

The Role of Basal Insulin Therapy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: The natural course of type 2 diabetes mellitus (DM) is characterized by insulin resistance followed by a progressive decline in β -cell function, which results in relative insulin deficiency. At diagnosis, a patient with type 2 DM has only 50% of β -cell function remaining. Given this inevitable decline in β -cell function and insulin secretion, most patients with type 2 DM will require insulin therapy at some point.

Objective: The objective of this article was to provide a brief overview of physiologic insulin secretion and to discuss the role of basal insulin therapy in patients with type 2 DM.

Methods: Materials for this article were identified through searches (2000–2005) of MEDLINE and Google, as well as from the author's personal files. Search terms included *basal insulin*, *titration*, *hypoglycemia*, *glycemic control*, and *basal-bolus therapy*.

Results: The efficacy of insulin either as monotherapy or in combination with oral agents in type 2 DM is well established. Insulin therapy has also been shown to improve insulin sensitivity and, in some cases, reverse insulin resistance, possibly by elimination of glucose toxicity. In recent years, the availability of insulin formulations with more favorable pharmacokinetic profiles has reduced concerns about hypoglycemia and weight gain, facilitating the use of insulin in patients with type 2 DM. For insulin-naïve patients who are inadequately controlled on oral antidiabetic drugs, the addition of a single basal insulin dose at bedtime has been found to reduce glycosylated hemoglobin (A1C) levels, with a low risk of nocturnal hypoglycemia. Basal insulins (ie, glargine, detemir) have also been shown to induce less weight gain, a significant concern for both patients and providers. The use of long-acting basal insulins may also reduce inpatient variability in fasting blood glucose values. Moreover, the long-acting basal insulins such as glargine and detemir can be administered QD, which may enhance the potential for patient compliance. Aggressive titration of insulin doses based on a target fasting plasma glucose level of 100 to 120 mg/dL is essential to achieving target A1C levels (<7.0%). As β -cell function declines, patients may require a switch to basal-bolus insulin therapy. Although the long- and intermediate-acting insulin formulations are comparable with regard to efficacy as the basal component in basal-bolus therapy, the long-acting insulins have been associated with lower rates of nocturnal hypoglycemia, which can have a positive effect on glycemic control during the daytime.

Conclusion: Basal insulins, both intermediate- and long-acting formulations, are playing an increasingly important role in the treatment of type 2 DM. (*Insulin*. 2006;1:51–60) Copyright © 2006 Excerpta Medica, Inc.

Key words: basal insulin, type 2 diabetes mellitus, insulin, basal-bolus therapy.

INTRODUCTION

The natural course of type 2 diabetes mellitus (DM) is characterized by insulin resistance followed by a progressive decline in β -cell function, which results in relative insulin deficiency. Early in the course of type 2 DM, pancreatic β -cells hypersecrete insulin to compensate for insulin resistance in the peripheral tissues. Eventually, β -cell exhaustion occurs, resulting in insufficient insulin secretion to maintain glycemic control.¹ In addition, hyperglycemia may have a direct toxic effect on β -cells: persistently elevated glucose levels may result in dedifferentiation of β -cells or in β -cell apoptosis without a compensatory increase in proliferation.¹

Indeed, at diagnosis, a patient with type 2 DM has only 50% of β -cell function remaining.² With every year of living with uncontrolled DM, β -cell function declines further. Therefore, a patient who has lived for 12 years with type 2 DM may be as profoundly insulin deficient as a patient with type 1 DM. Given this inevitable decline in β -cell function and insulin secretion, most patients with type 2 DM will require insulin therapy at some point. Results from the United Kingdom Prospective Diabetes Study (UKPDS) showed that 53% of patients initially randomized to treatment with a sulfonylurea eventually required insulin therapy within 6 years of follow-up to maintain adequate glycemic control.³

With every year of living with uncontrolled DM, β -cell function declines further.

The efficacy of insulin either as monotherapy or in combination with oral agents in type 2 DM is well established. In addition to the insulin treatment arm in the UKPDS, a substudy of that trial demonstrated that early addition of insulin to oral antidiabetic drug (OAD) therapy, soon after failure of the oral therapy, can safely maintain glycosylated hemoglobin (A1C) near target levels.³ In this study protocol, patients received insulin therapy if maximal doses of the sulfonylurea did not maintain fasting plasma glucose (FPG) levels <108 mg/dL. Sulfonylurea therapy was continued unchanged and ultralente insulin (human or bovine) was added, with the starting dose based on FPG. Insulin doses were increased as necessary to maintain FPG <108 mg/dL. Patients receiving early insulin therapy had lower median A1C values than those receiving insulin alone, and a higher proportion of patients achieved the target A1C of <7.0%. Moreover, the incidence of major hypoglycemia was lower in the group treated with a sulfonylurea plus insulin than in the group treated with insulin alone.³

Insulin therapy has been shown to improve insulin sensitivity and, in some cases, reverse insulin resistance, possibly by elimination of glucose toxicity.⁴⁻⁷ Also, the availability of insulin formulations with more favorable pharmacokinetic profiles has reduced concerns about hypoglycemia and weight gain, facilitating the use of insulin in patients with type 2 DM. In addition, insulin therapy may be a cost-effective therapeutic option in type 2 DM. In a study by Schwartz et al,⁸ therapy with insulin and metformin was more cost-effective than triple OAD therapy (sulfonylurea + metformin + thiazolidinedione).

