

Comparing the Efficacy, Safety, and Utility of Intensive Insulin Algorithms for a Primary Care Practice

Jeff Unger

Received: December 7, 2010 / Published online: January 25, 2011
© The Author(s) 2011. This article is published with open access at Springerlink.com

ABSTRACT

Diabetes management is firmly based within the primary care community. Landmark randomized, controlled trials have demonstrated that even modest reductions in glycated hemoglobin (HbA_{1c}) can yield improvements in economic and medical end-points. Diabetes is a chronic, progressive disease associated with loss of pancreatic β -cell function. Therefore, most patients will eventually require insulin therapies in order to achieve their individualized targeted HbA_{1c} as their β -cell function and mass wanes. Although clinicians understand the importance of early insulin initiation, there is little agreement as to when to introduce insulin as a therapeutic option. Once initiated, questions remain as to whether to allow the patients to self-titrate their dose or whether the dosing should be tightly regulated by the clinician. Physicians have many evidence-based basal insulin protocols from which to choose, all of which have been

shown to drive HbA_{1c} levels to the American Diabetes Association target of $\leq 7\%$. This article will discuss ways by which insulin therapies can be effectively introduced to patients within busy primary care practices. Published evidence-based basal insulin protocols will be evaluated for safety and efficacy.

Keywords: algorithms; basal insulin; physiologic insulin replacement therapy

INTRODUCTION

With over 90% of all Americans being managed for diabetes by their primary care physicians (PCPs), a substantial amount of American healthcare dollars could be saved by initiating intensified care with family physicians and internists.¹ Of the \$174 billion total cost for managing patients with diabetes in 2007, \$58 billion was directed towards treating long-term complications.² Diabetes contributes to prolonged hospital admissions, more frequent outpatient clinic visits, as well as emergency department and home healthcare utilization.² In 2007, 23% of inpatient costs in the United States were attributed to diabetes-related illnesses.² Although there is general agreement

Jeff Unger (✉)
Associate Director of Metabolic Studies,
Catalina Research Institute, 14726 Ramona Ave.,
Suite 110, Chino, CA 91710, USA.
Email: Jungermd@aol.com

among patients and practitioners that PCPs are overworked and undercompensated, the desire to become more adept at managing diabetes appears to be becoming a popular trend.

In some communities, a patient may wait 3 months or longer before they have their initial consultation visit with an endocrinologist. Out of necessity, more community-based PCPs have become as proficient at initiating and titrating insulin as their referral sources, thus allowing patients to receive timely and aggressive diabetes management. Improvement in economic and medical end-points can be achieved with even modest reductions in glycated hemoglobin (HbA_{1c}). This article will discuss ways by which intensive insulin therapy can be rationally introduced to patients in busy primary care practices, many of which do not have access to certified diabetic educators, nurse practitioners, or physician assistants. In these practices, the physician alone may be the designer, presenter, and educator for a given intensification regimen. These treatment protocols can be introduced in a rapid and efficient manner allowing the physician to move quickly to their next patient.

PHYSIOLOGIC INSULIN-REPLACEMENT THERAPY OVERVIEW

The ultimate goal of insulin-replacement therapy is to mimic the normal insulin response in both the fasting and postprandial state. Euglycemic individuals produce enough endogenous insulin from their functioning pancreatic β cells to maintain their glucose levels within the narrow range of 85-140 mg/dL.³ The glucose concentration normally varies little despite wide daily fluctuations in food intake and activity level. Insulin secretion from the β cells and insulin action at peripheral sites, such as the liver, skeletal muscle, and adipose tissue,

are uniquely paired to provide minimization of diurnal glycemic variability. Following a meal, the postprandial glucose peak mostly occurs between 1 and 2 hours with a mean peak time of 75 minutes.⁴ Rapid-acting insulin analogs display a maximum effect at approximately 100 minutes after a subcutaneous injection.⁴ Therefore, injection of a rapid-acting insulin analog should occur 15 minutes prior to eating so that the insulin peak action is better synchronized with the glycemic excursions after a meal. This will minimize the anticipated postprandial glycemic spike.⁴

