

Benefits of Early Initiation of Insulin Therapy to Long-Term Goals in Type 2 Diabetes Mellitus

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ABSTRACT

Background: The natural history of type 2 diabetes mellitus (DM) includes a progressive worsening of glycemic control and accelerated cardiovascular risk. Aggressive glycemic control early in the course of the disease has the potential to significantly reduce the risk of DM-related microvascular and macrovascular complications.

Objective: The purpose of this article was to present the rationale and evidence supporting early initiation of insulin therapy, even on a short-term basis, for the treatment of type 2 DM. The article also summarizes the current understanding of the impact of insulin therapy on this disease.

Methods: English-language articles were identified primarily through searches of PubMed (1991–2005). Search terms included *insulin*, *insulin therapy*, *early use*, *beta-cell*, and *type 2 diabetes*.

Results: Current algorithms for the treatment of patients with type 2 DM take a stepwise approach, beginning with the introduction of an oral antidiabetic agent and intensification of the oral regimen over time as the patient fails to achieve glycemic control. However, a lengthy stepwise approach with oral antidiabetic therapy alone is often inadequate and prolongs the patient's exposure to glucotoxic effects, which in turn contribute to microvascular and macrovascular complications. Conversely, early introduction of insulin therapy, even on a short-term basis, may alter the course of the disease and minimize its clinical sequelae. This approach is a reversal of the traditional treatment algorithm and places the emphasis on treatment success, as opposed to intensification based only on treatment failure. However, barriers to the initiation of insulin therapy on the part of the physician and the patient are pervasive.

Conclusions: A fundamental change in the approach to DM management and attitudes toward the use of insulin for people with type 2 DM is necessary. Insulin should not be viewed as a treatment option of last resort. The initiation of insulin early in the course of disease may help patients achieve long-term glycemic control and improved quality of life. (*Insulin*. 2006;1:2–12) Copyright © 2006 Excerpta Medica, Inc.

Key words: A1C, insulin, insulin resistance, obesity, type 2 diabetes mellitus, glycemic control, metabolic memory.

INTRODUCTION

Diabetes mellitus (DM) has reached epidemic proportions in the United States, with an estimated 18.2 million people affected by the disease (6.3% of the population).¹ Of these cases, 13 million have been diagnosed, and 90% to 95% have type 2 DM.¹ Unfortunately, and despite abundant evidence regarding the increased risk of serious microvascular and macrovascular com-

plications associated with poor glycemic control, only a small proportion of patients with type 2 DM attain the recommended treatment goals.

The American Diabetes Association recommends that patients with DM achieve control of blood pressure (BP) (target, <130/80 mm Hg), lipids (targets, low-density lipoprotein [LDL] <100 mg/dL, triglycerides <150 mg/dL, and high-density lipoprotein [HDL] >40 mg/dL), and

glycemia (target glycosylated hemoglobin [A1C], <7.0%).² However, an analysis of data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 showed that only 7.3% of adults with DM achieved the recommended treatment targets for plasma glucose, BP, and serum cholesterol.³ Notably, while the proportion of patients achieving BP and lipids goals has improved from NHANES III (1988–1994) to NHANES IV (1999–2000), the proportion achieving the A1C goal has actually decreased (from 44% to 37%).³

One reason why many patients with type 2 DM fail to achieve glycemic control is that oral therapy regimens are often insufficient, due to the progressive nature of the disease that goes from insulin resistance to β -cell failure and ultimately insulin deficiency.^{4,5} Furthermore, the stepwise approach of adding additional oral agents in current treatment algorithms often only prolongs the failure to achieve glycemic control and increases the patient's risk of DM-related complications and the likelihood of β -cell failure.

