

Chapter

9

**INSULIN THERAPY IN
TYPE 2 DIABETES**

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Insulin is the most powerful and effective pharmacologic tool available to treat diabetes. Its potential to lower plasma glucose levels is limited only by hypoglycemia. As is the case with oral agent treatment, sustained near-normoglycemia to forestall the onset and progression of long-term complications is the primary treatment goal of insulin therapy.

**ACHIEVING AND SUSTAINING NORMOGLYCEMIA
WITH INSULIN THERAPY**

As discussed elsewhere in this book, the target glycemic level is as near to normal as possible, as measured using hemoglobin A1C (A1C). Normal A1C is 4% to 6%. CADRE proposes a “realistic target,” characterized as the lowest A1C level possible without unacceptable hypoglycemia, with the clear recommendation of “action suggested” at A1C levels $>7.0\%$. This position is clinically oriented and is supported by evidence-based interventional outcome studies on diabetic complications.¹⁻³

The progressive course of type 2 diabetes reflects the relentless decline in pancreatic β -cell function and endogenous insulin secretion, which is presumed to begin years before diagnosis⁴ (Fig. 9-1). As a result, most patients will eventually require insulin replacement therapy. Insulin therapy earlier during the course of diabetes can compensate for insufficient endogenous secretion, reducing strain on the β -cell and potentially preserving its function.^{5,6} In addition, effective insulin therapy can help improve insulin resistance by correcting glucotoxicity and lipotoxicity.⁷⁻¹¹

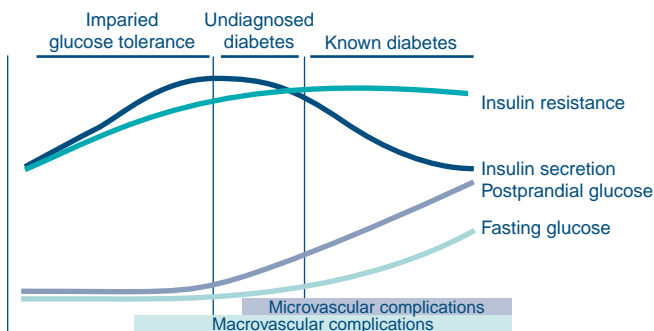


FIGURE 9-1. *Natural history of type 2 diabetes.* Type 2 diabetes is characterized by higher-than-normal insulin resistance accompanied by a progressive decline in β -cell function, and consequent insulin secretion. The insulin secretory defect begins before the disease is typically diagnosed. Adapted with permission from Ramlo-Halsted BA, Edelman SV.⁴

The use of insulin has traditionally been postponed for years and reserved as a last resort after all other options—diet, exercise, and oral antidiabetic agents alone or in multiple combinations—have failed to produce or maintain adequate glycemic control. However, this long-established paradigm is changing in light of recent results from studies showing the effectiveness of early addition of basal insulin to an oral agent in patients with type 2 diabetes.^{6,12}

Thus, the primary objective of insulin therapy is to achieve and maintain near-normal glycemic control by replacing the progressive deficit of insulin in type 2 diabetes. To achieve this objective, insulin-replacement strategies should be implemented as soon as necessary—based on A1C targets—with a more physiologic replacement regimen, designed to simulate nondiabetic patterns of insulin secretion to safely achieve near-normal 24-hour fasting and postprandial glucose profiles. Insulin therapy should no longer be viewed as a last resort, but as an effective therapeutic tool that should be used much earlier to achieve and sustain target-level glycemic control.

This chapter focuses on the use of insulin to treat type 2 diabetes. For information on type 1 diabetes, see reference 13.