The objective of this article was to provide a brief overview of physiologic insulin secretion and to discuss the role of basal insulin therapy in patients with type 2 DM.

MATERIALS AND METHODS

Materials for this article were identified through searches (2000–2005) of MEDLINE and Google, as well as from the author's personal files. Search terms included *basal insulin*, *titration*, *hypoglycemia*, *glycemic control*, and *basal-bolus therapy*.

PHYSIOLOGIC INSULIN SECRETION

The normal pattern of insulin secretion involves both basal and bolus (prandial) components. Actions of bolus and basal insulin maintain plasma glucose levels within a fairly narrow range, between 70 and 120 mg/dL in the fasting state and <180 mg/dL after meals.

Basal insulin, which is secreted continuously between meals and during the night at a rate of 0.5 to 1 U/h, inhibits hepatic glucose production and regulates uptake of glucose in the peripheral insulin-sensitive target tissues (muscle and adipose tissue). Basal insulin secretion provides serum con-

centrations of 5 to 15 mU/mL. The prandial component of insulin secretion is stimulated by ingestion of a meal, resulting in serum concentrations of 60 to 80 mU/mL during the period from just before the meal to 30 minutes after the meal. Replication of this meal-related insulin secretion with rapid-acting insulin preparations is often called "bolus insulin" (as opposed to basal insulin replacement).

Stimulated insulin secretion consists of 2 phases: phase I insulin release (which lasts ~10 minutes, suppresses hepatic glucose production, regulates postprandial glycemic excursions, and facilitates phase II release) and phase II insulin secretion (which slowly decays over 2–3 hours and facilitates uptake of carbohydrates from the circulation into the peripheral tissues). After 2 to 4 hours, insulin concentrations return to basal levels. In type 2 DM, the phase I insulin spike is absent, while phase II release is delayed and inadequate.⁹

The goal of insulin therapy is to mimic the physiologic pattern of endogenous insulin secretion. Short-acting insulins are used for bolus therapy to control postprandial glucose levels, whereas intermediate- or long-acting insulins are used for basal therapy. The function of basal insulin in these regimens is to sustain plasma glucose control for ~24 hours, its role being particularly important in the postabsorptive state (ie, overnight and in the period before the premeal bolus injection).

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BASAL INSULINS

The basal insulins are categorized based on their longer duration of action (**Table I**). They include the regular insulins (neutral protamine Hagedorn [NPH] or isophane, lente, and ultralente) and the insulin analogues (glargine and detemir).^{1,10}

Table I. Pharmacokinetic properties of basal insulin preparations.^{1,10}

Insulin Preparation	Onset of Action, h	Peak Action, h	Duration of Action, h
NPH (or isophane)	1–3	4–8	13–16
Lente	1–3	4–8	13–20
Ultralente	2–4	8–14	<20
Glargine	2–4	None	>24
Detemir	1–2	None	~6–24 (dose-dependent)

NPH = neutral protamine Hagedorn.

Regular basal insulins are obtained from human or porcine pancreatic cells and have the same amino acid sequence as naturally occurring insulin. The duration of action of the regular basal insulins varies from 13 to 20 hours. However, the pharmacokinetic and pharmacodynamic profiles of these agents may vary considerably between patients and within the same patient.¹ The intermediate-acting regular insulin preparations such as NPH and lente insulin normally require BID injections to achieve the required basal levels over 24 hours. These agents have an onset of action of 1 to 3 hours, with peak effects occurring between 4 and 8 hours after administration.¹ The peaks in insulin activity may lead to hypoglycemia, particularly nocturnal hypoglycemia after the second daily injection. Ultralente insulin has a later peak action (8–14 hours), with a duration of action of <20 hours. However, ultralente insulin is associated with considerable day-to-day variability and erratic peaks, which may result in unpredictable hypoglycemia.¹ Lente and ultralente insulins are rarely used in current therapy.