Insulin is normally secreted in two phases. In the fasting state, insulin is produced at the rate of approximately 1 unit per hour in order to minimize the effect of hepatic glucose production.³ Basal insulin limits lipolysis and free fatty acid production, which, in susceptible individuals, induces insulin resistance in the postabsorptive state.³ Eating prompts a five- to tenfold rise in portal vein insulin concentration to minimize postprandial hyperglycemia.³ First-phase insulin response occurs quickly just prior to eating and ends rapidly so that the body does not experience an abrupt rise in blood glucose levels. As the carbohydrates for the meal are consumed, a second-phase insulin response continues from the β cells until all carbohydrates have been absorbed from the gastrointestinal tract and the plasma glucose levels have normalized. The postabsorptive state may last up to 6 hours depending on the content of the meal. Food that is high in fat (such as pizza) may delay the absorption of carbohydrates significantly.³

Patients with type 2 diabetes have peripheral insulin resistance and inadequate insulin secretion by pancreatic β cells. During meals, the reduced first-phase insulin secretion results in postprandial hyperglycemia and a 35% decrease in hepatic glycogen storage.⁵ A 55% increase in nocturnal hepatic gluconeogenesis drives

excessive glucose production⁵ favoring fasting hyperglycemia. Ultimately, genetically prone individuals with progressive β -cell dysfunction experience a state of chronic hyperglycemia that is unresponsive to oral antidiabetic agents. In order to achieve the recommended HbA_{1c} target of 6.5%-7%, exogenous insulin therapy must often be initiated.⁶

Physiologic insulin-replacement therapies in patients with type 2 diabetes include basal plus bolus regimens as well as mixed insulins and insulin pump therapies. Newer insulin analogs are preferred over human insulin preparations due to their increased predictability of absorption, minimization of hypoglycemic risk, and improved day-to-day intrasubject variability.⁷

Keys to Initiating Insulin Therapy in Primary Care

There is little agreement as to the most appropriate time to initiate insulin therapy in patients with type 2 diabetes. However, the American Association of Clinical Endocrinologist Consensus Panel Statement for Glycemic Control provides some guidance by recommending that insulin should be considered for any type 2 patient having an HbA_{1c} >9% or any symptomatic individual with an HbA_{1c} >8.5%.⁸ Increasing prescriber's acceptance of these expert opinions would seem prudent, as early insulin initiation appears to have a significant glucose lowering effect and can minimize long-term complications related to chronic hyperglycemia.⁹ As PCPs express concern about lack of resources, reimbursement, or lack of experience with insulin initiation, diabetes intensification is too often delayed. Simplifying the treatment algorithms for initiating and titrating insulin may entice patients as well as prescribers towards earlier intensification of treatment regimens. Early use of insulin therapy is often necessary

for timely achievement of targeted glycemic goals including HbA_{1c}, as well as fasting and postprandial glucose levels. For patients with type 2 diabetes, glycemic targets can be achieved using a basal insulin plus oral agents, basal-bolus insulin, and premixed insulin analogs.³ Table 1 lists the strategies that should be considered when initiating insulin therapy for patients with type 2 diabetes.

Approximately 10% of patients diagnosed with type 2 diabetes actually have latent autoimmune diabetes in adults (LADA).¹⁰ This slowly progressive form of autoimmune diabetes is characterized by mature age at diagnosis, the presence of pancreatic autoantibodies (glutamic acid decarboxylase-65 antibodies), and the lack of absolute insulin requirement at diagnosis. Although LADA patients present with more preserved β -cell function than those with classic type 1 diabetes mellitus, these individuals experience a rapid and progressive loss of β -cell function, necessitating intensive insulin intervention. Oral agents are not effective at maintaining glycemic control in patients with LADA.