Early introduction of insulin therapy to inadequate oral treatment regimens can help patients achieve and maintain glycemic control, thereby reducing the risk of DM-related complications.⁶ Moreover, a number of reports suggest that induction of normoglycemia with intensive short-term insulin therapy can help patients achieve long-term glycemic control, which can be maintained for months or even years.^{7–11} Aggressive glycemic control early in the course of the disease has the potential to significantly reduce the risk of DM-related microvascular and macrovascular complications.^{12,13}

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The purpose of this article was to present the rationale and evidence supporting early initiation of insulin therapy, even on a short-term basis, for the treatment of type 2 DM. The article also summarizes the current understanding of the impact of insulin therapy on this disease.

MATERIALS AND METHODS

English-language articles were identified primarily through searches of PubMed (1991–2005). Search

terms included *insulin*, *insulin therapy*, *early use*, *beta-cell*, and *type 2 diabetes*.

NATURAL HISTORY OF TYPE 2 DIABETES MELLITUS: THE TICKING CLOCK

Cardiovascular disease (CVD) is the primary cause of death in people with DM, accounting for ~65% of mortality.¹⁴ Notably, increased cardiovascular risk actually precedes the formal diagnosis of type 2 DM by many years.^{15–17} In other words, “the clock starts ticking” years before the onset of clinical DM. This “ticking clock” hypothesis is based partly on observations of participants in an 8-year follow-up of the San Antonio Heart Study.¹⁶ Patients who did not have a diagnosis of DM at the time of baseline examination but went on to develop type 2 DM had substantially higher levels of total cholesterol and LDL cholesterol, triglycerides, body mass index (BMI), and BP, as well as lower levels of HDL cholesterol, compared with patients who did not develop type 2 DM.¹⁶ Thus, patients who developed DM exhibited several risk factors for CVD before the onset of DM.

More recent studies also support the conclusion that increased CVD risk precedes the formal diagnosis of DM. Specifically, a meta-analysis of 95,783 individuals who had a total of 3707 cardiovascular events over 12.4 years found that the progressive relationship between elevated plasma glucose and CVD risk begins at a level well below the cutoff for a formal diagnosis of DM.¹⁵ Furthermore, in the Nurses' Health Study, an increased risk for myocardial infarction and stroke was evident well before the diagnosis of DM and appeared to increase at least 15 years before a DM diagnosis.¹⁷ The risk for CVD increased further after clinical diagnosis of DM; the highest incidence was found in women with DM diagnosed at study entry. Finally, data from the Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition indicate that a patient's A1C level predicts all-cause, cardiovascular, and ischemic heart disease mortality continuously across the male population—among individuals both with and without DM—and at A1C levels below those considered indicative of DM.¹⁸ This study found that men with A1C levels that were higher but still within the normal range (A1C, 5.0%–6.0%) had a significantly increased risk of coronary heart disease events (age-adjusted relative risk, 1.56 [95% CI, 1.09–2.24]) compared with men with A1C levels <5.0%. Furthermore, every 1.0% increase in A1C was associated with

a 28% increase in risk of death, independent of age, BP, serum cholesterol, BMI, or cigarette smoking habit.^{18,19}

It is likely that the observed increased risk of CVD before the diagnosis of DM is the consequence of long-standing metabolic defects that underlie the pathophysiology of type 2 DM. As shown in **Figure 1**, these defects include insulin resistance and insulin deficiency, as well as components of the metabolic syndrome that include the prothrombotic state, inflammation, dyslipidemia, elevated triglycerides, and low HDL cholesterol.^{12,20,21} Although the temporal sequence of these two defects is the subject of debate, both clearly contribute to the pathophysiology of type 2 DM. Insulin

resistance and declining β -cell function most likely begin years before the diagnosis of type 2 DM. Based on data from the United Kingdom Prospective Diabetes Study (UKPDS), it has been estimated that the loss of normal insulin secretory capacity begins >10 years before the diagnosis of type 2 DM.²² This is important, since insulin is anti-inflammatory, decreases both reactive oxygen species and interleukin-6, and improves the prothrombotic state.

