Early Insulin Initiation—A Review of the Literature and Case Studies

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Abstract

The prevalence of type 2 diabetes (T2D) in the United States has increased in the last decade. Clinical guidelines direct patients with newly diagnosed T2D to a stepwise approach to glycemic management that includes diet, exercise, sequential oral antidiabetic drug (OAD) treatment (from monotherapy to combination therapy), and insulin treatment in order to help prevent microvascular and macrovascular complications. Studies have shown that patients with T2D benefit from early initiation of glycemic therapy to reduce glycated hemoglobin (A1C); however, OADs have been associated with limited A1C reductions leading to patients requiring insulin. Therefore, early initiation of insulin may help more patients to achieve and maintain long-term glycemic control. Insulin initiation is, however, frequently hindered by patient anxiety, clinician inertia, and patient and physician misconceptions about the role of insulin in glycemic control. This review examines the literature on insulin therapy in patients with T2D, focusing on the efficacy and advantages of early basal insulin analog therapy and real-life clinical experience that is illustrated in 3 case studies of patients with T2D. Early insulin initiation should be considered for a wide range of patients, from those with slightly elevated A1C to those with frank diabetic ketoacidosis.

INTRODUCTION

The prevalence of type 2 diabetes (T2D) in the United States has increased in the last decade, and with it the number and diversity of patients in need of effective glycemic control (1). An estimated 25.8 million people in the United States now have the disease (1), including a growing number of adolescents and young adults in whom the condition is attributed to the disquieting rise in obesity (2). Clinical guidelines direct patients with newly diagnosed T2D to a stepwise approach to glycemic management, starting with changes to diet and exercise regimens followed by the sequential use of oral antidiabetic drugs (OADs) and increasingly intensified insulin treatment (3). With disease progression and the gradual decline in beta-cell function, OADs eventually fail to maintain glycemic target levels and most patients will require insulin (3,4).

RATIONALE FOR EARLY INSULIN INITIATION

In T2D, early, intensive, and, consequently, tight glycemic control is clinically important because it limits exposure to high glucose levels and the associated microvascular and macrovascular toxic effects (5,6,7). Each percentage point decrease in glycated hemoglobin (A1C) correlates with substantial reductions in the risk of both microvascular and macrovascular complications (6). Even a short burst of intensive glycemic therapy soon after diagnosis appears to have long-term effects on patients with diabetes (8,9); this phenomenon has been referred to as ‘metabolic memory,’ although the pathophysiological mechanisms involved are unclear (8). Ten-year follow-up data from the United Kingdom Prospective Diabetes Study (UKPDS) Group showed that patients with T2D (n=3277) who had effective intensive treatment with sulfonylurea, insulin or, if more than 120% of ideal bodyweight, metformin soon after diagnosis continued to benefit from treatment (9). After 10 years, rates of any diabetes-related end point (defined as sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction; [p=0.04]; microvascular disease [p=0.001]; and diabetes-related death [p=0.01]) were significantly reduced in patients who had received sulfonylurea or insulin compared with patients who received conventional dietary therapy. Similarly, significant risk reductions were seen for any diabetes-related end point (p=0.01), diabetes-related death (p=0.01), myocardial infarction (p=0.005), and death from any cause (p=0.002) in patients who received metformin. There are, however, limits to the benefits derived from A1C reduction. In the Action to

Control Cardiovascular Risk in Diabetes (ACCORD) study, intensive therapy aimed at achieving an A1C level below 6.0% in patients with T2D (n=10 251) provided some microvascular benefits but this was countered by an increase in total and cardiovascular disease-related mortality, increased weight gain, and higher risk for severe hypoglycemia (10).

Early initiation of insulin may help more patients to achieve and maintain long-term glycemic control through targeted titration and protection of beta-cell function (11). Importantly, insulin can be carefully titrated to achieve individualized target A1C levels provided hypoglycemia does not occur, while OADs are associated with limited A1C reductions of 0.8% to 2% (12-14). Early insulin therapy in patients with newly diagnosed T2D aids the recovery and maintenance of beta-cell function, while OADs that increase the production of endogenous insulin may speed failure of beta-cell function (15,16). In a study of 382 patients with newly diagnosed T2D randomized to short-term intensive insulin (continuous subcutaneous infusion or multiple daily injections) or OADs, beta-cell function (estimated using the homoeostasis model assessment [HOMA]) was sustained in the insulin groups, but declined significantly in the OAD group at 1-year follow-up (16). In a second study, beta-cell function was also assessed using HOMA, in conjunction with the level of intact proinsulin secretion, and was shown to improve immediately after switching from sulfonylurea to preprandial therapy with a rapid-acting insulin analog compared with continuing oral therapy ($p<0.05$) (15). When the effects of the sulfonylurea glibenclamide and insulin on markers of beta-cell function were compared, deterioration of C-peptide response to glucagon and serum proinsulin levels were observed over time. In addition, deterioration of glycemic control was faster in the glibenclamide group such that, by year 4 of treatment, A1C levels were significantly lower in patients receiving insulin ($p=0.04$) (17). It is hoped that normalization of blood glucose levels with insulin therapy in individuals with early T2D may prevent cardiovascular disease (the leading cause of death) and T2D progression (18). This hypothesis is currently being tested in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (19); preliminary data from a subgroup of 75 patients with early T2D randomized to insulin glargine or standard care show that fasting plasma glucose (FPG) (5.1 vs 6.1 mmol/L, respectively; $p=0.019$) and A1C (5.7 vs 5.9%; $p<0.025$) were significantly lower in patients receiving insulin (20).