Basal Insulin Intensification Protocols

The American Diabetes Association consensus statement for managing hyperglycemia recommends that basal insulin be initiated if a patient is symptomatic or has an HbA_{1c} >8.5% while using metformin in conjunction with lifestyle intervention.⁶ Several recently published studies have demonstrated the safety and efficacy of patient-directed basal insulin algorithms.¹¹⁻¹⁴

The primary objective of the AT.LANTUS trial (A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar) was to compare the safety and efficacy of insulin adjustments. Over a period of 26 weeks, 4500 patients were given

Table 1. Strategies for initiating and titrating insulin for treatment-naive patients with type 2 diabetes.

- Suggest that insulin will help patient achieve glycemic targets and minimize the risk of long-term complications.
- Allow patients to actively participate in their insulin dose titration.
- Always praise patients on insulin for their efforts at achieving their glycemic targets at their visits. Remember, patients who are using insulin do not have normal functioning pancreases. They are calculating their doses of insulin, themselves, perhaps multiple times each day. Insulin prescribers should do everything possible to help them become successful in insulin dosing.
- Individualize therapy to meet the needs of each patient. Determine which treatment algorithm might work best for every patient.
- Enforce and emphasize the importance of lifestyle intervention. This should minimize weight gain and reduce postprandial glucose excursions.
- Consider having group office visits run in conjunction with a certified diabetic educator. Often 8-20 patients can be seen at these group visits, which are time efficient and reimbursable by third party payers.
- Provide each patient with an individualized written insulin protocol to which they can refer to.
- Prescribe insulin pen devices whenever possible. Dose titration of insulin is much more accurate with pens than with vials and syringes.
- Teach patients on the importance of identifying and appropriately managing hypoglycemic events.
- When initiating basal insulin use 0.4 units/kg/day as your starting dose. Continue metformin if possible.
- If patient requires more than 60 units of basal insulin per day and their HbA_{1c} is >7%, add a rapid acting insulin analog to the largest meal of the day. The dose for the rapid acting insulin is 0.1 units/kg per meal.
- If HbA_{1c} is not reduced to target after 3 months of basal plus bolus, add a second injection at the next largest meal of the day. Repeat the HbA_{1c} at 3 months and if still above target add a third mealtime injection.
- Patients on basal bolus insulin therapy should consider modified paired glucose testing in order to fine-tune their treatment regimen.

HbA_{1c}=glycated hemoglobin.

insulin glargine (Lantus) once daily.¹³ Half the patients were randomized to clinic-based weekly dose adjustments based upon the average blood glucose levels taken 3 days prior to the week's end as shown in Table 2.¹³ In AT.LANTUS the incidence of nocturnal, severe, and symptomatic hypoglycemia were not statistically significant between the two groups of patients. In the patient-led titration algorithm, the fasting blood sugar levels (achieved by the patients) were lower than those in the physician-led titration algorithm. This was also evidenced with a higher dose of insulin that was used in the patient-led treatment algorithms. The most significant change was a significant drop in HbA_{1c} in the patient-led titration algorithm. The reduction in HbA_{1c} for the patient self-directed protocol was

-1.22% vs. -1.08% for the clinic-based algorithm ($P<0.001$). These compelling data suggest that treatment goals can be achieved by patients who are empowered to titrate their own insulin regimens.

The Canadian Insight Trial,¹² evaluated the efficacy of a simplified basal insulin dose titration regimen initiated within either an endocrine or primary care setting. Four hundred and five patients with type 2 diabetes with HbA_{1c} 7.5%-11% and taking zero to one oral agents were randomized to receive either basal insulin glargine via a self-titration algorithm or conventional therapy with physician-adjusted doses of oral agents for 24 weeks. The primary outcome was the time to achieve two consecutive HbA_{1c} values $\leq 6.5\%$. The patients

Table 2. Insulin glargine (Lantus) dosing regimen algorithms applied to achieve normal blood glucose targets in subjects with uncontrolled blood sugar with type 2 diabetes mellitus.¹³ (A) Clinic-based dosing protocol. (B) Patient-driven protocol.