OVERCOMING BARRIERS TO INSULIN THERAPY

Historically, there have been many real and perceived barriers to initiation of insulin therapy in patients with type 2 diabetes. These include:

- ▲ Misconceptions and stigmas about the significance of insulin and complications
- ▲ Limitations of insulin formulations
- ▲ Complexity of insulin regimens
- ▲ Limited time and resources in busy primary care settings
- ▲ Skepticism that patients can reach glycemic targets
- ▲ Risk of hypoglycemia
- ▲ Weight gain
- ▲ Misconceptions about the association of insulin with atherogenesis
- ▲ Fear of needles

Many of these barriers are relics of outdated insulin preparations and delivery systems as well as the “last resort” approach to insulin therapy. In fact, administering insulin in a manner that mimics normal physiology, as discussed later in this chapter, is the key to overcoming many of the barriers listed above. However, there are three major barriers that discourage some physicians from using insulin in the treatment of type 2 diabetes: excessive concerns with weight gain, the potential risk of hypoglycemia, and, most notably, the misconception or the myth that insulin therapy may increase the risk of cardiovascular (CV) disease (Table 9-1). A fourth major barrier involves the use of needles and lancets, which are obviously necessary for administration of insulin and proper glucose monitoring. Each of these barriers deserves separate consideration.

Table 9.1 Overcoming Major Barriers to Insulin Therapy in Patients With Type 2 Diabetes

Barriers	Effects of Insulin Therapy
Insulin resistance	Improves insulin sensitivity by reducing glucotoxicity
Cardiovascular risk	No evidence of atherosclerotic effects Reduces cardiovascular risk factors
Weight gain	Modest and avoidable
Hypoglycemia	Rarely causes severe events when used properly

Source: Reprinted from Rosenstock,³¹ with permission.

Weight Gain

Although modest weight gain during insulin therapy is a well-recognized phenomenon, the benefits of improved glycemic control clearly surpass the impact of weight gain.¹ This increase in weight within the range of 2-5 kg may be explained in part by lack of adherence to dietary regimens, as well as decreased caloric loss from glycosuria due to improved glycemic control. In addition, when clinically appropriate, weight gain can be minimized by combining insulin with metformin.^{14,15}

Hypoglycemia

The risk of mild to severe hypoglycemia is generally increased with intensive insulin therapy, but this increase depends on a number of factors, including age, weight, degree of insulin resistance, duration of disease, presence or absence of diabetic neuropathy, endogenous insulin secretion, glycemic goal, and history of hypoglycemic episodes. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that over a 10-year period, the incidence of hypoglycemia in patients randomized to intensive

insulin therapy was, as expected, greater than that of patients assigned to treatment with sulfonylurea or metformin. However, most episodes of hypoglycemia were mild to moderate in intensity, and the 12-month average incidence of severe episodes was 2% to 3%, approximately 10 times lower than that for patients with type 1 diabetes.^{1,2,16,17}

Nevertheless, hypoglycemia remains the major limiting factor for insulin adjustments and achievement of near-normoglycemia. Indeed, the frequency and severity of hypoglycemia will likely become even more relevant to clinicians as increasingly aggressive guidelines for fasting and postprandial glucose targets and for A1C are established.¹⁸

Note that CADRE's position on A1C targets specifically includes hypoglycemia in the decision-making process to establish a realistic goal for each patient. Patients at higher risk of hypoglycemia may not be able to safely achieve A1C levels within the near-normal range. The lowest possible A1C level will vary according to each individual's risk of hypoglycemia.

Myth of Insulin and Atherosclerosis

To date, there is no evidence linking exogenous insulin therapy and atherosclerosis, nor is there any evidence indicating that insulin therapy increases the risk of cardiovascular events. In fact, in the UKPDS, insulin therapy was associated with a nearly significant ($P = 0.052$) reduction of myocardial infarction.^{1,3} Moreover, the 5-year Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, in which at least 3 months of intensive insulin therapy was given to patients immediately after a myocardial infarction, demonstrated a 28% relative risk reduction of mortality after 5 years of insulin therapy.¹⁹ The DIGAMI findings suggest that insulin may be the most appropriate treatment for patients with type 2 diabetes with evidence of cardiovascular disease, particularly at myocardial infarction.

Patient Education to Overcome Fear of Needles

Two genuine barriers that remain are the need for injections and invasive blood glucose monitoring. Effective education on the

proper role of insulin, started at the time of diagnosis of diabetes, may go far to overcome these obstacles. Future acceptance and adherence to earlier insulin replacement therapy will be facilitated if the patient has a better understanding of the role of insulin therapy in the overall management of type 2 diabetes. The patient should understand that, at some point, lifestyle changes and oral agents may not be sufficient to attain treatment goals.

