience less hypoglycemia with the newer insulin analogues, many remain on the older-type insulins. In addition, a reluctance to use glucose monitoring as a technique for prospectively planned insulin doses further leads to higher risk of hypoglycemia. While the target A1C remains $\leq 7\%$ for the person with type 2 diabetes, in some patients this is an unattainable goal because of other aspects of their disease. Thus, A1C targets must be set for each individual patient.

The role of education cannot be underestimated. If the patient is advised which insulins would be most advantageous and how

to use them, the issues of excessive weight gain and difficulties in managing their program can be reduced and even eliminated.

WHEN TO INTENSIFY INSULIN THERAPY

Step 1: Assessment

Basal insulin administration is designed to achieve the FPG glycemic target, which is 4 to 7 mmol/L. To reach this target, the basal insulin dose must be titrated. Once the FPG target has been attained, and if the A1C value remains elevated at >7%, then an assessment of the PPG values must be made. The goal will be a PPG <8 mmol/L. By measuring PPG 2 to 3 hours after a meal, it can quickly be determined if this target is being reached. These measurements will also establish after which meals the PPG value is elevated above the target. For example, PPG may be consistently elevated after the largest meal of the day, but not following other meals.

Step 2: Intensification—type 2 diabetes

Once the FPG target of 4 to 7 mmol/L has been reached using basal insulin, an assessment must be made of the PPG values throughout the day. Self-glucose monitoring measurements can be made 2 to 3 hours after meals to determine whether the largest meal of the day and/or other meals have glucose values above the target of 8 mmol/L.

Once it has been determined which meals are associated with an elevated PPG, then rapid-acting insulin can be introduced prior to the meal and titrated to achieve the target glucose value of <8 mmol/L. To simplify the titration for the person requiring intensification of insulin administration, the first dose of rapid-acting insulin can be introduced prior to the largest meal of the day. The dose can then be titrated to achieve the target value. Again, a simple assessment of PPG after the other meals can be used to quickly determine whether additional rapid-acting insulin will be required before those meals where the PPG is elevated.

If it is not practical for the patient to measure PPG, then the glucose level prior to the next meal will give a good indication of the presence of hyperglycemia, with a target glucose value of 4 to 7 mmol/L.

WHICH INSULINS?

Rapid-acting insulin analogues

The rapid-acting insulin analogues—insulin aspart, insulin lispro and insulin glulisine—provide several advantages over regular human insulin: they can be given immediately prior to a meal, with a meal or just after a meal, and provide a more dependable and faster action than regular human insulin.

Multiple clinical trials have been conducted in which rapid-acting insulin has been added to a basal regimen. The studies have demonstrated the ease of intensifying the insulin regimen to achieve glucose targets both safely and efficiently. In the Treating To Target in Type 2 diabetes (4-T) study (16), one of the treatment arms used the initial administration of a long-acting basal insulin, insulin detemir (Levemir), which was then followed by intensification with insulin aspart. Investigators achieved a decrease in A1C of 1.2% and a median A1C of 6.9%. In all, 63% of the participants attained an A1C below 7% but only 0.9% experienced major hypoglycemia. Similarly, in the TITRATE study (17) an intensive treat-to-target protocol safely and effectively achieved A1C targets in the majority of participants. Other studies using glulisine or lispro have provided insulin algorithms that allow for the development of simple clinical programs to intensify bolus insulin regimens (18,19).

One such program is the Stepwise approach (20). This method uses a simple titration regimen that allows a patient to individually titrate the insulin dose to achieve glucose targets (Table 1):

Table 1. Adding rapid-acting insulin to a basal regimen (20)

- Titrate basal insulin to achieve FPG <7 mmol/L.
- Start 4 units of rapid-acting insulin before the largest meal of the day.
- Titrate dose to achieve a glucose value of 4–7 mmol/L before the next meal or bedtime.
- Add 4 units of rapid-acting insulin before the second-largest meal of the day if A1C remains elevated or glucose value before next meal is >7mmol/L.
- Titrate dose to achieve a glucose value of 4–7 mmol/L before the next meal.
- Add 4 units of rapid-acting insulin before the third meal of the day if A1C remains elevated or glucose value before next meal is >7mmol/L.
- Titrate dose to achieve a glucose value of 4–7 mmol/L before the next meal.

- Step 1: 4 units of rapid-acting insulin is given immediately prior to the largest meal of the day.
- Step 2: Using self-glucose monitoring, the plasma glucose prior to the next meal, or before bed if insulin is given before evening meal, is then measured. If the glucose value is >7 mmol/L, then 1 unit of rapid-acting insulin is added to the dose the following day, before the meal. If the glucose value is <4 mmol/L, then the insulin dose is reduced by 1 unit the next day. The titration continues until the target glucose has been met.