(A)

Self-monitoring fasting blood glucose (mg/dL)	Units/day increase insulin dose
≥180	8
140-180	6
120-140	4
100-120	2

- Initial dose insulin glargine 10 units at bedtime. Adjust weekly.
- Measurements used to calculate dose adjustments were monitored 3 days prior to dose titration.
- No increase in dose permitted if any blood glucose reading is <72 mg/dL.

(B)

- Initial dose glargine 10 units at bedtime.
- Self-titrate two units every 3 days to target fasting blood glucose <100 mg/dL (equivalent to the highest FBG value over the previous 7 days).

randomized to the insulin glargine group were initiated on 10 units of insulin to be taken at a consistent time each evening before bedtime. Fasting glucose levels were checked daily. The dose of insulin glargine was increased 1 unit each evening until patients achieved a fasting glucose level of 99 mg/dL. The PCPs achieved a greater reduction in fasting plasma glucose with insulin glargine than with oral agents (fasting plasma glucose: -74.5 mg/dL vs. -44.1 mg/dL, $P=0.0001$; specialists: -62.4 mg/dL vs. -39.4 mg/dL, $P=0.0013$). The PCPs reduction in HbA_{1c} was also superior to that achieved by the specialists when insulin use was compared with that of oral agent dose titration (-1.64% vs. -1.26%, $P=0.0058$; specialists -1.41% vs. -1.24%, $P=0.3331$). PCPs were more aggressive in their use of insulin, whereas the specialists used more oral agents. No differences in the rates of hypoglycemia were noted between the cohorts. The Canadian Insight Trial suggests that PCPs could easily and safely implement a patient-driven, single-unit, basal dosing-adjustment protocol within their clinical practice.

The PREDICTIVE 303 protocol¹⁴ (The Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation 303 Study) is a patient-driven algorithm tested within the primary care setting. The primary end-point of this safety and efficacy study was to determine whether treatment-naive patients could be “empowered” to adjust their insulin dose simply by monitoring their fasting glucose levels. In addition, could their dosing adjustments result in improved glycemic targets and less hypoglycemia compared to a standardized clinic-based dosing protocol? A total of 5619 patients with type 2 diabetes, having an HbA_{1c} ≤12% were randomized with receive insulin detemir via a pre-determined, self-adjusted protocol (Table 3)¹⁴ or one that was physician directed. After 26 weeks both cohorts demonstrated equal HbA_{1c} reductions of approximately 0.6% from the mean baseline of 8.5%. Although the incidence of overall hypoglycemia was not statistically significant between the two groups, the patient-directed

Table 3. The pre-determined, self-adjusted PREDICTIVE 303 protocol*.¹⁴

Average fasting glucose over previous 3 days	Basal insulin dose adjustment based on glucose average
<80	Reduce dose by three units
80-110	Maintain same dose of insulin. (No changes needed.)
>110	Increase dose by three units

*Patients continued their oral antidiabetic doses at stable doses during the trial. Dose reductions or discontinuation of sulfonylureas and glinides were permitted if patients were experiencing hypoglycemia. The initial dose of insulin detemir was 0.1-0.2 units/kg or 10 units daily at dinner or bedtime.

cohort demonstrated slightly higher rates of nocturnal hypoglycemia.¹⁴

In this subgroup analysis of insulin-naive patients (ie, those only receiving oral antidiabetics prior to enrolment in the study), the overall hypoglycemia rates at baseline were lower than in the full population and remained relatively stable after 26 weeks. At 26 weeks, there was no significant difference between the two arms ($P=0.46$). Rates of nocturnal hypoglycemia were low at baseline and week 26 in both the self-adjusted and investigator-adjusted groups. The rate of nocturnal hypoglycemia at 26 weeks was significantly lower in the investigator-adjusted group than in the self-adjusted group ($P=0.03$). The PREDICTIVE 303 study, therefore, suggests that patients who are insulin naive can safely adjust their insulin doses when given a specific goal-directed algorithm.¹⁴