Since the start of the 21st century, an evidence-based shift towards early insulin initiation in T2D management has been underway (12,21). Insulin initiation is, however, frequently hindered by patient anxiety and clinician inertia. This paper will review the literature on insulin initiation in patients with T2D, focusing on the efficacy and advantages of early basal insulin analog therapy and real-life clinical experience. In addition, factors involved in the early initiation of basal insulin analog therapy will be illustrated in case studies from three patients with diverse medical histories and treatment requirements.

CURRENT ALGORITHMS FOR ACHIEVING GLYCEMIC CONTROL WITH BASAL INSULIN

From 1999 to 2000, only one-third of US adults receiving treatment for T2D reached an A1C <7% (22). Since then, a number of algorithms for the treatment of T2D have been developed to reduce the incidence of hyperglycemia and resulting health problems. These algorithms standardize a stepwise approach to glycemic control that involves lifestyle modifications, sequential OAD treatment from monotherapy to combination therapy, and insulin. In particular, 2 algorithms have come to dominate treatment practice in the United States: the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) algorithm (23) and the American Diabetes Association (ADA)/
European Association for the Study of Diabetes (EASD) algorithm (3,14,24). Both algorithms stress tight glycemic control, rapid addition of medications or transition to new regimens when goals are not met, and early insulin therapy.

The AACE/ACE algorithm sets an A1C target of ≤6.5% and stratifies treatment into 3 groups according to A1C status (6.5% to 7.5%, 7.6% to 9.0%, and >9.0%). Insulin is recommended as initial therapy in patients with A1C >10%. In all groups, insulin is initiated only after failure of OAD therapy; the type of insulin, regimen (basal, premixed, basal–bolus, or prandial) and number of doses are determined by the stage of the disease and the needs of the patient. Earlier initiation of insulin is recommended for patients with special circumstances such as those in whom OADs are contraindicated. The algorithm advises monitoring of blood glucose levels and titration of medication every few months, with treatment intensified or new therapies added as needed to achieve and maintain A1C goals (23).

The ADA/EASD algorithm introduces insulin therapy early

in the treatment of T2D, with prompt intensification to achieve A1C <7.0% (3). For initial therapy at diagnosis, the algorithm recommends metformin plus lifestyle changes. If the maximum tolerated dose of metformin fails to achieve glycemic targets, addition of a basal insulin or a sulfonylurea is recommended. If A1C targets are still not achieved, it is recommended that insulin therapy be initiated or intensified. In this algorithm, the type of insulin and the regimen used depend on such factors as the patient's weight and lifestyle, motivation to monitor blood glucose, blood glucose patterns, and any previous medications used. In addition, treatment goals are individualized for each patient. The algorithm advocates clinician and patient education to overcome barriers to insulin use and ensure its appropriate and optimal use.

When using such algorithms as those of the AACE/ACE and ADA/EASD, it is important that the recommendations are followed carefully, as stepwise treatment of this nature may result in patients with T2D being undertreated (25-27). During OAD therapy, for example, failure to introduce the next therapeutic step in a timely manner can result in extended periods of hyperglycemia (25). Furthermore, insulin may be viewed by patients and clinicians as a treatment of last resort, meaning that many patients continue to receive OAD therapy for a protracted period despite a lack of efficacy (26), thus compromising their long-term health. A retrospective longitudinal cohort study reported that, although more than 80% of 3891 patients with T2D prescribed sulfonylurea/metformin (SU/MET) achieved the then-recommended A1C target of 8%, this was not sustained in most patients (27). Despite excessive A1C levels, patients continued SU/MET therapy for a mean of 3 years, resulting in a sustained glycemic burden equivalent to nearly 32 months of A1C levels at 9%. In addition, 18% of patients who never attained A1C ≤8% with SU/MET continued that therapy for an average of 30 months, with average A1C levels of 10%. It seems likely that the problem of inadequately treated patients will worsen in the future, as a result of the increase in early-onset disease (<40 years of age), which is significantly associated with higher levels of A1C, fasting glucose, and postprandial glucose (2).