- Step 3: After the first bolus dose has been optimized, but the A1C remains elevated, then a second bolus is added before the second-largest meal of the day, commencing with 4 units before the meal and measuring glucose prior to the next meal. Titration of the insulin will be continued, as described with the first bolus.
- Step 4: After the second bolus dose has been optimized, but the A1C value remains elevated, then the third bolus can be added before the third meal and titration continues as described.

Premixed insulins

These insulins allow the patient to have the benefit of a longer-acting insulin as well as a faster-acting insulin combined in one injection. Good glucose control can be obtained over a 24-hour period using the premixed insulins twice a day. The premixed insulins are available in a human insulin formulation—human regular/NPH insulin—as well as an insulin analogue formulation. The major disadvantage of the human insulin formulations is the risk of hypoglycemia related to the longer action of the regular insulin and a lack of predictability of the action of the NPH insulin.

Premixed insulin analogues offer some advantage because of their predictable time-action and reduced risk of hypoglycemia. Several formulations are available including premixed insulin lispro with 25% rapid-acting lispro and 75% intermediate-acting Protamine (Humalog Mix 25), insulin lispro 50/50 (Humalog Mix 50), and biphasic insulin aspart 30 (NovoMix 30) with 30% rapid-acting insulin aspart and 70% intermediate protaminated aspart. Clinical trials have demonstrated that a patient can be initiated on the premixed insulins commencing as an add-on to oral drug therapy or by substituting for a basal insulin (21). The safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes was examined in a subgroup analysis of the 6-month observational study of safety and effectiveness of NovoMix 30 for the treatment of diabetes (IMPROVE) (22). This study demonstrated that patients could be transferred from human premixed insulin to a premixed analogue insulin with significant improvements in glycemic control combined with a reduced risk of hypoglycemia. Algorithms are available to allow easy and safe titration of the premixed insulin to achieve established glucose targets (23, 24). A convenient and safe regimen is to commence with 10 units of the premixed insulin before breakfast and before

supper (Table 2). The prebreakfast insulin dose will affect the presupper glucose value and can be adjusted to achieve a presupper glucose value of <7 mmol/L. Similarly, the presupper glucose can be adjusted to provide target glucose values before breakfast. Hypoglycemic events are decreased with the premixed analogue insulins compared to human premixed insulin. Glucose monitoring can be kept to a minimum, measuring mainly at the key insulin adjustment time periods of prebreakfast and presupper. However, because of the rapid-acting component of premixed insulins, it is valuable to monitor glucose values prior to lunch and bedtime, to ensure that glucose values are not demonstrating the presence of hypoglycemia. If hypoglycemia is a problem at these times, then the morning insulin may need to be reduced and on occasions either a rapid-acting insulin or a small dose of the premixed insulin added at lunchtime to help prevent prelunch hypoglycemia with associated achievement of target glucose at suppertime.

Table 2. Initiating premixed insulin (23,24)

Initiating premixed insulin therapy in an insulin-naïve patient

- **Step 1:** Commence with 10 units of premixed insulin before breakfast and before supper.
- **Step 2:** Increase the prebreakfast insulin dose by 2 units every 2–3 days until presupper glucose is <7 mmol/L.
- **Step 3:** Increase the presupper insulin dose by 2 units every 2–3 days until prebreakfast glucose is <7 mmol/L.
- **Step 4:** Keep glucose monitoring requirements to a minimum measuring specifically before breakfast and before supper. It is valuable to occasionally check the prelunch and prebedtime glucose levels to ensure there is no evidence of hypoglycemia.

Initiating premixed insulin in a patient using basal insulin

- **Step 1:** Stop the basal insulin dose.
- **Step 2:** Divide the total basal insulin dose, giving half the dose as premixed insulin before breakfast and half the dose before supper.
- **Step 3:** Titrate premixed insulin doses before breakfast and before supper as described above.

INSULIN PUMP THERAPY

The development of highly sophisticated insulin pumps has provided the possibility of insulin pump therapy being available to patients with type 1 or type 2 diabetes. Continuous glucose-monitoring systems have further enhanced the ability to achieve

close to perfect glucose control throughout the 24-hour period. For a patient to be considered for pump therapy, it is important to establish that they fit certain criteria:

- Be knowledgeable about their diabetes management.
- Understand the concepts of insulin titration.
- Be prepared to do multiple glucose-monitoring tests throughout the day and to interpret these values.
- Understand the concepts of nutrition, particularly carbohydrate counting.
- Be relatively independent in their diabetes management.

Insulin requirements tend to be much higher in the insulin-resistant patient with type 2 diabetes and, thus, insulin algorithms need to be appropriately adjusted to achieve euglycemia.