Most importantly, insulin should not be presented as a threat or a last-ditch effort. The patient needs to understand that insulin therapy should not be viewed as a punishment or sign of failure. Instead, the concept of insulin as a treatment to be expected in the management of type 2 diabetes should be explained at the initial diagnosis, even if the patient's blood glucose levels at that time can be adequately controlled by lifestyle changes and oral agents. Moreover, it should be made clear that for type 2 diabetes, insulin therapy can be started gradually in combination with oral agents, as part of a simple regimen, with relatively few glucose tests required, and accompanied by a low risk of hypoglycemia.

Finally, at diagnosis, a simple educational demonstration to the patient of an insulin injection using saline may be a powerful strategy to dispel fears, stigmas, and any myths involving needle injections.

Future Advances

Future advances may simplify insulin therapy for type 2 diabetes by overcoming the need for injections. Pulmonary systems that can deliver insulin by inhalation are anticipated to ease the introduction of insulin therapy, increase patient acceptance and adherence, and reduce clinicians' reluctance to use insulin in a timely way.²⁰⁻²²

PHYSIOLOGIC INSULIN REPLACEMENT

The barriers to insulin replacement therapy can also be reduced by taking a more gradual approach to meeting physiologic needs. Ideal insulin replacement therapy in type 2 diabetes may

Table 9-2 Physiologic Insulin Replacement Therapy: Applying the Basal/Bolus Insulin Concept

Basal insulin

- ▲ Nearly constant day-long insulin level
- ▲ Suppress hepatic glucose production overnight and between meals
- ▲ Cover 50% of daily needs

Bolus insulin (mealtime)

- ▲ Immediate rise and sharp peak at 1 h
- ▲ Limit postmeal hyperglycemia
- ▲ Cover 10–20% of total daily insulin requirement at each meal

Ideally, each component should come from a different insulin, with a specific profile.

Modified from Rosenstock,³¹ with permission.

eventually require a combination of insulin preparations, taken two, three, or four times daily, to reproduce both the basal (fasting and between-meal) and the prandial/postprandial secretion patterns normally produced in the absence of diabetes (Table 9-2, Fig. 9-2). However, this complete “basal-bolus” regimen is rarely needed early during the course of type 2 diabetes. In most cases, initial use of a single injection of a longer-acting basal insulin will effectively control the rate of hepatic glucose production during the night and normalize fasting glucose levels. If started early, when the patient has better pancreatic β -cell reserve, this simple approach may also assist in controlling day-time glucose levels, allowing partial recovery of endogenous insulin secretion by eliminating the adverse effects of previously poor metabolic control.¹⁸

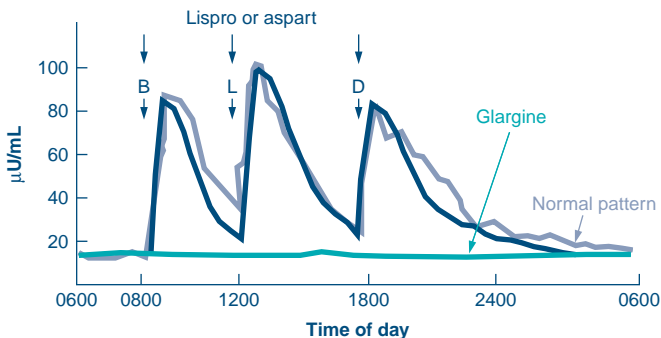


FIGURE 9-2. *Basal-bolus insulin treatment.* Insulin replacement therapy should mimic, as closely as possible, the normal pattern of meal-stimulated endogenous insulin secretion. In this illustration, the insulin analogue glargine replaces basal insulin, while the analogues lispro or aspart are used to replace postprandial insulin.