One of the barriers to early initiation of insulin therapy may be the misconceptions of patients and physicians about the role of insulin in glycemic control (28). For instance, in an international survey of patients with T2D, nurses and physicians found that patients often believe the efficacy of insulin to be low, and consider that they are in some way 'to blame' if they need insulin therapy, while healthcare professionals often believe that insulin should be delayed until 'absolutely necessary' (29). When differences between patients who were prescribed but never initiated insulin and those who were dispensed insulin were assessed, 35% of those who never initiated insulin believed that insulin causes blindness, renal failure, amputations, heart attacks, strokes, or early death (30). Others who never initiated insulin had injection phobia, claimed that they planned to 'work harder on behavioral goals,' or had inadequate health literacy or limited self-management training. Clinician failure to prescribe insulin in a timely manner has been attributed to clinical inertia, personal preferences, and inadequate resources (31). Some of the misconceptions about insulin treatment have arisen from the use of human insulins such as neutral protamine Hagedorn (NPH), which has a distinct peak in action that increases the risk of hypoglycemia and necessitates 2 or more injections for adequate basal 24-hour coverage. NPH is also variably absorbed, even within an individual patient, leading to unpredictable glycemic effects (32). Overall, the considerable barriers to insulin that exist suggest that management of glycemic control in T2D may need to go beyond the standardized approach (33). Indeed, some authors consider the development of an individualized plan (34) and a fast-track service for initiation of insulin (35) critical to effective glycemic control.

LITERATURE REVIEW OF INITIATING BASAL INSULIN

Recent evidence indicates that basal insulin provides a simple, effective, and well-tolerated option for insulin initiation. In an open-label, controlled, multicenter trial, 708 people receiving a maximally tolerated dose of SU/MET and with A1C levels of 7% to 10% were randomized to receive 1 of 3 insulin analog regimens: biphasic insulin twice daily; prandial insulin aspart 3 times daily; or basal insulin detemir once daily (twice daily if needed) (36). After 1 year of the 3-year trial, the different insulin regimens were compared with regard to A1C levels, hypoglycemic events, and weight gain (Table 1). The 3 insulin analog regimens were similar in glycemic efficacy for patients with a baseline A1C of <8.5%, but significantly different above this level, with patients receiving basal insulin significantly less likely to achieve A1C ≤6.5% compared with those receiving biphasic insulin (p=0.007). This difference may reflect worsening postprandial glycemia in patients with more advanced disease. Basal insulin was associated with fewer hypoglycemic events and less weight gain (Table 1), supporting its use in the initiation of insulin treatment (ie, as

a first add-on therapy in patients treated with OADs). Similar results were obtained in a 44-week, parallel, open-label study investigating whether the addition of once-daily basal insulin glargine (n=205) was non-inferior to prandial insulin lispro 3 times daily (n=210) in overall glycemic control in adults with T2D inadequately controlled by OADs (37). Overall, the authors concluded that a basal insulin analog provided the simplest and most effective option for early initiation of insulin therapy; compared with prandial insulin lispro, basal insulin glargine was associated with a lower risk of hypoglycemia (5.2 vs 24.0 events per patient–year; $p<0.0001$), as well as fewer injections and less need for blood glucose self-monitoring. Weight gain was 3.0 ± 4.3 kg with insulin glargine and 3.5 ± 4.5 kg with insulin lispro. A post-hoc analysis of the Predictable Results and Experience in Diabetes through Intensification and Control to Target International Variability Evaluation 303 (PREDICTIVE 303) study evaluated data from 1653 insulin-naïve patients with T2D who were uncontrolled on OADs (mean ± SD baseline A1C, 8.82 ± 1.50%) and who were initiated on once-daily insulin detemir for 12 weeks (38). After the addition of insulin detemir, A1C decreased by a mean of 1.25 ± 1.25% ($p<0.0001$), with 30% of patients achieving A1C <7% at 12 weeks. There were no significant changes to the number of total or nocturnal hypoglycemic events after the addition of insulin, nor were any serious drug reactions reported. Body weight, however, decreased by a mean of 0.5 ± 3.3 kg ($p<0.0001$) with weight loss or no weight change occurring in a substantial number of patients across several body mass index (BMI) categories.