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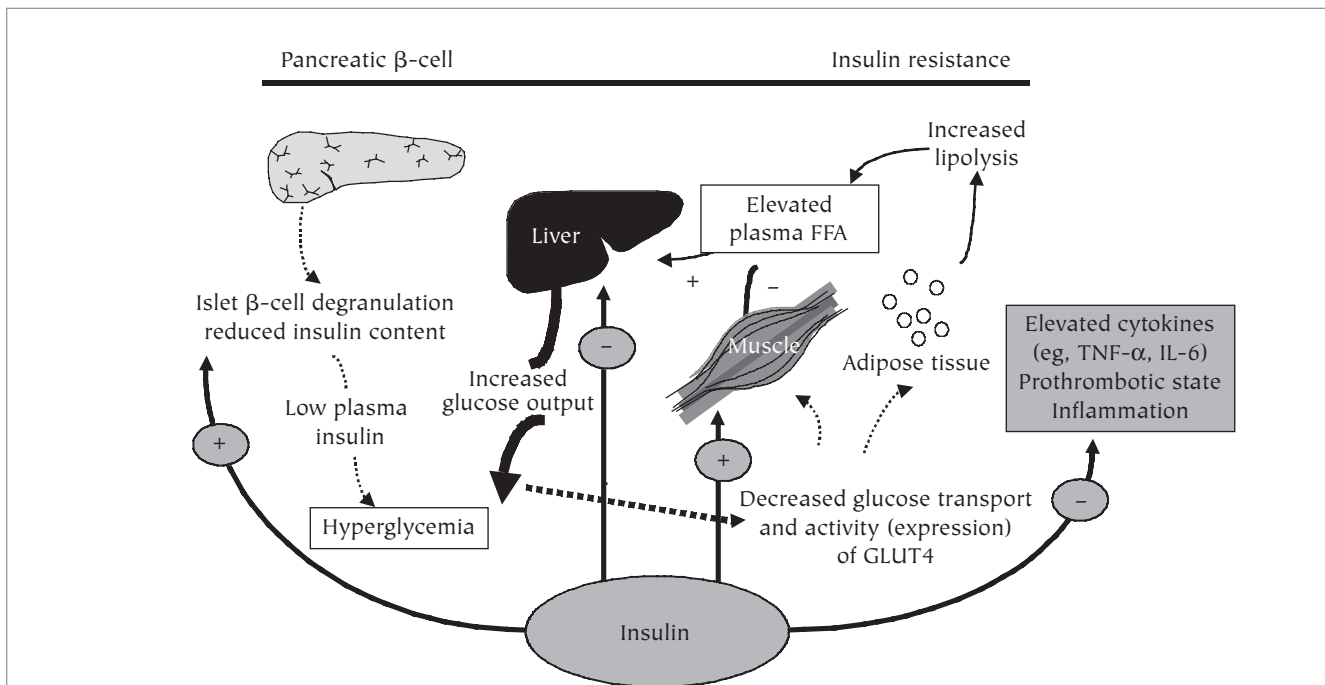


Figure 1. Declining β -cell function and insulin resistance precede development of type 2 diabetes mellitus (DM). Both insulin resistance and insulin deficiency contribute to the pathogenesis of type 2 DM. Insulin resistance causes reduced suppression of hepatic glucose production, reduced muscle glucose uptake, and elevated adipose tissue release of free fatty acids (FFAs) and cytokines. The schema shows that progressive β -cell dysfunction and reduced insulin secretion lead to a state of insulin deficiency relative to the amount of insulin needed to overcome insulin resistance. Increased hepatic glucose output is characteristic of all patients with type 2 DM and is responsible for fasting hyperglycemia. The range of 70% to 80% of all glucose uptake is by skeletal muscle, and this is dependent on insulin action. Also, increased adipose tissue release of FFAs and oxidation of FFAs in liver and adipose tissue increase the rate of gluconeogenesis, and further impair insulin action on muscle. Finally, the release of cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), induces resistance to the mechanism of action of insulin, presumably by inducing serine phosphorylation of the insulin receptor. Insulin exerts positive effects on all these abnormalities, not only the hyperglycemia. GLUT4 = glucose transporter 4.