ADJUSTMENT OF ORAL ANTIHYPERGLYCEMIC AGENTS

Many patients remain on combinations of oral antihyperglycemic drugs, such as metformin and sulfonylureas, when on basal insulin therapies. Once intensification using rapid-acting insulin has commenced, there is little need to continue with sulfonylurea therapies. Metformin can be continued at its current dose.

IS INTENSIVE MANAGEMENT SAFE?

While intensive glucose management has proven to be successful in reducing microvascular complications, the results are not so clear as relates to macrovascular disease. The ACCORD trial (7) attempted to rapidly reduce the A1C level to below 6%, but the intensive glucose-control arm of the study was terminated before the trial was completed because of higher all-cause mortality in this group. Fears were raised that even lowering A1C below 7% maybe harmful to patients with type 2 diabetes.

Further analysis of the data revealed that the increased mortality in ACCORD occurred mainly in patients who had responded poorly to intensive treatment, had higher A1C levels, were older, and had significant cardiovascular risk factors. Patients who commenced the study with lower A1C or quickly responded to intensive treatment appeared to be at less risk. Thus, an acceptable approach would be to identify patients who have poor glycemic control, who are older, and who have previously failed to respond to more intensive treatment. These patients would benefit from a more individualized approach and less aggressive glycemic targets. However, the data from ACCORD should not be used as an excuse to allow patients to remain in poor control or to not receive early, aggressive therapy, when appropriate.

NUTRITION

A thorough review of nutritional concepts is required before commencing insulin. Many patients may not, in fact, have had a recent review of their nutritional requirements, and with the commencement of insulin therapy, issues such as adjustment of food for activities, illness and changing insulin doses, must all be considered. Carbohydrate counting can be most useful in predicting the quantities of insulin that will be required for any particular meal. Some patients, however, are reluctant to go through the process of carbohydrate counting, but by using information gathered from PPG measurement, how much insulin is required for any specific type of food can be quickly established. Most patients will become quite proficient at assessing the quantity of insulin to be taken prior to a meal, given the type of food and activities planned after the meal.

EDUCATION

An effective educational program is essential before commencing insulin. Once the patient has learned the techniques of insulin injection, understanding the concepts of insulin adjustments will enable the patient to remain confident in making appropriate insulin dose changes to fit their varied lifestyle. Establishing a process of follow-up further enables the patient to learn the appropriate techniques of insulin adjustment and become increasingly independent in this self-management. Follow-up can be arranged by visits to the diabetes educator, but simple techniques—such as telephone calls and faxed information—permit easy interaction between patient and educator. Recently, the use of Internet data transfer has proved to be most successful in lowering A1C and keeping the time commitment of both patient and educator to a minimum (25).

With the increasing number of patients who will require insulin therapy, the development of effective, time-efficient educational programs with comprehensive follow-up can prove to be most beneficial.

SUMMARY

It is clear that there have been many barriers preventing patients from reaching established glycemic targets. Recent research emphasizes the importance of early, aggressive management, and this will certainly require the use of insulin. Early introduction of insulin therapy will make a difference to glucose control in the patient with type 2 diabetes. While basal insulin therapy will provide good glucose control early in the disease, with the progressive nature of type 2 diabetes, intensification of insulin will be required. The large selection of insulins and insulin algorithms available

to the healthcare provider ensures that good glucose control is possible in patients with type 2 diabetes and that glycemic targets can be met. While it is difficult to fully understand the delays that appear to take place in intensifying insulin therapy, there are now few barriers to prevent success.

When considering a patient for intensification of insulin, the answer now is quite clear: just do it!

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Self-Monitoring of Blood Glucose in People with Type 2 Diabetes

Self-management of diabetes remains one of the cornerstones of diabetes self-care. As such, Self-Monitoring of Blood Glucose (SMBG) is an important and essential tool for people living with diabetes, and should be individualized for each patient.

The Canadian Diabetes Association has developed three SMBG tools—one for healthcare providers and two for people living with diabetes—to not only identify SMBG recommendations

and pattern management for healthcare providers, but to provide essential information and education for patients for optimal self-management.

Building these tools into your practice and working with your patients on their individual needs for SMBG will ensure that they receive the best support and enable them to take effective action on their SMBG results.

For more information about SMBG and to download these tools, visit www.diabetes.ca/SMBG.

INSULIN THERAPY...CONTINUED FROM PAGE 10

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Canadian Diabetes and Canadian Journal of Diabetes, are amalgamating in 2012!

The amalgamated *Canadian Journal of Diabetes* will continue to provide high quality information about diabetes and its management. Readers of the journal will notice the addition of articles that help to advance the practice of diabetes care and education, which has been the mandate of *Canadian Diabetes*.

If you are already a member of one of the professional sections of the Canadian Diabetes Association you will continue to receive this valuable information. If not then become a member today by signing up at www.diabetes.ca/professionals/members-only.