EFFICACY OF INSULIN INITIATION

The basal insulin analogs, insulin glargine and insulin detemir, have more predictable, relatively flat time–action profiles, a slower rate of distribution to peripheral tissues, and a longer duration of action than human insulin preparations, leading to a decreased risk of nocturnal hypoglycemia (39-41). These agents may, therefore, help to ease the transition to insulin therapy. In addition, these preparations can be delivered on a convenient, once-daily basis using simple-to-use insulin delivery devices, thus improving quality of life. Despite their advantages over human insulins, however, experience has shown that the task of convincing clinicians to use insulin analogs is a daunting one. In addition, in the author's experience, health insurance providers may hinder switching from human insulin to an insulin analog by restricting insurance coverage.

In most studies of basal insulin initiation, NPH human insulin is compared with insulin analogs. In general, the results show similar efficacy in terms of target A1C, but superiority of the insulin analogs in terms of fewer hypoglycemic events and, in some studies, less weight gain (42-45). These secondary benefits are probably related to the pharmacokinetic and pharmacodynamic improvements of these agents described above (41). In the Treat-To-Target trial, overweight patients (n=756) with A1C >7.5% despite ongoing treatment with 1 or 2 OADs were randomized to the addition of NPH insulin or insulin glargine to their current therapy (43). In the 24-week study, approximately 60% of patients attained the target A1C level of <7%, but 25% more patients on insulin glargine attained the target without nocturnal hypoglycemia (33.2 vs 26.7%; $p<0.05$). Similar results were obtained in the 9-month LANMET study, in which 110 insulin-naïve patients with poorly controlled T2D (A1C ≥8.0%) receiving OADs were randomized to metformin with either insulin glargine or NPH insulin. Symptomatic hypoglycemia was significantly lower during the first 12 weeks in the insulin glargine group (4.1 vs 9.0 episodes/patient–year with NPH insulin; $p<0.05$), but not significantly different thereafter, indicating the importance of longer-term studies. In a 26-week study, addition of insulin detemir to OAD in 476 patients with A1C 7.5% to 10.0% decreased A1C levels from 8.6% to 6.8% (–1.8%), compared with a decrease from 8.5% to 6.6% (–1.9%) for NPH insulin (45). Insulin detemir was, however, associated with significantly less weight gain compared with NPH insulin (1.2 vs 2.8 kg; $p<0.001$), as well as reductions in the risk of hypoglycemia (47% reduction vs NPH insulin; $p<0.001$) and nocturnal hypoglycemia (55% reduction; $p=0.001$). A meta-analysis of results from four 24- to 28-week studies (n=1142) that compared insulin glargine with once- or twice-daily NPH insulin also indicated that once-daily insulin glargine was as effective as NPH insulin in achieving A1C ≤7% (30.8% vs 32.1% of patients, respectively) with a significantly decreased risk for hypoglycemia (54.2% vs 61.2%; $p=0.0006$) (44).

INITIATION OF INSULIN IN REAL-LIFE OBSERVATIONAL STUDIES AND WITH PATIENT-DRIVEN DOSE ADJUSTMENTS

The best information on how basal insulin is initiated and titrated in patients with T2D in real-life clinical practice comes from observational studies. Such studies can also provide insights into the effects of patient self-management protocols on glycemic control. For example, increased frequency of patient monitoring by physicians during insulin titration was shown to improve glycemic control in the

Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study (46). During titration of insulin glargine in 7893 adults with T2D, patients monitored each week by their physician showed significantly greater A1C reduction than those using a normal titration schedule (physician monitoring every 6 weeks, with no unsolicited contact between visits) (1.5% vs 1.3%, respectively; p<0.0001). In addition to increased physician monitoring, patient involvement in self-care protocols can also improve glycemic control. The Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) study (n=405) compared a simple patient-driven protocol for initiation and self-titration of basal insulin therapy using insulin glargine with usual OAD-based clinical care (47). Patients randomized to insulin glargine were instructed to titrate their insulin dose by 1 unit (U)/day if their FPG was >5.5 mmol/L. Results showed that patients receiving insulin glargine were 1.68-times more likely to achieve 2 consecutive A1C levels ≤6.5%, with significantly lower mean A1C levels (p=0.0007), compared with those receiving OADs. They also had a greater reduction in FPG (p=0.0001), non–high-density lipoprotein cholesterol (p=0.02), and triglycerides (p=0.020) than the OAD group. Those using the patient-driven protocol also reported greater treatment satisfaction (using the Diabetes Treatment Satisfaction Questionnaire) than with usual clinical care (p=0.045). The differences between the 2 treatment regimens were not affected by whether treatment was given at a family practice or specialist center.