CHARACTERISTICS OF AVAILABLE INSULINS

Basal Insulin Replacement Options

Human insulins: NPH, lente, and ultralente

The intermediate-acting insulins neutral protamine hagedorn (NPH) and lente have been used to approximate basal secretion in regimens of 1 or 2 daily doses. These insulins have a slow onset of action with a pronounced peak effect between 4 and 8 hours after injection (Table 9-3, Fig. 9-3, Fig. 9-4).^{13,23} Both preparations exhibit variability of action (both between patients and with repeated injections in the same person) depending on characteristics of the injection site, insulin dosage, skin temperature, and most notably whether proper resuspension of insulin crystals (by agitation of the vial or cartridge) was done before injection. These preparations carry the disadvantage of requiring a rigid time schedule for meals to match the peak effect of the insulin dose administered several hours earlier, which minimizes the risk of hypoglycemia. Moreover, when regular (unmodified human) insulin is used to control postprandial glycemia, the pronounced peak effects of NPH and lente may overlap with its effects, con-

Table 9-3 Pharmacokinetics of Human Insulin and Analogues

	Onset of Action	Peak (h)	Duration of Action (h)
Human insulin			
Regular	0.5–1 h	2–4	6–8
NPH	2–4 h	4–10	12–20
Lente	2–4 h	4–10	12–20
Ultralente	4–6 h	Unpredictable	18–20
Analogue			
Lispro	5–15 min	1–2	4–5
Aspart	5–15 min	1–2	4–5
Glulisine ^a	5–15 min	1–2	4–5
Glargine	2–4 h	Flat	~24
Detemir ^a	2–3 h	6–10	16–22

The time course of action of any insulin may vary between individuals, or at different times in the same individual. Consequently, the data presented should be considered only as a general guideline.

^aIn development.

Source: Refs. 13, 23, 27, 32.

tributing to an increased risk of hypoglycemia, especially at night. Another lente formulation, ultralente, has a more gradual and late peak with longer duration of action than NPH or lente, but its effects are similarly erratic and unpredictable.

Long-acting insulin analogues: glargine and detemir

Insulin glargine is the first insulin analogue with a prolonged duration of action (Table 9-3, Fig. 9-3, Fig. 9-4). Changes in the amino acid sequence of human insulin produce a shift in the isoelectric point, which results in a clear preparation that is soluble only at acidic pH 4. In subcutaneous tissues, which have a neutral pH, the reduced solubility of glargine stabilizes the hexameric form of insulin and delays dissociation into dimers and monomers and subsequent absorption into the systemic circulation. Consis-

tent with its slow absorption rate, insulin glargine has a flat 24-hour profile, allowing for once-daily administration with no pronounced peak of action and less variability than NPH, lente, and ultralente (Fig. 9-3).²⁴⁻²⁶

Insulin detemir is another long-acting analogue in development. It is expected to be approved and commercially available in the near future. The basis for its protracted action is attachment of a fatty acid side chain to the insulin molecule, promoting binding and high affinity for serum albumin. Glycemic clamp studies show that the profile of detemir is flatter than NPH, but it has a discernible peak and a duration of action of less than 24 hours. Like glargine, it shows less variability of action than human insulin preparations. Like NPH and lente insulins, it may need to be taken twice daily to best supplement basal insulin requirements, but it needs to be administered at a higher molar dose.^{26,27}

Mealtime Insulin Replacement Options

Regular human insulin

Regular human insulin is widely used to replace meal-stimulated endogenous insulin secretion. However, it is slowly absorbed into the systemic circulation with a consequent slow onset of action (Table 9-3, Fig. 9-3). The time it takes to reach peak concentrations requires that regular insulin be administered 20 to 30 minutes before a meal to avoid or minimize a potential mismatch with the hyperglycemic peaks that follow meal ingestion.^{13,23} This conventional recommendation for regular insulin administration is inconvenient and unrealistic and poses a risk of pre-meal hypoglycemia if the meal is inadvertently delayed. Furthermore, the duration of action of regular insulin, especially when large doses are used, is much longer than the physiologic insulin peak in response to a meal, thereby increasing the risk of late postprandial hypoglycemia.