However, PREDICTIVE 303 was not a treat-to-target study, but a study powered to evaluate the safety and efficacy of self-dose adjustment empowerment within a primary care setting. In order to determine whether patients could use the PREDICTIVE 303 protocol to achieve an aggressively targeted HbA_{1c}, the TITRATE study was developed.¹² TITRATE compared the efficacy and safety of two fasting plasma glucose titration

targets (80-110 mg/dL and a more aggressive target of 70-90 mg/dL) using a patient-directed treat-to-target algorithm for once-daily basal insulin in insulin-naive subjects with type 2 diabetes. Two hundred and forty-four patients, who were suboptimally treated with oral agents and had HbA_{1c} levels between 7% and 9%, were randomized to either the 80-110 mg/dL or the 70-90 mg/dL treatment arms. The dose titration for both arms of the study are shown in Table 4.^{11,12}

Overall, both treatment groups achieved a mean HbA_{1c} level of 6.9% at the end of the 20 week study. The majority of subjects in both titration groups also achieved the American Diabetes Association recommended HbA_{1c} level of <7%. At the end of the study period, 64.3% of subjects in the 70-90 mg/dL cohort achieved HbA_{1c} levels <7% compared with 54.5% of subjects in the 80-110 mg/dL group (95% CI: 1.03-3.37, odds ratio 1.86, $P=0.04$). The overall rates of hypoglycemia episodes were low and were comparable between treatment groups. A single event of major hypoglycemia was reported in the 70-90 mg/dL group. Mean weight changes

Table 4. The TITRATE protocol*.¹¹

Average fasting plasma glucose of 3 consecutive days	Insulin detemir dose adjustment
Using 70-90 mg/dL target	
<70	-3 units
70-90	No adjustment
>90	+3 units
Using 80-110 mg/dL target	
<80	-3 units
80-110	No adjustment
>110	+3 units

*Patients continued their oral antidiabetic doses at stable doses during the trial. Dose reductions or discontinuation of sulfonylureas and glinides was permitted if patients were experiencing hypoglycemia. The initial dose of insulin detemir was 0.1-0.2 units/kg or 10 units daily at dinner or bedtime.

from baseline to the end of the study were small and did not differ significantly between treatment groups. The TITRATE study, therefore, demonstrates that lowering the fasting glucose target using a self-directed algorithm with once-daily insulin detemir is safe and increases the likelihood of achieving the American Diabetes Association target HbA_{1c} level of <7%. Despite the aggressive fasting blood glucose targets set by TITRATE, hypoglycemia rates were minimal.¹²

As diabetes is a progressive disorder, pancreatic β -cell dysfunction necessitates the addition of mealtime insulin to minimize postprandial excursions.^{15,16} Glucose fluctuations during the postprandial period elicit more oxidative stress than chronic, sustained hyperglycemia and can lead to endothelial dysfunction, vascular inflammation, and microvascular complication.¹⁷ In turn, endothelial dysfunction has been implicated in the development of vascular disease, such as atherosclerosis.¹⁸ Pharmacologic interventions (eg, rapid-acting insulin analogs) reduce oxidative stress, vascular inflammation, and improve endothelial dysfunction.¹⁹

The Treating To Target in Type 2 Diabetes Study (the 4-T Study), provides some insight into when insulin should be initiated in patients and at what time during the course of their disease prandial insulin might be initiated.²⁰ Over 700 individuals with type 2 diabetes who were on dual oral agent therapy were randomized into this study. They were randomized into the three groups. One group was randomized to biphasic insulin aspart 70/30 twice daily. The second group was randomized to prandial insulin, aspart, three times daily. The third randomization was using basal insulin detemir once daily at bedtime. The trial used a clinically relevant protocol with clinic visits every 3 months, a schedule similar to that routinely followed in the primary care setting. After 1 year, patients who continued to have unacceptable rates of hyperglycemia