The “clock” for microvascular complications of type 2 DM also begins “ticking” before the diagnosis of DM. Data obtained from the UKPDS demonstrated that substantial microvascular—as well as macrovascular—abnormalities were present in ~50% of the patients at the time of diagnosis of type 2 DM.²³ This evidence emphasizes the importance of early diagnosis and aggressive initiation of therapy to prevent further tissue damage and associated morbidity in patients with type 2 DM.

SUBOPTIMAL DIABETES MELLITUS MANAGEMENT

Glycemic control in most patients with type 2 DM who are treated with oral agents alone will eventually deteriorate due, in part, to the progressive nature of the disease, leading to a need for combination oral therapy and then insulin therapy to continue to achieve glycemic targets.^{6,24} The failure rate is 5% to 10% per year,¹³ so that in 10 years all will require insulin. In clinical practice, patients who start oral antidiabetic therapy are typically titrated to the maximally recommended dosage, followed by the addition of a second or even third oral agent.^{24,25} With this stepwise approach, the patient is ultimately being treated for failure, with intensification of the regimen occurring only after failure to achieve glycemic control over time.

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In the UKPDS, <25% of the patients achieved A1C levels <7.0% with monotherapy after 9 years.⁴ More importantly, the UKPDS demonstrated a progressive decline in glycemic control over time in patients treated with sulfonylurea or metformin monotherapy, with >50% of the patients requiring insulin by the end of 6 years of observation.⁶

For many patients, oral antidiabetic agents also may be limited in their capacity to reduce A1C levels (<2%) to treatment target goals. At maximum doses and in combination, oral agents typically provide a 2% to 3% reduction in A1C (**Table I**).¹ This implies that patients with an initial A1C level >10.0% may not attain glycemic goals with oral therapy alone.

Inadequate or suboptimal glycemic control can lead to chronic hyperglycemia, which in turn can lead to glucotoxicity and irreversible effects on insulin secretion and disposal. Chronic hyperglycemia can induce β -cell death via apoptosis²⁶ and is also capable of inducing insulin resistance.²⁷ Furthermore, due to declining β -cell function over time, the window of opportunity to correct hyperglycemia and reverse the abnormalities in both insulin secretion and insulin sensitivity is limited. To compensate for β -cell failure, early introduction of insulin therapy may be an appropriate therapeutic approach to achieve optimal glycemic control.

In addition, in vitro and in vivo studies demonstrate that insulin has anti-inflammatory properties; inhibits lipolysis; suppresses tumor necrosis factor- α , interleukin-6, and nuclear factor κ B; and reduces oxidative and nitrosative stress.^{12,20,21} As previously noted,²³ evidence of DM-related tissue damage at the time of diagnosis supports an immediate, aggressive approach to arrest or delay the microvascular and macrovascular complications associated with DM.

BENEFITS OF EARLY INITIATION OF INSULIN THERAPY

Rapid, early establishment and maintenance of glycemic control can correct the abnormalities in insulin secretion and insulin action caused by hyperglycemia, thereby reducing the risk of microvascular and macrovascular complications associated with increased glucose levels. Thus, rather than taking a stepwise ap-

proach with gradual intensification of an oral therapy regimen based on failure to achieve glycemic control, an ideal algorithm would reverse the traditional algorithm by calling for early introduction of insulin therapy (**Figure 2**). This calls for a fundamental change in the approach to the treatment of type 2 DM.

The introduction of insulin therapy early in the course of DM, either as a temporary measure to achieve glycemic control quickly or as a long-term therapeutic approach to maintain tight glucose control, is an opportunity to alter the course of DM progression. Data from the UKPDS indicate that after insulin is introduced, either alone or in combination with oral therapy, the long-term outcome is improved glycemic control (**Figure 3**).⁶