Rapid-acting insulin analogues: aspart and lispro

Two fast-acting insulin analogues, lispro and aspart, each have an increased rate of dissociation into monomers. Thus, their absorption profiles allow for more physiologic replacement of mealtime

insulin secretion. Because of their rapid onset of action, unlike regular insulin, lispro and aspart may be administered immediately before, with or just after meals (Table 9-3, Fig. 9-3). From a patient's perspective, these characteristics allow more flexibility in the timing of administration relative to meal consumption, making the use of these analogues more convenient and effective. In studies comparing lispro or aspart pharmacokinetics with those of regular insulin, the overall properties of the rapid-acting analogues demonstrated profiles that more closely provide physiologic insulin coverage in response to meals, with peak action at approximately 60 minutes after administration.²⁸⁻³¹ However, the duration of activity of these rapid-acting insulin analogues is shorter (4 to 5 hours), necessitating basal insulin replacement. Insulin glulisine, another rapid-acting analogue in development with a profile of action similar to that of insulin lispro and aspart, is expected to be commercially available soon.³²

INSULIN IN THE MANAGEMENT OF TYPE 2 DIABETES

Newly Diagnosed Type 2 Diabetes With A1C >10%

Insulin therapy can be used in patients with significant hyperglycemia at diagnosis to reestablish prompt glycemic control (see Chapter 8). Once glycemic levels are under control, this initial phase of intensive insulin therapy can be followed by oral agents with or without continuation of the insulin. Over time, however, with the progressive worsening of underlying β -cell dysfunction, most patients will eventually require insulin therapy.

Starting Insulin Therapy After Oral Agent Therapy in Type 2 Diabetes

Most clinicians would agree that insulin therapy should be started when oral agents "fail." How we define failure becomes a matter of clinical judgment. Recent results from the UKPDS demonstrated the benefit of adding insulin to existing sulfonylurea therapy, in this case when patients' fasting glucose levels exceeded 108 mg/dL.¹² CADRE recommends that insulin therapy should be considered for a patient with an A1C level of >7% despite maximized lifestyle

intervention and oral agent therapy (ie, combination therapy with two oral agents; see Chapter 8) and for whom there would be additional benefit from further improvement of glycemic control.

Adding basal insulin to existing oral therapy

A practical approach to overcome the complexity of insulin regimens in type 2 diabetes is to start with evening basal insulin replacement³¹ (Table 9-4). Starting basal insulin replacement while continuing the use of oral agents has several advantages:

1. Only one daily injection is usually required, without the need to mix different insulin preparations.

Table 9-4 Practical Guidelines: Starting Basal Insulin

- ▲ Continue oral agent(s) at same dosage (eventually reduce)
- ▲ Add single, evening insulin dose (~10 units)
 - ▲ Glargine (bedtime or anytime at the same time daily)
 - ▲ NPH or detemir^a (bedtime)
- ▲ Adjust dose weekly according to average FBG monitoring
- ▲ Insulin adjustments weekly as needed
 - ▲ Increase by 2 units if FBG 100–20 mg/dL
 - ▲ Increase by 3 units if FBG 121–140 mg/dL
 - ▲ Increase by 4 units if FBG 140–160 mg/dL
 - ▲ Increase by 5 units if FBG 161–180 mg/dL
 - ▲ Increase by 6 units if FBG >180 mg/dL
- ▲ Stop titration or reduce insulin if FBG <72 mg/dL or evidence of hypoglycemia

FBG, fasting blood glucose.

^aWhen available.

Source: Adapted from Rosenstock,³⁹ with permission.

2. Titration can be accomplished in a slow, safe, and simple fashion.
3. A lower total dose of insulin will be needed, because of the complementary effects of the individual therapies.

The complementary effects of combining oral agents with basal insulin have been demonstrated in a number of studies adding once-daily ultralente, dinnertime 70/30 mix, bedtime NPH, or bedtime or morning glargine to sulfonylureas alone or in combination with metformin.^{12,14,33-41} In all these studies, a single evening or bedtime injection of basal insulin with continued use of one or more oral agents was shown to lower fasting hyperglycemia, with a beneficial carryover effect on glycemic levels later in the day. The result was significant improvement in A1C levels. By improving overnight glucose control enough to correct glucotoxicity, the injected long-acting insulin may enable the oral agents to exert their full effect on potentiating postprandial insulin secretion. The final result is improved glycemic control, with a reduced need for exogenous insulin as endogenous insulin becomes more available.