(defined as HbA_{1c} >10% after one measurement, two consecutive HbA_{1c} measurements \geq 8% at or after 24 weeks of therapy, or an HbA_{1c} >6.5% at the end of year 1) were eligible for intensification of their insulin regimens. Therapy with sulfonylurea was replaced with an additional type of rapid acting or mixed insulin regimen as follows: (1) insulin aspart was added three times daily to the insulin detemir-initiated arm starting with 10% of the current total daily basal dose (minimum of four units; maximum of six units).²⁰ (2) insulin detemir (10 units) was added at bedtime to the insulin aspart-initiated arm; (3) insulin aspart was added at midday to the insulin aspart mix 70/30-initiated arm starting with 10% of the current total daily dose (minimum of 4 units; maximum of 6 units). This practice is not typically prescribed in the US.

The primary outcome of the first 4-T Study published in 2007²¹ was HbA_{1c} <6.5%. There were small but significant differences between the three groups. The group with the highest HbA_{1c} was those individuals randomized to basal insulin at bedtime and those with the lowest HbA_{1c} had received prandial insulin. However, none of the groups achieved the target hemoglobin HbA_{1c} of <6.5%. As expected, basal insulin resulted in optimal reduction of fasting blood glucose, whereas prandial insulin improved postmeal glucose excursions better than basal or mixed insulins. Less weight gain and fewer episodes of hypoglycemia were noted in the basal insulin cohort. Thus, after 1 year, the conclusions of the 4-T Study were as follows: (1) regimens using biphasic or prandial insulin reduced HbA_{1c} to a greater extent than basal, but were to be associated with a greater risk of hypoglycemia and weight gain; (2) most patients are likely to require more than one type of insulin to achieve target HbA_{1c} levels over time as very few individuals were able to maintain their HbA_{1c} levels at <6.5%.

The investigators noted a progression in the disease process for patients with type 2 diabetes and an inability to reduce a rise in HbA_{1c}; therefore, patients were randomized to be placed on prandial insulin.²¹ After an additional 2 years in the 4-T Study, the HbA_{1c} levels were identical between all three groups. What did reach statistical significance was the fact that those individuals initiated on basal insulin therapy alone at the end of 3 years had less grade 2 or grade 3 hypoglycemia, the more severe forms of hypoglycemia. This group also demonstrated the least amount of weight gain during the 3 year study.

The overall aggregate HbA_{1c} at the conclusion of the 3 year 4-T Study was 6.9% and did not differ significantly between treatment groups.²¹ However, patients commencing therapy with basal or prandial insulin more often achieved glycemic targets than those initiating therapy with biphasic insulin. The lowest weight gain and lowest rate of hypoglycemia occurred in the insulin detemir plus insulin aspart group, with 63% of patients achieving HbA_{1c} ≤7%. Finally, the 4-T Study supports starting insulin therapy with once-daily basal insulin and adding prandial insulin if glycemic goals are not met within 1 year.

Basal insulin was the most effective treatment regimen within the 4-T Study protocol because the insulin dose was progressively increased towards specific fasting and postmeal targets. Self-blood glucose values of each subject were analyzed by a computer management system at the time of each visit.²¹ An insulin-dosing regimen was then prescribed to target fasting glucose levels of 72-99 mg/dL and 2 hour postprandial levels of 90-126 mg/dL. Investigators and patients were encouraged to vary suggested insulin doses, as clinically appropriate, and to amend the doses between visits. Hypoglycemia was categorized as grade