When educating patients about self-management, physicians should stress the importance of appropriate dose adjustment, as some self-managed patients may be overzealous. The PREDICTIVE 303 study evaluated the efficacy of insulin detemir over a 6-month period in patients taught to use a simple self-adjusted dosing algorithm compared with those receiving standard-of-care physician-driven adjustments (48). Patients in the self-management group adjusted their insulin dose every 3 days based on the mean of 3 'adjusted' FPG (aFPG) values using a simple algorithm: mean aFPG <80 mg/dL, reduce dose by 3 U; aFPG 80 to 110 mg/dL, no change; and aFPG >110 mg/dL, increase dose by 3 U. Treatment was effective for most patients in both groups, although FPG decreased by significantly more in the self-managed patients compared with the physician-managed patients (– 34 vs – 22 mg/dL; p<0.0001). This decrease was accompanied by a higher rate of hypoglycemia in the self-managed group (6.44 vs 4.95 events/patient–year; p <0.0001), possibly because of more aggressive insulin dose adjustments. In the TITRATE study, patients receiving insulin detemir were randomized to 1 of 2 FPG titration targets: 80 to 110 mg/dL or 70 to 90 mg/dL (49). Patients titrating to the lower target experienced a significantly greater decrease in A1C at 20 weeks (from 8.0% to 6.8%) than those titrating to the higher target (from 7.9% to 7.0%; p=0.0019), with significantly more patients achieving A1C <7% (64.3% vs 54.5%; p=0.04). Overall hypoglycemia rates were similar between the 2 groups (7.73 and 5.27 events/subject/year for the lower and higher target, respectively).

Face-to-face interaction between patients and healthcare workers can be beneficial when setting up an insulin self-management program. In 77 African-American adults with T2D, participation in face-to-face weekly meetings over a 6-month period led to a significant reduction in A1C compared with a control period in which the patients received weekly newsletters (p<0.01) (50). For many patients, achieving the goals of tight glycemic control and prevention of the severe complications of diabetes requires the formation of close relationships between patients and healthcare professionals as well as patient education to enable self-management of titration.

INSULIN EFFICACY AND DOSE REQUIREMENTS ACCORDING TO DIFFERENCES IN BASELINE CHARACTERISTICS

People with T2D vary in terms of their baseline characteristics, and these differences may affect insulin efficacy and dose requirements. In real-life clinical practice, therefore, insulin therapy should be tailored to the individual. We are not yet at the stage where ‘insulin tailoring’ is an exact science, however, and further information on the relationship between baseline characteristics and response to treatment is needed.

One category of patients who require higher insulin doses than average are those who are overweight, as these individuals have greater insulin resistance and deficiency than those of average body weight (51). Insulin doses are also generally higher in men than in women because of greater insulin resistance. This may be related to the differential distribution of adipose tissue, which is concentrated in the visceral and hepatic regions in men compared with more peripheral and subcutaneous distribution in women (52,53). A study of 57 middle-aged and older overweight or obese men and women confirmed that older men are more insulin resistant than older women,

but the study was unable to attribute this difference to abdominal fat distribution, which was lower in men (54). A degree of protection against insulin resistance in women may also be provided by their higher estrogen levels, which promote a more insulin-sensitive environment (52).

The presence of comorbid conditions or concomitant therapies may also affect insulin dosing regimens. For example, the use of thiazolidinediones in patients receiving insulin has been associated with an increased risk of heart failure (55). If insulin therapy is to be initiated, it may be advisable therefore to discontinue thiazolidinedione treatment.

Notably, the presence of multiple comorbid illnesses or functional impairments is an important predictor of limited life expectancy and diminishing expected benefits of intensive glucose control (56). As a result, some clinicians may be deterred from prescribing intensive treatments. Insulin therapy may, however, improve some comorbid conditions such as the progressive anemia seen in patients with impaired renal function. In a retrospective analysis of 203 patients with type 1 diabetes receiving human insulin (n=86) or an insulin analog (n=117), those receiving human insulin experienced a decline in hemoglobin levels with decreasing kidney function ($p<0.003$), compared with no significant change in those receiving an insulin analog ($p=0.4$) (57). The results were not affected by baseline characteristics, such as age, sex, BMI, or inflammatory markers.