Insulin analogues are synthesized using recombinant DNA technology and differ from naturally occurring insulin by one or more amino acids, resulting in an altered pharmacokinetic profile. For example, in insulin glargine, the asparagine at position 21 of the A subunit is replaced by glycine, and the carboxyl terminus of the B subunit has 2 additional arginines. This shifts the isoelectric point of the molecule such that it is less soluble at physiologic pH than the native insulin molecule, resulting in slower absorption and a longer duration of action.^{11,12} Insulin glargine, unlike the regular insulins, has no pronounced peak and a duration of action of >24 hours that is independent of the dose administered; therefore, it provides a fairly constant supply of basal insulin. Insulin detemir, approved by the US Food and Drug Administration in June 2005, is a soluble, long-acting basal insulin analogue. Insulin detemir is an acylated derivative of human insulin that binds tightly to albumin, with little free or unbound drug present in the serum.¹³ It has a fairly flat pharmacokinetic profile, with a slight peak at 6 to 8 hours and a dose-dependent duration of action ranging from 5.7 hours for doses of 0.1 U/kg and 23.2 hours for doses of 1.6 U/kg.¹⁰

BASAL INSULIN REGIMENS

Basal insulins can be used to augment OAD therapy in patients who have some remaining endogenous insulin secretion or can be used with rapid-acting insulins (referred to as basal-bolus insulin therapy) in patients who are or have become insulin dependent. **Table II** provides a summary of some of the major clinical trials of long-acting basal insulins.^{14–21}

Adding Basal Insulin to Oral Antidiabetic Drug Therapy

In patients with type 2 DM who do not achieve glycemic control with OADs alone, insulin therapy can be initiated by adding a single dose of long-acting basal insulin. This strat-

egy has been demonstrated in randomized, controlled studies to be effective at improving glycemic control, without a significant risk of nocturnal hypoglycemia.^{14,15} In general, insulin therapy is started when maximal doses of 2 or more OADs (ie, sulfonylurea + metformin ± thiazolidinedione) fail to achieve glycemic control. Both sulfonylureas and metformin are rapid-acting agents, with effects seen within a few days. The doses of these agents can be titrated up at weekly intervals, with maximal doses reached within 2 to 4 weeks.²² The thiazolidinediones have a slower onset of action, and their peak effects may only be observed after several months.²² Therefore, if OADs do not achieve glycemic targets within 1 to 3 months, insulin therapy may be started by adding a basal insulin to the OAD regimen.

If oral antidiabetic drugs (OADs) do not achieve glycemic targets within 1 to 3 months, insulin therapy may be started by adding a basal insulin to the OAD regimen.

A large trial by Yki-Jarvinen et al¹⁴ demonstrated the effectiveness of adding a single injection of basal insulin to OAD therapy. A total of 426 patients with type 2 DM whose disease was inadequately controlled with OAD therapy (consisting of sulfonylureas alone or in combination with acarbose or metformin, or metformin alone) were randomly assigned to receive a single daily injection of insulin glargine or human NPH insulin while continuing their oral medications at prestudy doses. The initial dose of insulin, as well as the dose adjustments, was left to the discretion of the investigators. However, when possible, dose titrations were to be adjusted to achieve a target fasting blood glucose (FBG) of ≤120 mg/dL. At the end of 52 weeks, mean A1C values decreased significantly from baseline in both groups (from 9.1% to 8.3% in the insulin glargine group and from 8.9% to 8.2% in the NPH insulin group; $P < 0.001$ vs baseline for both). In patients achieving the target FBG after 52 weeks, there was no significant difference in mean A1C between the insulin glargine and NPH insulin groups (7.8% vs 7.6%). Mean daily insulin dose at end point was 21 U in the NPH insulin group and 23 U in the insulin glargine group ($P = NS$). Postdinner glucose concentrations were significantly lower with insulin glargine at end point (9.9 mmol/L vs 10.7 mmol/L; $P < 0.02$), as was the incidence of nocturnal hypoglycemia (9.9% vs 24.0%; $P < 0.001$).¹⁴

In the Treat-to-Target Trial (a multicenter, randomized, open-label, parallel-group study), 756 overweight adults with inadequate control taking 1 or 2 oral agents were randomly assigned to receive basal insulin with insulin glargine or NPH insulin at bedtime while continuing OAD therapy at the same doses.¹⁵ The starting dose of both insulins was 10 IU. The dosage of insulin was then titrated using a simple algorithm, with an FPG target of ≤100 mg/dL (**Table III**). The main end points were FPG, A1C, incidence of hypoglycemia, and percentage of patients reaching the target A1C