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LONG-TERM BENEFITS OF SHORT-TERM INSULIN THERAPY

A number of clinical studies have demonstrated that induction of normoglycemia with intensive short-term insulin therapy may have positive long-term effects on glycemic control in patients with type 2 DM.^{7-11,28-30} In a recent study, Li et al¹¹ examined whether long-term glycemic control can be achieved without medica-

tion after transient use of continuous subcutaneous insulin infusion (CSII) in 138 treatment-naïve patients with newly diagnosed type 2 DM and severe fasting hyperglycemia >199.8 mg/dL (>11.1 mmol/L). Patients were hospitalized and treated with CSII for 2 weeks, resulting in a total of 126 patients achieving optimal glycemic control (fasting plasma glucose [FPG] <109.8 mg/dL [<6.1 mmol/L] and postprandial plasma glucose <144 mg/dL [<8.0 mmol/L]) within 6.3 (3.0) days (mean [SD]). The percentage of patients maintaining near euglycemia at months 3, 6, 12, and 24 were 72.6%, 67.0%, 47.1%, and 42.3%, respectively. Furthermore, patients who maintained glycemic control for >12 months (remission group) showed significant improvement in β -cell function ($P = 0.002$), particularly with respect to restoration of the first-phase insulin response ($P = 0.033$).¹¹

Similar results have been reported in other studies.^{7,8} A recent South Korean study examined 91 patients with type 2 DM with a mean (SD) baseline A1C level of 13.2% (4.9%).⁸ After a mean (SD) of 53.6 (38.9) days of CSII therapy, 34% of all patients experienced remission (A1C, 6.4% [3.1%]; FPG, 103 [47] mg/dL [5.7 (2.6) mmol/L]) lasting for an average of 13.6 (8.9) months.

The demonstration of long-term glycemic control or remission without medication after short-term intensive insulin therapy in some patients suggests that the initial defect in β -cell function was reversed by the period of insulin-induced normoglycemia.^{7,11} Based on

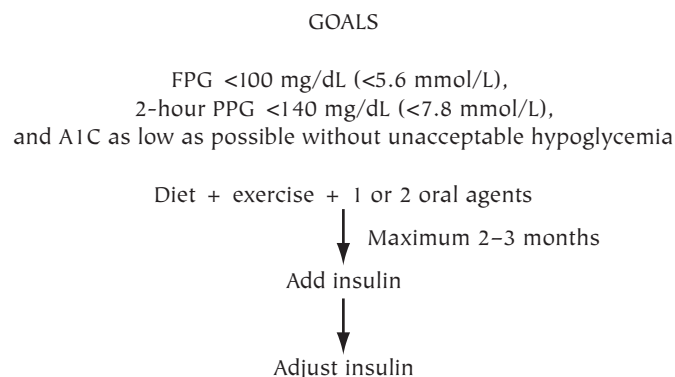


Figure 2. A suggested algorithm for early initiation of insulin therapy in the treatment of patients with type 2 diabetes mellitus. This approach is a reversal of the traditional treatment algorithm, with an emphasis on treatment success as opposed to intensification based on treatment failure. Typically 1 to 2 oral agents = one half the maximal dose of a sulfonylurea plus metformin or a glitazone. FPG = fasting plasma glucose; PPG = postprandial glucose; A1C = glycosylated hemoglobin.