INSULIN INITIATION IN NEWLY DIAGNOSED PATIENTS, AND PATIENTS SWITCHING FROM HUMAN INSULIN TO AN INSULIN ANALOG

The scenario for insulin initiation may vary from patient to patient, and not all patients receive insulin as part of a stepwise process. Switching insulin formulation may be necessary or desirable in some patients, either from human insulin to a basal insulin analog, or from one basal analog to another. In a sub-analysis of the PREDICTIVE study, switching patients with T2D (n=2137) from NPH insulin (once or twice daily) to insulin detemir (once daily) was associated with A1C reductions of 0.56% ($p<0.001$) during the 12-week follow-up (58). Switching was also associated with a decreased incidence of hypoglycemia (based on patients' records and diaries) from 13.8 to 3.3 episodes/patient–year; $p <0.001$) and was not associated with any adverse drug reactions. In another sub-analysis of PREDICTIVE, switching patients receiving OADs with NPH insulin (n=175) or insulin glargine (n=118) to insulin detemir and the same OAD regimen resulted in improvements in glycemic control (NPH group: A1C, –0.2%; $p<0.05$; insulin glargine group: A1C, –0.6%; $p<0.0001$), with a reduced risk of hypoglycemia and a small reduction in body weight (59).

In some patients, intensive insulin treatment may be used as a precursor to treatment with OADs. Intensive lowering of glycemic levels with insulin therapy in newly diagnosed patients can, however, result in extended normoglycemia without further immediate need of glucose-lowering medications (16,60,61). For example, a study in 382 patients with newly diagnosed T2D randomized to short-term intensive insulin therapy (continuous subcutaneous infusion or multiple daily injections) or OADs found that more patients receiving insulin achieved target levels of glycemic control (16). In the insulin groups, >95% of patients achieved normoglycemia within 5.6 days compared with 83.5% in 9.3 days in the OAD group ($p<0.0001$ vs continuous subcutaneous infusion and $p=0.01$ vs multiple daily injections). Remission rates after 1 year were significantly higher in the insulin groups (45% to 51%) compared with the OAD group (26.7%; $p=0.0012$).

CASE STUDIES

Patient 1 is a 34-year-old African–American woman who works as a teacher. She is 1.72 m (67.75") in height with a body weight of 77.1 kg (170 lb; BMI, 26 kg/m^2). She has a strong family history of diabetes, and has had T2D for 4 years (A1C, 7.4%), for which she is receiving glimepiride extended-release and glipizide/rosiglitazone. On physical examination, she had no signs of retinopathy, neuropathy, or nephropathy, and her blood urea nitrogen (BUN) and creatinine were normal. The patient was lost to follow-up for 1 year, after which metformin 1 g was added to her treatment regimen. Several months later, her FPG was 148 mg/dL and her A1C was 8.3%.

Patient 2 is a 47-year-old African–American woman who has had T2D for ≥15 years and has received a sulfonylurea for some time. After being lost to follow-up for 10 years, she returned to the practice with an FPG of 127 mg/dL and A1C of 9.8%.

Patient 3 is a 32-year-old African–American male who presented to the hospital with lethargy and weakness. Based on a blood glucose level of >1000 mg/dL and detection of ketones in his urine, a diagnosis of diabetic ketoacidosis was made. He was started on intravenous (IV) insulin, with IV normal saline for hydration.

Figure 1

Table 1. Glycemic control and weight gain in patients with T2D receiving 1 of 3 insulin analog regimens (36)

	Biphasic insulin	Prandial insulin	Basal insulin
A1C ≤6.5% (% patients)	17.0	23.9	8.1
Hypoglycemic events (n)	5.7	12.0	2.3
Weight gain (kg)	4.7	5.7	1.9

A1C=glycated hemoglobin; T2D=type 2 diabetes.

DISCUSSION

Patient 1 has an A1C >7%, and is therefore at risk for macrovascular (stroke, myocardial infarction, limb loss) and microvascular (kidney failure, circulation problems, blindness, neuropathy) complications. As she is overweight but not obese; one treatment option would be to add a newer drug, such as a dipeptidyl peptidase-4 (DPP-4) inhibitor or glucagon-like peptide 1 (GLP-1) analog, to her regimen. However, these agents have less potential to lower A1C than does insulin. Additionally, since the patient is already receiving 4 oral agents, the cost of adding a fifth agent is likely to be prohibitive. She appears therefore to be an ideal candidate for insulin initiation with a basal analog insulin, starting with 10 U at bedtime and titrating by 2 U every 2 days to obtain an FPG of <120 mg/dL. This regimen – starting with a single injection with the evening meal that can be given using a pen device and 31- or 32-gauge needles – provides the best chance to overcome possible fears relating to insulin use. Alternatively, a premixed biphasic insulin could be used instead of a basal insulin. In an observational study, patients with A1C 7.5% to 10% initiated biphasic insulin aspart 70/30 with a single injection of 12 U (or 70% to 100% of prior basal insulin dose if appropriate) within 15 minutes of starting dinner (62). Results showed that self-titration, with addition of prebreakfast and, subsequently, prelunch doses if A1C remained uncontrolled, was an effective and well-tolerated approach.