Table II. Summary of major clinical trials of long-acting basal insulins.¹⁴⁻²¹

Study Reference	No. of Patients	Regimens	Primary End Point	Rate of Hypoglycemia
Long-acting insulin analogues versus NPH insulin as add-on therapy				
Yki-Jarvinen et al ¹⁴	426	QD insulin glargine or QD NPH insulin added to OAD therapy (SU ± acarbose/metformin or metformin alone)	A1C: 8.3% (insulin glargine) vs 8.2% (NPH insulin) ($P < 0.001$)	Nocturnal: 9.9% (insulin glargine) vs 24.0% (NPH insulin) ($P < 0.001$)
Riddle et al (Treat-to-Target Trial) ¹⁵	756	Insulin glargine or NPH insulin at bedtime added to OAD therapy at prestudy doses	A1C: 6.96% (insulin glargine) vs 6.97% (NPH insulin) ($P = NS$) Mean FPG: 117 mg/dL (insulin glargine) vs 120 mg/dL (NPH insulin) ($P = NS$) % of Patients achieving A1C goal: 58.0% (insulin glargine) vs 57.3% (NPH insulin) ($P = NS$)	13.9 (insulin glargine) vs 17.7 (NPH insulin) events/patient-year ($P < 0.02$)
Rosenstock et al ¹⁶	518	Insulin glargine SC QD at bedtime or NPH insulin QD at bedtime or BID (morning and bedtime) ± meal-time regular insulin	Mean A1C decrease: -0.41% (insulin glargine) vs -0.59% (NPH insulin) ($P = NS$)	Nocturnal: 31.3% (insulin glargine) vs 40.2% (NPH insulin) ($P = 0.016$)
Raslova et al ¹⁷	395	Insulin detemir + prandial insulin aspart ($n = 195$) or NPH insulin + human regular insulin at meal-time ($n = 200$)	A1C: 7.46% (insulin detemir) vs 7.52% (NPH insulin) ($P = 0.515$)	38% lower with insulin detemir ($P = 0.14$)
Haak et al ¹⁸	505	Insulin detemir or NPH insulin QD or BID + mealtime insulin aspart	A1C: 7.6% (insulin detemir) vs 7.5% (NPH insulin) ($P = NS$)	No between-group difference

(continued)

goal without documented nocturnal hypoglycemia. Mean baseline A1C was 8.61% in the insulin glargine group and 8.56% in the NPH insulin group.¹⁵

At the end of the 24-week study, mean A1C values had decreased to 6.96% in the insulin glargine group and 6.97% in the NPH insulin group ($P = NS$).¹⁵ Mean FPG at end point was 117 mg/dL with insulin glargine and 120 mg/dL with NPH insulin ($P = NS$). Approximately 60% of patients achieved the A1C target of $\leq 7.0\%$ (58.0% of patients taking insulin glargine and 57.3% of patients taking NPH insulin; $P = NS$). The mean daily insulin dose at end point was 47.2 IU for insulin glargine and 41.8 IU for NPH insulin ($P < 0.005$). Thus, the simple addition of bedtime insulin (with systematic aggressive titration) was effective at achieving the recommended A1C targets after only 6 months in the majority of patients who could not achieve glycemic control with oral agents alone. Moreover, this regimen, regardless of type of insulin used, was associated with a low rate of day-

time hypoglycemia. With respect to nocturnal hypoglycemia, which can affect glycemic control during the day, insulin glargine was more effective at reducing A1C without documented hypoglycemia at night. The percentage of patients achieving the target A1C goal without documented hypoglycemia was 33.2% in the insulin glargine group versus 26.7% in the NPH insulin group ($P < 0.05$).¹⁵

In the Treat-to-Target Trial, the simple addition of bedtime insulin (with systematic aggressive titration) was effective at achieving the recommended A1C targets after only 6 months in the majority of patients who could not achieve glycemic control with oral agents alone.

The Treat-to-Target Trial¹⁵ has thus presented a paradigm for initiation of insulin therapy that allows simple introduc-

Table II. (Continued)

Study Reference	No. of Patients	Regimens	Primary End Point	Rate of Hypoglycemia
Basal insulins versus premixed insulins				
Janka et al ¹⁹	364 (ITT population)	QD morning insulin glargine + glimepiride and metformin (n = 177) or BID premixed insulin (70% human NPH insulin/30% regular insulin) without OADs (n = 187)	A1C: 7.15% (insulin glargine + OAD) vs 7.49% (premixed insulin) % of Patients achieving A1C goal: 49.4% (insulin glargine + OAD) vs 39.0% (premixed insulin) % of Patients achieving A1C goal without nocturnal hypoglycemia: 45.5% (insulin glargine + OAD) vs 28.6% (premixed insulin) (P < 0.002)	4.07 (insulin glargine + OAD) vs 9.87 (premixed insulin) events/patient-year (P < 0.001)
Raskin et al ²⁰	233	BID BIAsp 70/30 or QD insulin glargine added to metformin ± TZD	Mean A1C: 6.91% (BIAsp 70/30) vs 7.41% (insulin glargine) (P < 0.01) A1C reduction from baseline: -2.79% (BIAsp 70/30) vs -2.36% (insulin glargine) (P < 0.01)	Minor hypoglycemia: 43% (BIAsp 70/30) vs 16% (insulin glargine) (P < 0.05)
Long-acting insulin analogues versus incretin mimetics				
Heine et al ²¹	551	QD insulin glargine or BID exenatide	Baseline mean A1C: 8.3% (insulin glargine) vs 8.2% (exenatide) A1C reduction from baseline at week 26: -1.11% for both insulin glargine and exenatide (difference of 0.017 percentage point; 95% CI, -0.123 to 0.157)	Symptomatic hypoglycemia: 6.3 (insulin glargine) vs 7.3 (exenatide) events/patient-year (CI, -1.3 to 3.4 events/patient-year)

NPH = neutral protamine Hagedorn; OAD = oral antidiabetic drug; SU = sulfonylurea; A1C = glycosylated hemoglobin; FPG = fasting plasma glucose; ITT = intent-to-treat; BIAsp = biphasic insulin aspart; TZD = thiazolidinedione.

tion of a single injection with rapid attainment of fasting glycemic goals through titration of the insulin dose being done every few days by either the clinic staff (by telephone) or by the patient, who can be instructed on such self-titration fairly easily.