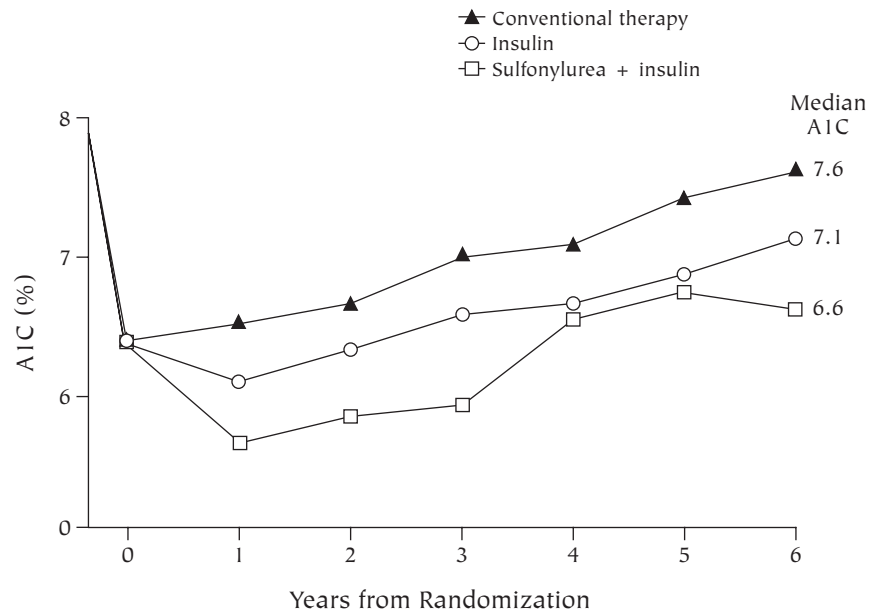


Figure 3. Early introduction of insulin alters the progression of type 2 diabetes mellitus. Introduction of insulin, either alone or in combination with oral therapy, results in better long-term glycemic control than conventional therapy with oral agents alone in patients with type 2 diabetes mellitus. Over a period of 6 years, glycosylated hemoglobin (A1C) levels were consistently lower in insulin-treated patients. Copyright © 2002 American Diabetes Association. From *Diabetes Care*, Vol. 25, 2002;330–336.⁶ Reprinted with permission from *The American Diabetes Association*.

these studies, patient characteristics that may be associated with a greater likelihood of achieving remission after CSII therapy include a shorter duration of DM, lower postprandial blood glucose levels, higher BMI, and fewer chronic complications attributable to DM.⁸

Other clinical studies have demonstrated that long-term benefits, similar to those seen in studies with CSII, can also be attained with short-term treatment regimens of multiple daily insulin injections.^{9,10} In a recent study by Ryan et al,⁹ 16 patients with newly diagnosed type 2 DM achieved and maintained glycemic control for up to 1 year after a short-term (2- to 3-week) insulin therapy regimen consisting of short-acting insulin before each meal and intermediate-acting insulin at bedtime. At the 1-year follow-up, all patients maintained glycemic control, nearly 50% maintained good glycemic control without medications, and the mean (SD) A1C level fell from an initial value of 11.8% (0.3%) to 6.6% (0.3%).⁹ On completion of the study, 7 of the 16 patients maintained glycemic control with diet therapy alone. Overall, the intensive insulin therapy was associated with an improvement in the insulin AUC in response to an oral

glucose load immediately after the insulin treatment period and 1 year later ($P < 0.01$); these findings suggest improved insulin secretion and at least a partial restoration of β -cell function.⁹

MECHANISMS CONTRIBUTING TO LONG-TERM BENEFITS OF INSULIN THERAPY

As described earlier, short-term glycemic control using intensive insulin treatment, with the aim of achieving 24-hour blood glucose profiles near physiologic levels, has the potential to improve insulin action and insulin secretion in patients with severe type 2 DM and secondary failure of oral antidiabetic agents. Theoretically, this approach should be more successful early in the course of the disease when greater residual β -cell function is most likely present and the likelihood of reversing the effects of glucotoxicity is greater. However, the mechanisms underlying the impact of short-term insulin therapy are not completely understood.

One possibility is improved insulin sensitivity. Scarlett et al³⁰ noted that transient insulin therapy in patients with untreated type 2 DM ameliorated the postreceptor defect in insulin-mediated glucose disposal

as measured by the euglycemic glucose-clamp method. They concluded, however, that the postreceptor defect in insulin action is secondary to a relative state of insulin deficiency, rather than a primary defect.

Hyperglycemia in vivo impairs β -cell function, leading to reduced insulin secretion and diminished peripheral insulin sensitivity.²⁷ Accordingly, short-term correction of the hyperglycemia through intensive insulin therapy can be an effective approach to restore insulin secretion. Amelioration of glucose toxicity and restoration of β -cell function may be the physiologic basis for maintenance of glycemic control even after intensive insulin treatment is discontinued. Notably, one common feature in studies demonstrating remission or reduced severity of DM after intensive insulin therapy is that the intervention occurs while β -cell function is adequate to provide sufficient residual endogenous insulin secretion. This suggests that short-term insulin therapy may be more effective if used early in the course of disease before substantial loss of β -cell function.