Patient 2 was lost to follow-up for many years, and her most recent A1C of 9.8% suggests that her diabetes may have been poorly controlled for all or most of that time. It is extremely important to lower her A1C level and thereby decrease her risk of macro- and microvascular complications. The use of additional oral agents would be unlikely to reduce her A1C to target levels, and she would therefore be a good candidate for initiation of an insulin analog premix with her evening (or largest) meal. As with patient 1, the insulin dose would be titrated after initiation to achieve FPG <120 mg/dL. Alternatively, the patient could be started on 2 insulin doses per day, with evening insulin levels titrated based on morning blood glucose levels to achieve FPG <120 mg/dL, and morning insulin titrated based on afternoon blood glucose levels to achieve random blood glucose <140 mg/dL. When the patient is comfortable with insulin therapy, it is possible to switch to insulin pump therapy, although this requires frequent blood glucose monitoring and may involve referral to a diabetologist. Options for oral therapy in this patient include metformin, if kidney function is normal, and a thiazolidinedione plus a GLP-1 analog if body weight is not under control.

Patient 3 has a blood glucose level >1000 mg/dL and urinary ketones; this shows that tight glucose control is needed. After he is resuscitated with IV insulin and normal saline, this patient is likely to require insulin. Initiation of a basal–bolus regimen, with basal insulin at bedtime plus bolus insulin with each meal, allows coverage of postprandial and fasting blood glucose, and involves frequent glucose monitoring. The patient should also be given advice on a diet and exercise regimen and receive follow-up on a regular basis.

Based on these 3 case studies, it can be seen that insulin initiation is suitable for a wide range of patients, from those with slightly elevated A1C to those with frank diabetic ketoacidosis. For each patient, the insulin regimen should be chosen carefully to best suit individual needs in terms both of glycemic control and lifestyle.

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References

1. Centers for Disease Control. National diabetes fact sheet. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevetion, 2011.
2. Kim KS, Oh HJ, Kim JW, et al. The clinical characteristics of the newly diagnosed early onset (< 40 years old) diabetes in outpatients' clinic. Korean Diabetes J 2010; 34:119-125.
3. Nathan DM, Buse JB, Davidson MB, et al. 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.
4. Logtenberg SJ, Kleefstra N, Ubink-Veltmaat LJ, Houweling ST, Bilo HJ. Intensification of therapy and no increase in body mass index with longer disease duration in type 2 diabetes mellitus (ZODIAC-5). Fam Pract 2007; 24:529-531.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837-853.
6. Stratton IM, Kohner EM, Aldington SJ et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia 2001;44:156-163.
7. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321:405-412.
8. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643-2653.
9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577-1589.
10. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010; 376:419-430.
11. Vinik A. Advancing therapy in type 2 diabetes mellitus with early, comprehensive progression from oral agents to insulin therapy. Clin Ther 2007; 29:1236-1253.
12. Marre M. Before oral agents fail: the case for starting insulin early. Int J Obes Relat Metab Disord 2002; 26(Suppl 3):S25-S30.
13. Rosenstock J. Basal insulin supplementation in type 2 diabetes; refining the tactics. Am J Med 2004; 116(Suppl 3A):10S-16S.
14. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; 29:1963-1972.
15. Pfutzner A, Lorra B, Abdollahnia MR, et al. The switch from sulfonylurea to preprandial short- acting insulin analog substitution has an immediate and comprehensive beta-cell protective effect in patients with type 2 diabetes mellitus. Diabetes Technol Ther 2006; 8:375-384.
16. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008; 371:1753-1760.
17. Alvarsson M, Sundkvist G, Lager I, et al. Effects of insulin vs. glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up. Diabetes Obes Metab 2008; 10:421-429.
18. Roman G, Hancu N. Early insulin treatment to prevent cardiovascular disease in prediabetes and overt diabetes. Horm Metab Res 2009; 41:116-122.
19. Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). Am Heart J 2008; 155:26-32.
20. Hanefeld M, Koehler C, Hoffmann C, Wilhelm K, Kamke W, Gerstein H. Effect of targeting normal fasting glucose levels with basal insulin glargine on glycaemic variability and risk of hypoglycaemia: a randomized, controlled study in patients with early Type 2 diabetes. Diabet Med 2010; 27:175-180.
21. Riddle MC. The underuse of insulin therapy in North America. Diabetes Metab Res Rev 2002; 18(Suppl 3):S42-S49.
22. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; 27:17-20.
23. 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.
24. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008; 31:173-175.
25. Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 2002; 347:1342-1349.
26. Grant RW, Buse JB, Meigs JB. Quality of diabetes care in U.S. academic medical centers: low rates of medical regimen change. Diabetes Care 2005; 28:337-442.
27. Nichols GA, Koo YH, Shah SN. Delay of insulin addition to oral combination therapy despite inadequate glycemic control: delay of insulin therapy. J Gen Intern Med 2007; 22:453-458.
28. Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: what is the evidence? Clin Diabetes 2009; 27:60-68.
29. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005; 28:2673-2679.
30. Karter AJ, Subramanian U, Saha C, et al. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. Diabetes Care 2010; 33:733-735.
31. Joy SV. Clinical pearls and strategies to optimize patient outcomes. Diabetes Educ 2008; 34(Suppl 3):54S-59S.
32. Gin H, Hanaire-Broutin H. Reproducibility and variability in the action of injected insulin. Diabetes Metab 2005; 31:7-13.
33. Riddle MC. Starting and advancing insulin for type 2 diabetes: algorithms and individualized methods are both necessary. J Clin Endocrinol Metab 2008; 93:372-374.
34. Meneghini L. Demonstrating strategies for initiation of insulin therapy: matching the right insulin to the right patient. Int J Clin Pract 2008; 62:1255-1264.
35. Burden M, Byard C, Gregory R, Khulpateea A, Burden A. Setting up a fast-track insulin start clinic for type 2 diabetes. Nurs Times 2005; 101:28-30.
36. 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.
37. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008; 371:1073-1084.
38. Meneghini LF, Dornhorst A, Sreenan S. Once-daily