1 (symptoms only) if a patient had symptoms with a self-measured capillary glucose level of 56 mg/dL or more, grade 2 (minor) if the patient had symptoms with a self-measured capillary glucose level of <56 mg/dL, or grade 3 (major) if third-party assistance was required. Unfortunately, the computer-generated dosing protocol suggestions are not clinically available to practicing physicians and were used solely for those investigators and patients enrolled in the 4-T Study. Nevertheless, initial intensification of therapy in patients with poorly controlled type 2 diabetes with basal insulin appears to be a prudent choice. Fasting hyperglycemia contributes more than postprandial hyperglycemia to HbA_{1c} levels during periods of poor glycemic control.²²

CHOOSING THE OPTIMAL INSULIN-REPLACEMENT PROTOCOL

Optimal diabetes management should be patient-centered. With the exception of the 4-T Study, all of the protocols mentioned in this manuscript allowed patients (including those who are insulin naive) to titrate their own insulin regimens. Insulin pen delivery devices should be used to titrate and administer insulin due to their ease of use and dosing accuracy. Patients may find increasing insulin 1 to 2 units more difficult when using a syringe and vial versus dosing with a pen device.²³ One should consider stopping oral agents when insulin is initiated. However, continued use of metformin appears to be a rational choice as metformin may minimize weight gain associated with insulin use. Metformin has also been associated with a lower cancer mortality rate compared with nonuse of the drug.²⁴

Using the TITRATE protocol as a model, one would initiate basal insulin at the dose

of 0.1-0.2 units/kg once daily (usually at bedtime). The desired targeted fasting blood glucose level could be identified for the patient. Although TITRATE had a very aggressive target of 70-90 mg/dL or 80-110 mg/dL, certainly less stringent glycemic goals could be recommended to each patient based upon individualized treatment targets, duration of diabetes, age, history of hypoglycemic unawareness, or history of cardiovascular disease.

The most important aspect of dose titration is minimization of the risk of hypoglycemia. The PREDICTIVE 303 and TITRATE studies both demonstrated that overall and nocturnal hypoglycemia rates are minimized using the protocols shown in Tables 3 and 4.¹¹⁻¹⁴

Perhaps the easiest and safest protocol to initiate would mirror that used in the Canadian Insight Trial (Table 5).¹² The starting dose of insulin would be very conservatively placed at 10 units to be given at a consistent time of the day. The patient would monitor their blood glucose level on a daily basis and continue to increase their basal insulin dose until they reach a fasting glucose target of <100 mg/dL.

If the HbA_{1c} remains above target at that time, prandial insulin injected 10-15 minutes prior to the patient's largest daily meal should be added to the patient's regimen. The HbA_{1c} should be

monitored once again after 3 months. If the HbA_{1c} remains above target, another mealtime insulin injection for the second largest meal of the day should be initiated. If after an additional 3 months, the HbA_{1c} remains elevated, a third mealtime injection should be prescribed. While the mealtime regimen is being adjusted, the PREDICTIVE 303 protocol should be continued allowing patients to continually monitor and adjust all of their daily insulin doses.¹⁴

CONCLUSION

Basal insulin regimens are a safe and effective means by which hyperglycemia can be initially managed within the primary care setting. Allowing patients the opportunity to adjust and titrate their basal insulin dose using individualized treatment protocols will allow most patients to achieve their glycemic targets without having to refer them to specialists. The safety and efficacy of different aggressive treatment algorithms, many of which have been clinically tested within the primary care arena, should provide physicians and their patients with the encouragement they need to aggressively manage hyperglycemia in a timely manner.