Basal Insulins Versus Premixed Insulin Formulations

Addition of basal insulin to OAD therapy appears to be an effective approach to achieving glycemic control compared with initiating insulin-only therapy with premixed formulations of insulin. A recent multinational, multicenter study by Janka et al¹⁹ included 364 insulin-naive patients in the intent-to-treat population whose disease was inadequately controlled with OAD therapy consisting of a sulfonylurea and metformin. Patients were randomly assigned to QD morning insulin glargine plus glimepiride (another sulfonylurea) and metformin (n = 177) or to BID premixed insulin (70% human NPH insulin/30% regular insulin

Table III. Forced weekly titration schedule used in the Treat-to-Target Trial.

Mean of Self-Monitored FPG Values from Previous 2 Days	Increase of Insulin Dosage, IU/d
≥180 mg/dL (10.0 mmol/L)	8
140–180 mg/dL (7.8–10.0 mmol/L)	6
120–140 mg/dL (6.7–7.8 mmol/L)	4
100–120 mg/dL (5.6–6.7 mmol/L)	2

FPG = fasting plasma glucose.

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[70/30]; metformin was not included in this arm using premixed insulin) without OADs ($n = 187$). In both groups, insulin was titrated using a weekly forced-titration algorithm to a target FBG of ≤ 100 mg/dL; in the NPH insulin group, predinner blood glucose was also titrated to a preprandial blood glucose target of ≤ 100 mg/dL. At the end of the 24-week study, mean A1C levels decreased from 8.85% to 7.15% in the insulin glargine plus OAD group and from 8.83% to 7.49% in the premixed insulin group; the difference in A1C improvement between groups was significant ($P < 0.001$). The A1C target was achieved by 49.4% of patients in the insulin glargine plus OAD group versus 39.0% in the premixed group ($P < 0.06$ for the between-group difference). Significantly more patients in the insulin glargine plus OAD group achieved the target A1C goal without documented nocturnal hypoglycemia (45.5% vs 28.6%; $P < 0.002$ for the between-group difference).¹⁹

Another recent trial by Raskin et al²⁰ randomized 233 insulin-naive patients whose disease was inadequately controlled (A1C $\geq 8.0\%$) with metformin alone or in combination with other OADs to treatment with biphasic insulin aspart (BIAsp) 70/30 or QD insulin glargine; no sulfonylureas were included in these regimens. Metformin doses were titrated up to 2550 mg/d before insulin therapy was initiated. Secretagogues and α -glucosidase inhibitors were discontinued, but thiazolidinedione therapy was continued. Patients received 5 to 6 units of BIAsp 70/30 BID or 10 to 12 units of insulin glargine QD at bedtime; insulin doses were titrated to target blood glucose (80–110 mg/dL) using algorithm-directed titration. The comparisons are not optimal since the 70/30 insulin has the advantage of addressing prandial insulin replacement needs as well as the fasting glucose; in contrast, the insulin glargine treatment group did not have adequate prandial insulin replacement (particularly in the absence of a sulfonylurea). After 28 weeks, the mean (SD) A1C value was significantly lower in the BIAsp 70/30 group (6.91% [1.17%] vs 7.41% [1.24%]; $P < 0.01$) and the A1C reduction from baseline was significantly greater (-2.79% [0.11%] vs -2.36% [0.11%]; $P < 0.01$), particularly for patients with baseline A1C values $> 8.5\%$ (-3.13% [1.63%] vs -2.60% [1.50%]; $P < 0.05$). The rate of minor hypoglycemia was significantly lower in the group treated with QD basal insulin (16% vs 43%; $P < 0.05$) as was the mean weight gain (3.5 kg vs 5.4 kg; $P < 0.01$).²⁰

The collective data from these randomized trials suggest that the addition of a long-acting basal insulin administered QD at bedtime or in the morning, along with aggressive dose titration based on FBG measurements, is an effective approach to achieving glycemic targets in patients with type 2 DM whose disease is suboptimally controlled with oral agents. Moreover, such a regimen is associated with a low incidence of daytime and nocturnal hypoglycemia and does not appear to further increase the incidence of hypoglycemia normally observed with OAD combination therapy. In addition, it is a simple and nonthreatening way to introduce insulin therapy to patients who are often concerned about

the complexity of insulin therapy, the need for frequent injections, the risk of hypoglycemia, and the disruption of daily activities.²³ Basal insulin can be conveniently administered QD, with little disruption to activities of daily living and a low risk of daytime and nocturnal hypoglycemia.