insulin detemir in a cohort of insulin-naive patients with type 2 diabetes: a sub-analysis from the PREDICTIVE study. Curr Med Res Opin 2009; 25:1029-1035.
39. Oiknine R, Bernbaum M, Mooradian AD. A critical appraisal of the role of insulin analogues in the management of diabetes mellitus. Drugs 2005; 65:325-340.
40. Hirsch IB. Insulin analogues. N Engl J Med 2005; 352:174-183.
41. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. Diabetes Obes Metab 2009; 11:5-19.
42. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better postdinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. Diabetes Care 2000; 23:1130-1136.
43. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26:3080-3086.
44. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28:950-955.
45. Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29:1269-1274.
46. Kennedy L, Herman WH, Strange P, Harris A. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial. Diabetes Care 2006; 29:1-8.
47. Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabet Med 2006; 23:736-742.
48. Meneghini L, Koenen C, Weng W, Selam JL. 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.
49. Blonde L, Merilainen M, Karwe V, Raskin P. 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.
50. Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in "real-world" settings: an empowerment-based intervention. Patient Educ Couns 2010; 79:178-184.
51. Mudaliar S, Edelman SV. Insulin therapy in type 2 diabetes. Endocrinol Metab Clin North Am 2001; 30:935-982.
52. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med 2009; 6(Suppl 1):60-75.
53. Jovanovic L. Sex differences in insulin dose and postprandial glucose as BMI increases in patients with type 2 diabetes. Diabetes Care 2009; 32:e148.
54. Ferrara CM, Goldberg AP, Nicklas BJ, Sorkin JD, Ryan AS. Sex differences in insulin action and body fat distribution in overweight and obese middle-aged and older men and women. Appl Physiol Nutr Metab 2008; 33:784-790.
55. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc 2003; 78:1088-1091.
56. Huang ES, Zhang Q, Gandra N, Chin MH, Meltzer DO. The effect of comorbid illness and functional status on the expected benefits of intensive glucose control in older patients with type 2 diabetes: a decision analysis. Ann Intern Med 2008; 149:11-19.
57. Hasslacher C, Collenberg E, Mocks J. Effect of insulin analogs on the decline of hemoglobin in diabetic patients with nephropathy. Exp Clin Endocrinol Diabetes 2010; 118:341-345.
58. Sreenan S, Virkamaki A, Zhang K, Hansen JB. Switching from NPH insulin to once-daily insulin detemir in basal-bolus-treated patients with diabetes mellitus: data from the European cohort of the PREDICTIVE study. Int J Clin Pract 2008; 62:1971-1980.
59. Dornhorst A, Luddeke HJ, Koenen C et al. Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE. Diabetes Obes Metab 2008; 10:75-81.
60. Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care 1997; 20:1353-1356.
61. Li Y, Xu W, Liao Z et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. Diabetes Care 2004; 27:2597-2602.
62. Garber AJ, Wahlen J, Wahl T et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab 2006; 8:58-66.

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