ACKNOWLEDGMENTS

Dr. Unger has received consulting fees from Roche Pharmaceuticals, Novo Nordisk, and Takeda. He has received fees for non-CME services from Novo Nordisk, Amylin Pharmaceuticals, Lilly Pharmaceuticals, and Roche Pharmaceuticals. In addition, Dr. Unger has performed contracted research for Novo Nordisk, Sanofi-Aventis, Roche Pharmaceuticals, Takeda Pharmaceuticals, and Amylin Pharmaceuticals. Dr. Unger is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Table 5. Basal insulin single unit dosing protocol.¹²

- Initiate basal insulin at 10 units.
- Administer insulin injection at the same time each day as basal insulin duration is 24 hours.
- Monitor your blood glucose level after fasting each morning.
- Each night increase dose until your fasting glucose level is below 100 mg/dL.
- Notify your physician if you feel shaky, sweaty, confused, or have a blood glucose level <56 at any time of the day.

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

REFERENCES

1. Unger J. Introduction to diabetes. In: Unger J, ed. *Diabetes Management in Primary Care*. 1st Edition. Philadelphia, PA: Lippincott, Williams and Wilkins; 2007:1-42.
2. American Diabetes Association. Economic costs of diabetes in the US in 2007. *Diabetes Care*. 2007;31:596-615.
3. Unger J. Physiologic insulin replacement therapy. In: Unger J, ed. *Diabetes Management in Primary Care*. 1st Edition. Philadelphia, PA: Lippincott, Williams and Wilkins; 2007:192-264.
4. Luijck Y, Van Bon AC, Hoekstra JB, et al. Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care*. 2010;33:2152-2155.
5. Krssak M, Brehm A, Bernroider E, et al. Alterations in postprandial hepatic glycogen metabolism in type 2 diabetes. *Diabetes*. 2004;53:3048-3056.
6. Nathan DM, Buse JB, Davidson MB, et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32:193-203.
7. Hirsch IB. Insulin analogues. *N Engl J Med*. 2005;352:174-183.
8. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009;15:540-559.
9. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
10. Unger J. Latent autoimmune diabetes in adults. *Am Fam Physician*. 2010;81:843-847.
11. Blonde L, Merilainen M, Karwe V, et al. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets – the TITRATE study. *Diabetes Obes Metab*. 2009;11:623-631.
12. Harris S, Yale J-F, Dempsey E, et al. Can family physicians help patients initiate basal insulin therapy successfully? Randomized trial of patient-titrated insulin glargine compared with standard oral therapy: lessons for family practice from the Canadian INSIGHT trial. *Can Fam Physician*. 2008;54:550-558.
13. Davies M, Storms F, Shutler S, et al. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes. Comparison of two treatment algorithms using insulin glargine. *Diabetes Care*. 2005;28:1282-1288.
14. Meneghini L, Koenen C, Weng W, et al. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes-results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab*. 2007;9:902-913.
15. Liebl A. Insulin intensification-the rationale and the target. *Int J Clin Pract Suppl*. 2009;164:1-5.
16. Karl DM. The use of bolus insulin and advancing insulin therapy in type 2 diabetes. *Curr Diab Rep*. 2004;4:352-357.
17. Unger J. Reducing oxidative stress in patients with type 2 diabetes mellitus: a primary care call to action. *Insulin*. 2008;3:176-184.
18. Cosentino F, Hishikawa K, Katusic ZS, et al. High glucose increases nitric oxide synthase expression and superoxide anion generation in human aortic endothelial cells. *Circulation*. 1997;96:25-28.
19. Scognamiglio R, Negut C, de Kreutzenberg SV, et al. Effects of different insulin regimens on postprandial myocardial perfusion defects in type 2 diabetic patients. *Diabetes Care*. 2006;29:95-100.
20. Holman RR, Farmer AJ, Davies MJ, et al.; 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361:1736-1747.
21. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716-1730.

22. Lasserson DS, Glasziou P, Perrera R, et al. Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetologia*. 2009;52:1990-2000.
23. Korytkowski M, Bell D, Jacobsen C, et al. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther*. 2003;25:2836-2848.
24. Landman GWD, Kleefstra N, van Hateren KJJ, et al. Metformin associated with lower cancer mortality in type 2 diabetes. *Diabetes Care*. 2010;33:322-326.