In a small sample of 12 patients with uncontrolled type 2 DM (duration, 1–25 years), despite maximal-dose glibenclamide (glyburide) and metformin therapy, CSII for ~17 days produced immediate improvements in glucose control (mean FPG, 126 mg/dL [7 mmol/L] after CSII vs 302 mg/dL [16.8 mmol/L] before CSII) and maximum incremental C peptide responses to glucagon.²⁹ Despite a transient improvement in β -cell function, only 6 out of 12 patients maintained adequate glucose control using oral antidiabetic medications. Interestingly, age, duration of DM, and C peptide response to glucagon were not predictive of the restoration of the response to oral agents.²⁹

Further studies are needed to determine the differentiating characteristics of patients likely to experience a sustained glycemic improvement from short-term intensive insulin therapy. Controlled studies comparing insulin with other intensive therapeutic regimens also are needed to further clarify the disease-modifying properties of intensive glycemic control in DM. Future studies could investigate the possibility that glitazones may preserve β -cell function³¹ and that a number of incretins (such as glucagon-like peptide [GLP] and GLP-1) may prevent β -cell apoptosis.

BARRIERS TO INITIATION OF INSULIN THERAPY

To effectively treat patients who have type 2 DM, a fundamental change in the approach to DM manage-

ment and attitudes toward the use of insulin will be necessary. In other words, insulin should not be thought of as a last line of therapy. Unfortunately, clinical inertia often results in failure to intensify treatment regimens in patients with DM who have inadequate glycemic control. In a recent analysis of administrative data for patients with DM in Ontario, Quebec, Canada, <50% of the patients with high A1C levels had intensification of their medicines, regardless of the specialty of their physician.³² However, specialists were more aggressive with insulin initiation than primary care physicians, which may have accounted for the lower A1C levels seen with specialist care.

Clinical inertia often results in failure to intensify treatment regimens in patients with DM who have inadequate glycemic control.

Several factors hinder the more widespread early initiation of insulin therapy in patients with type 2 DM. Both physician-related and patient-related factors (**Table II**) contribute to a general resistance to early initiation of insulin therapy.^{33–36} Among physicians, fear that patients will not like insulin and fear of potential adverse events, such as hypoglycemia, often prevent or delay the initiation of insulin therapy.^{33,34} Many physicians have the misperception that insulin is not an effective therapy for type 2 DM and/or that insulin regimens are too complicated for their patients.^{33,34} Among patients, fear of needles—as well as concerns about hypoglycemia, weight gain, and the inconvenience of scheduled injections and complicated regimens—often limit acceptance of insulin therapy.³⁵ Patients may perceive insulin as a therapy of last resort or even as a punitive measure due to personal failure.³⁵ Unfortunately, in an attempt to encourage compliance with oral medications, initiating insulin is often used as a threat by the physician in the event that the patient does not achieve glycemic control with current therapies.

Hypoglycemia is a risk with insulin use and can have an impact on treatment effectiveness. A recent study investigated how treatment behavior and therapeutic satisfaction were affected by hypoglycemia in patients with type 2 DM.³⁷ The study found that the more frequent the events of hypoglycemia, particularly

Table II. Barriers to initiation of insulin therapy.^{33,35,36}

Physician-Related Barriers	Patient-Related Barriers
Fear of Hypoglycemia Adverse health consequences of insulin itself	Fear of Hypoglycemia Adverse health consequences Medication errors Needles and pain Weight gain Inconvenience of scheduled injections and complicated regimen
Misperception of Regimens being too complex Therapy of last resort or limited efficacy in type 2 diabetes mellitus	Misperception of Personal failure Advanced stage and severity of their disease (ie, negative turning point in the course of diabetes mellitus) Therapy of last resort Cost of insulin, syringes, and self-monitoring

nocturnal hypoglycemia, the more patients decreased the dosage of insulin or intentionally tried to maintain higher blood glucose levels to avoid hypoglycemic episodes. Furthermore, the frequency of hypoglycemia was positively correlated with the degree of worry patients felt and negatively correlated with the level of satisfaction with their DM treatment regimen.³⁷