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DOSAGE AND TITRATION OF BASAL INSULIN THERAPY

One approach to initiating basal insulin therapy in patients whose disease is suboptimally controlled with OAD therapy is to add a single dose of 10 U of insulin glargine or NPH insulin at bedtime and increase the weekly insulin dose if FBG, as measured by self-monitoring of blood glucose, remains above the 100-mg/dL target (**Table IV**). Oral agents should be continued at the same dosage and may eventually have to be reduced. If 3 consecutive measurements of FBG are > 140 mg/dL, the weekly dose can be increased by 4 U. For FBG values between 121 and 140 mg/dL, the dose can be increased by 3 U per week, and for FBG values between 100 and 120 mg/dL, the dose can be increased by 2 U. It is important to continue insulin treatment until the target is reached (ie, FBG < 100 mg/dL).²⁴

The value of aggressive dose titration can be seen in a comparison of the Treat-to-Target Trial¹⁵ and the trial by Yki-Jarvinen et al.¹⁴ In the Treat-to-Target Trial, in which insulin doses were titrated to an ambitious FPG target of ≤ 100 mg/dL, mean A1C levels were reduced to $< 7.0\%$ by 6 months, whereas in the trial by Yki-Jarvinen et al, in which doses were titrated to a higher FPG target of ≤ 120 mg/dL, mean A1C levels were still well above target levels at the end of 1 year.

Davies et al²⁵ found that a simple but aggressive titration algorithm with insulin glargine could be easily and effectively implemented by both physicians and patients. In this large trial, which included 4961 patients with suboptimally controlled type 2 DM on previous OAD and/or insulin therapy, 2 algorithms for insulin glargine initiation and titration were compared. For insulin-naive patients, the starting dose was 10 IU/d in algorithm 1 and a dose equivalent to the FBG value in millimoles per liter over the previous 7 days in algorithm 2 (eg, if the FBG value was 12 mmol/L, the starting dose would be 12 IU). Patients already receiving QD basal NPH insulin were switched to an equivalent dose of insulin glargine. Patients receiving BID NPH insulin were switched to a dose of insulin glargine reduced by 20% to 30%. For patients on oral agents, the decision to discontinue or continue OAD therapy was left to the investigator. In the first algorithm, titration was managed by the physician at every visit; the dose of insulin glargine was increased by 2, 4, and 6 to 8 units, respectively, if the mean FBG measurements for the previous 3 days were 120 to < 140 mg/dL, 140 to < 180 mg/dL,

Table IV. Suggested dosing and titration schedule when adding basal insulin to oral antidiabetic drug (OAD) therapy.

Add single evening dose (10 U) to OAD regimen
 Glargine (bedtime or any time, same time daily)
 NPH (bedtime)

Adjust weekly dose based on self-monitored FBG measurements; increase insulin dose, if 3 consecutive measurements of FBG are as follows:

By 2 U if FBG = 100–120 mg/dL

By 3 U if FBG = 121–140 mg/dL

By 4 U if FBG = >140 mg/dL

Treat to an FBG target of <100 mg/dL

Reduce insulin dose if FBG <72 mg/dL or hypoglycemia occurs

NPH = neutral protamine Hagedorn; FBG = fasting blood glucose.

Note: Insulin detemir has not been studied as an add-on to OAD therapy in patients with type 2 diabetes mellitus and so was not included here. Reprinted from *The American Journal of Medicine*, Volume 116 (Suppl 3A), Pages 10S–16S, Rosenstock J. Basal insulin supplementation in type 2 diabetes: Refining the tactics.²⁴ Copyright 2004, with permission from Elsevier.

and ≥ 180 mg/dL. In the second algorithm, patients titrated the doses by themselves every 3 days, increasing the dose of insulin glargine by 2 U if the mean FBG measurements for the previous 3 days were ≥ 120 mg/dL; the adjustments were reviewed by the investigator at clinic visits or on the telephone. For FBG values between 100 and <120 mg/dL, the decision to increase the dose was left to the investigator. At baseline, 72% of patients had been treated previously with insulin (of these, 40.5% with NPH insulin and 23.2% with premixed formulations).²⁵

At the end of the study, a significant reduction in mean A1C value was achieved, with a greater decrease seen with the patient-managed algorithm compared with the physician-led algorithm (8.9% to 7.7% vs 8.9% to 7.9%, respectively; $P < 0.001$); a significantly greater proportion of patients using algorithm 2 achieved the target A1C level of <7.0% (30% vs 26%, respectively; $P = 0.004$).²⁵ The decrease in FBG value was also significantly greater with the patient-managed algorithm (–62 mg/dL vs –57 mg/dL; $P < 0.001$). The mean basal insulin dose at end point was significantly higher with algorithm 2 (45.0 IU vs 41.0 IU; $P < 0.003$). The incidence of severe hypoglycemia in patients achieving the target A1C level was 1.2% with algorithm 1 and 0.7% with algorithm 2, although the difference was not statistically significant.²⁵ The results of this study suggest that the addition of basal insulin to oral therapy or regular insulin therapy using a simple, patient-implemented algorithm to titrate insulin doses to a target A1C goal is effective at achieving glycemic control with a low incidence of hypoglycemia.