Furthermore, the recent "Treat to Target" study comparing basal replacement therapy with bedtime insulin glargine or NPH added to oral combination therapy in insulin-naïve patients also confirmed the efficacy of adding basal insulin to oral therapy. In this study, the insulins were administered using a simple but structured titration seeking fasting plasma glucose (FPG) levels of <100 mg/dL to reach A1C levels of <7%. A remarkable glycemic improvement was clearly demonstrated in the study population overall, with rare incidence of severe hypoglycemia and only a modest increase in body weight. A1C values decreased from 8.6% at baseline to 7.0% by the end of the study with both insulins. NPH and insulin glargine were equally effective, achieving A1C ≤7% in almost 60% of patients. The main difference between NPH and glargine was that the glargine group had a 21% to 48% risk reduction of various categories of hypoglycemia, especially nocturnal hypoglycemia, compared with the NPH group.⁴¹

The efficacy, safety, and ease of the basal insulin strategy make it especially accommodating to the needs of time-pressed clinicians in general practice, who manage the great majority of patients with type 2 diabetes. This approach also serves to dispel two major myths about insulin therapy: that it poses a dangerously high risk of hypoglycemia, and that it is too complex to be effective in the primary care setting.

Adding pre-meal insulin to existing oral therapy

An alternative way to initiate insulin therapy is to use mealtime insulin supplementation to limit postprandial hyperglycemic peaks, while continuing a sulfonylurea and/or a sensitizing agent such as metformin or a glitazone. Proof of this concept was demonstrated in a study using three injections of mealtime lispro insulin added to a sulfonylurea, resulting in a slightly lower A1C and better postprandial glucose levels but greater weight gain than that shown with NPH or metformin added to a sulfonylurea.⁴² However, for patients starting insulin therapy, taking multiple pre-meal injections is considerably more complex and less attractive than the once-daily evening dose of basal insulin. Perhaps in the future, when inhaled insulin becomes available, noninjectable pre-meal insulin replacement may become another standard way to begin insulin therapy, with later addition of basal insulin supplementation as required.

Advancing Insulin Therapy in Type 2 Diabetes

Over time, insulin regimens must be intensified to match the usual decline of endogenous insulin. This need is signaled by failure to maintain glycemic control at the A1C target. Several methods of intensifying therapy have been used.

Twice-daily injection options: split-mixed insulins

The twice-daily, split-mixed insulin regimen has been the most widely used way to intensify the previous regimen of once-daily basal insulin in combination with oral agents. When this regimen is started, oral agents are sometimes discontinued, but little experimental evidence supports the effectiveness of this switch from oral to insulin therapy alone.

The “split-mixed” regimen consists of a before-breakfast and before-supper mixture of NPH with regular human insulin or a rapid-acting insulin analogue (lispro or aspart). The prandial insulin of the morning dose is intended to control glycemic levels between breakfast and lunch, whereas the intermediate-acting insulin NPH peaks close to the midday meal and extends its action until supertime. At the evening meal, theoretically, the prandial component of the second split-mixed dose provides the insulin coverage between dinner and bedtime, whereas overnight coverage is provided by the NPH, which peaks in the middle of the night and often overlaps with the residual activity of the regular insulin. Adjustment of the dosing of both insulins is based on self blood glucose monitoring results, usually recommended to be done three or four times daily, before meals and at bedtime.

Several premixed insulin formulations are available and are widely used in the twice-daily injection regimen: 70/30 NPH/regular insulin, 70/30 protamine aspart (NPA)/aspart insulin, or 75/25 protamine lispro (NPL)/lispro. Although these formulations eliminate the need for patients to mix their own insulins, they lack flexibility for specific titrations of each insulin component based on self blood glucose monitoring. As a result, premixed insulins have major limitations in terms of reaching glycemic targets.^{31,39-40}

Twice-daily injection options: morning and evening NPH

Another option for intensification of a basal insulin plus oral agent regimen, suited to patients already taking a bedtime injection of NPH, is to add a second injection of NPH in the morning.¹⁴ However, coverage of early morning requirements with bedtime NPH is often inadequate, with frequent fasting hyperglycemia because of limited duration of effect. Increasing the bedtime NPH dose in an attempt to improve fasting hyperglycemia will often result in pronounced nocturnal insulin peaks that often lead to nocturnal hypoglycemia. Moreover, this method fails to address the increasing need for mealtime insulin supplementation that is usually present at this stage of treatment.