BASAL-BOLUS INSULIN THERAPY

As β -cell function worsens, patients on OAD therapy plus basal and/or regular insulin may need to transition to insulin-only therapy using basal and bolus insulins. The basal-bolus approach to insulin therapy involves administration of 2 types of insulin—a long-acting component to provide basal glycemic control and a short-acting compo-

nent to control glycemic excursions after meals. The basal-bolus approach closely mimics the physiologic pattern of insulin secretion and can be used in patients who are or have become insulin dependent.

The first step in initiating basal-bolus therapy is to establish a dosing regimen based on the patient's insulin needs. This is determined by physiologic glucose disposal characteristics (ie, glucose and A1C levels), as well as exercise and eating habits. Starting doses are then adjusted depending on the results of self-monitoring of blood glucose.

Basal-bolus therapy can be initiated with premixed formulations of long- and short-acting insulins (eg, 70% NPH insulin/30% regular insulin), which incorporate both types of insulin in a fixed ratio and are administered BID. However, these regimens are often too rigid and do not lend themselves to individualization of treatment. It is also difficult to titrate doses with fixed-ratio formulations. Moreover, because they are administered BID, they are therefore not consistent with normal 3-meals-per-day schedules. This results in periods of excessive and insufficient insulin, increasing the chances of hypoglycemia and compromising glycemic control.

A more effective approach is to administer a basal insulin (eg, NPH, glargine, or detemir) QD or BID to control FBG and separately administer a rapid-acting insulin (eg, regular human insulin or a rapid-acting analogue such as lispro, aspart, or glulisine) at mealtimes to control prandial glucose levels. The rapid-acting insulin analogues better mimic the action of prandial insulin secretion compared with regular human insulin.^{26,27} Compared with regular insulin, lispro and aspart have a shorter time to peak effect; more importantly, their duration of action is shorter (~3 hours vs 6–7 hours). This results in less sustained insulin action between meals and hence, a lower risk of hypoglycemia.

The basal-bolus combination of insulin glargine plus regular insulin was compared with NPH QD or BID plus regular insulin in a randomized, open-label, 28-week study involving 518 patients with type 2 DM who were previously

treated with NPH insulin with or without regular insulin at mealtimes.¹⁶ Patients were randomly assigned to receive insulin glargine subcutaneously QD at bedtime or NPH insulin QD at bedtime or BID (morning and bedtime), depending on their previous regimen of NPH insulin. Patients who had been taking regular insulin at mealtimes (~63% of patients in each group) continued to do so at the same doses. Mean A1C decreased by 0.41% in the insulin glargine group and by -0.59% in the NPH insulin group from a baseline value of ~8.5%, with no significant difference between groups. Treatment with insulin glargine was associated with less nocturnal hypoglycemia (31.3% vs 40.2%; $P = 0.016$) and weight gain (mean body weight increase, 0.4 kg vs 1.4 kg; $P < 0.001$). The authors concluded that QD bedtime administration of insulin glargine was as effective as QD or BID NPH insulin as the basal insulin component in patients with type 2 DM undergoing basal-bolus insulin therapy, with a possibly lower risk of nocturnal hypoglycemia. The lower risk of nocturnal hypoglycemia and overall hypoglycemia with insulin glargine was confirmed in a meta-analysis by Rosenstock et al,²⁸ which showed that the risk of overall symptomatic hypoglycemia was reduced by 11% ($P < 0.001$) and that of nocturnal hypoglycemia by 26% ($P < 0.001$) compared with NPH insulin. Another important result from this trial was that the median insulin dose was reduced 20% during the first week in patients who were previously on an insulin regimen of BID NPH insulin and randomized to QD insulin glargine. Based on these results, it is recommended that patients switching from BID NPH insulin to QD insulin glargine should start therapy at a 20% reduced dose.¹⁶

The combination of insulin detemir and insulin aspart has been evaluated as basal-bolus therapy in patients with type 2 DM in 2 recent multicenter, randomized trials.^{17,18} In the first trial, 395 patients with type 2 DM were randomly assigned to treatment with insulin detemir plus prandial insulin aspart ($n = 195$) or to NPH insulin plus human regular insulin at mealtime ($n = 200$) for 22 weeks.¹⁷ At the end of the study, A1C values were comparable between treatments, reaching 7.46% with insulin detemir plus aspart and 7.52% with NPH insulin plus regular human insulin ($P = 0.515$), with decreases of 0.65% and 0.58% from baseline, respectively. The insulin detemir regimen was associated with significantly less within-person variation in self-measured FPG values (SD of 1.20 mmol/L vs 1.54 mmol/L; $P < 0.001$) and less weight gain (0.51 kg vs 1.13 kg; $P = 0.038$), as well as a 38% lower rate of nocturnal hypoglycemia ($P = 0.14$).