Twice-daily injection options: basal glargine + rapid analogue at main meal

Basal insulin glargine in combination with oral agents can also be intensified by first adding an injection of a rapid-acting analogue before the main meal to correct the problematic postprandial hyperglycemia, which most often occurs after the evening meal. This option has not been well studied, but conceptually it is easy to implement especially when insulin glargine is used as the basal insulin. In this circumstance, the second injection of the rapid-acting analog is adjusted independently to control immediate postprandial hyperglycemia without impacting the effect of insulin glargine on overnight or on late between-meal glucose levels.

Multiple daily injections

Advancing the insulin regimen to multiple daily insulin (MDI) therapy using rapid-acting analogues at all meals to closely match normal prandial insulin patterns, and insulin glargine (or insulin detemir when available) to cover basal insulin requirements, will eventually be required by many patients³¹ (Table 9-5). This regimen allows increased flexibility providing a more physiologic insulin replacement with independent insulin adjustments based on glucose monitoring to guide insulin titrations. The MDI approach, either with continuation of oral therapies or without oral agents, can be progressively implemented according to the needs of the patient and the accomplishment of glycemic targets.

Insulin pump therapy for type 2 diabetes

The use of continuous subcutaneous insulin infusion (CSII) therapy, also known as insulin pump therapy, as an alternative to MDI therapy is highly controversial in type 2 diabetes. This is because of the expense and the need for a high degree of patient education and monitoring, as well as health care provider training. For more information on pump therapy, please refer to the American Diabetes Association (ADA) position statement on this topic.⁴³

Table 9.5 Practical Guidelines: Advancing Basal/Bolus Insulin

- ▲ Indicated when FBG acceptable (100 mg/dl) but
 - ▲ A1C remains >7% and/or
 - ▲ SBGM before lunch/dinner >160–180 mg/dL
- ▲ Insulin options
 - ▲ To glargine, add mealtime lispro or aspart at main meals
 - ▲ To bedtime NPH, add morning NPH or detemir^a and mealtime lispro, aspart, or glulisine^a
- ▲ Oral agent options
 - ▲ Continue sulfonylurea for endogenous secretion?
 - ▲ Continue metformin for weight control?
 - ▲ Continue glitazone for glycemic stability?

^aWhen available.

Sources: Adapted from Rosenstock,³¹ with permission.

Using Oral Agents with Multiple Injections of Insulin

The impact of stopping or continuing with the oral agents, once insulin administration is advanced to more than one injection per day, has not been studied systematically. It appears that insulin secretagogues may not be required if insulin is administered intensively. However, as discussed above, multiple studies with sulfonylureas in combination with exogenous insulin show a benefit with this strategy. It is conceivable that these agents can still enhance endogenous insulin secretion, leading to lower insulin requirements and perhaps smoother glycemic control.⁴⁴

In terms of insulin-sensitizing agents, the use of metformin, if tolerated and not contraindicated, appears obvious to reduce insulin resistance and to minimize weight gain.³¹ There is some experimental evidence suggesting that glitazone therapy may preserve β -

cell function and perhaps facilitate a more durable glycemic control.⁴⁵ However, few studies have been published in which insulin therapy was added to a combination of oral agents that included a glitazone.⁴¹ Glitazones have been used extensively as add-on therapy in patients with chronic hyperglycemia who were already on conventional, nonintensive insulin regimens. These studies have demonstrated improved A1C levels within the range of 0.8% to 1.2%, with reduction of insulin requirements.^{46,47} However, the use of a glitazone with insulin is controversial because of the potential for significant weight gain and fluid retention. There is a Food and Drug Administration (FDA) warning for glitazones in combination with insulin stressing caution in patients with edema, coronary artery disease, and mild forms of congestive heart failure (CHF) (not recommended in NYHA class III and IV). It may be better not to use these agents with insulin if there is any evidence of CHF until further long-term safety or surveillance studies are available.

SUMMARY

Early insulin replacement in type 2 diabetes involving insulin analogues with improved pharmacokinetic properties in combination with oral agents can attain target glycemic control in a simple, safe, and effective manner. This approach has the potential to raise the standards of diabetes care in general practice.

Future developments in the routes of reliable insulin administration with inhaled insulin, when available, as well as reliable insulin injection devices such as insulin pens, may facilitate the implementation and wider use of these progressive insulin regimens.

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