The second trial was a 26-week, multinational, open-label, parallel-group trial with 505 patients who were randomly assigned in a 2:1 ratio to treatment with insulin detemir or NPH insulin QD or BID (depending on their previous insulin regimen) as the basal component and mealtime insulin aspart as the bolus component.¹⁸ At study end, A1C levels decreased significantly from baseline in both the insulin detemir group (-0.2%; $P = 0.004$) and the NPH insulin group (-0.4%; $P < 0.001$); the between-group difference in A1C levels was not significant (insulin detemir, 7.6%; NPH insulin,

7.5%). It should be noted, however, that these patients did not have very high A1C levels at baseline (mean, 7.9%). Reductions in FPG values were similar in the 2 groups (insulin detemir, 0.5 mmol/L; NPH insulin, 0.6 mmol/L), as were the FPG concentrations at study end ($P = 0.66$). Compared with patients treated with NPH insulin, patients treated with insulin detemir experienced significantly less weight gain (1.0 kg vs 1.8 kg; $P = 0.017$) and less within-patient day-to-day variability in FBG values ($P = 0.021$). The risk of hypoglycemia and the frequency of adverse events were comparable for the 2 groups.

Thus, basal-bolus insulin therapy utilizing an intermediate- or long-acting basal insulin along with rapid-acting regular insulin or insulin analogue at mealtimes is an effective approach to mimicking physiologic insulin secretion and achieving glycemic targets in patients with type 2 DM who have become insulin dependent.

A recent study by Heine et al²¹ compared the effects of exenatide (a 39-amino acid peptide that belongs to an emerging class of compounds known as incretin mimetics) and insulin glargine on 551 patients with type 2 DM and inadequate glycemic control (defined as A1C values ranging from 7.0%–10.0%). This multicenter, 26-week, randomized trial found that exenatide and insulin glargine achieved similar improvements in overall glycemic control in patients with type 2 DM whose disease was suboptimally controlled with oral combination therapy. Furthermore, the overall rate of hypoglycemia was similar across both treatment groups, with a difference of 1.1 events/patient-year. This study also reported that body weight decreased 2.3 kg in the exenatide group and increased 1.8 mg in the insulin glargine group (difference, -4.1 kg; CI, -4.6 kg to 3.5 kg). However, nausea was more common in patients using exenatide compared with patients using insulin glargine (57.1% vs 8.6%, respectively), and the exenatide treatment group required BID injections compared with QD injection with insulin glargine. The long-term effects of exenatide are not known.²¹

The choice of basal insulin in basal-bolus insulin therapy depends on the specific patient characteristics. For example, a patient with very high FPG values may require very aggressive titration of insulin doses, which could increase the risk of hypoglycemia. Such patients may benefit from long-acting basal insulins that are associated with less daytime and nocturnal hypoglycemia. With respect to the use of insulin detemir, it is important for clinicians to take into account that its time-action profile is dependent on dosage; most trials of insulin detemir have used a BID dosage. One of the limitations of basal insulin analogues is that they cannot be mixed with regular insulin or short-acting analogues. Thus, the need for additional injections can be a burden for patients. QD formulations may be of benefit to patients who have difficulties with compliance.

CONCLUSIONS

Basal insulins, both intermediate- and long-acting formulations, are playing an increasingly important role in the treat-

ment of type 2 DM. For insulin-naïve patients whose disease is inadequately controlled with OAD therapy, the addition of a single basal insulin dose at bedtime has been found to significantly reduce A1C levels, with a low risk of nocturnal hypoglycemia. Basal insulins (ie, glargine, detemir) have also been shown to induce less weight gain, a significant concern for both patients and providers. The use of long-acting basal insulins may also reduce inpatient variability in FBG values. Moreover, the long-acting basal insulins such as glargine and detemir can be administered QD, which may enhance the potential for patient compliance. Aggressive titration of insulin doses based on a target FPG level of 100 to 120 mg/dL is essential to achieving target A1C levels (<7.0%). As β -cell function declines, patients may require a switch to basal-bolus insulin therapy. Although the long- and intermediate-acting insulin formulations are comparable with regard to efficacy as the basal component in basal-

bolus therapy, the long-acting insulins have been associated with lower rates of nocturnal hypoglycemia, which can have a positive effect on glycemic control during the daytime.

Aggressive titration of insulin doses based on a target fasting plasma glucose level of 100 to 120 mg/dL is essential to achieving target A1C levels (<7.0%).

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