Strategies to overcome barriers to early initiation of insulin therapy include patient education, as well as enhanced communication between the patient and physician to address patient concerns. In a recent study, patients undergoing structured DM self-management educational programs exhibited significant improvement ($P < 0.001$) in glycemic control, as measured by A1C testing and a corresponding improvement in quality of life, with increased energy and well-being, and reduced depression and anxiety.³⁸ Another study comparing the effects of insulin glargine versus rosiglitazone at achieving equivalent glycemic control reported improvements in vigor and decreases in symptom distress, depressed mood, and irritability in favor of insulin.³⁹

Fear of injection is a considerable patient-related barrier to insulin therapy. Clinicians need to be mindful of this and should spend time with the patient demonstrating the proper injection technique. As an alternative, newer pen devices may offer convenience with respect to dosing compared with the traditional needle and syringe. Thus, patient education—along with the use of insulin formulations that reduce the risk

of hypoglycemia and weight gain, simplified treatment regimens, and easy-to-use insulin delivery technologies—may be the key to help remove barriers to insulin use.

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OVERCOMING BARRIERS WITH BASAL INSULIN THERAPY

Simple insulin titration algorithms and once-daily dosing may help overcome barriers and facilitate early initiation of insulin therapy, even on a short-term basis, to help patients with type 2 DM achieve optimal glycemic control. The addition of a basal insulin to an oral treatment regimen allows patients to regain and achieve glycemic control. For example, in patients who did not achieve adequate glycemic control with sulfonylurea therapy alone, once-daily administration of neutral protamine Hagedorn (NPH) insulin at bedtime, either alone or in combination with sulfonylurea therapy, improved glucose control.⁴⁰ The efficacy of bedtime insulin therapy in this particular study was specifically attributed to suppression of basal hepatic glucose production.⁴⁰ Similarly, Taskinen et al⁴¹ showed that sup-

pression of overnight plasma free fatty acid levels with a decrease in hepatic glucose production may be the reason for the clinical effectiveness of bedtime basal insulin therapy in overweight patients with inadequately controlled type 2 DM.

In the Treat-to-Target Trial, the addition of once-daily basal insulin therapy to oral therapy, with systematic titration of insulin doses (insulin glargine or NPH) until a defined FPG target was achieved, produced a substantial improvement in glycemic control (mean A1C at end point, <7.0%).³⁶ Although most patients (~60%) achieved A1C levels \leq 7.0% with either insulin glargine or NPH, insulin glargine therapy, due to its consistent time-action profile with no pronounced peak,³⁶ was associated with a significantly lower rate of nocturnal hypoglycemia (4 all reported events for insulin glargine vs 6.9 for NPH [$P < 0.001$]), expressed as events per patient-year. Furthermore, a recent meta-analysis of controlled trials of a similar design for insulin glargine versus once- or twice-daily NPH insulin in adults with type 2 DM demonstrated a 46% reduction in the risk of severe hypoglycemia and a 59% reduction in the risk of severe nocturnal hypoglycemia with insulin glargine.⁴²

These studies^{36,42} demonstrate that simple insulin dosing algorithms can be developed and used in a way that is effective in helping patients achieve glycemic target goals with a reduced incidence of hypoglycemia. One strategy for initiating and advancing basal insulin therapy in type 2 DM is provided in **Table III**.³⁶ An alternative strategy is to increase the dose of basal insulin by 2 IU every 3 days until a target FPG of \leq 100 mg/dL is achieved.⁴³

Early introduction of insulin into the treatment paradigm not only affords realization of optimal glycemic control, it also establishes a positive approach to insulin therapy. Physicians and patients may be less reluctant to return to insulin therapy when necessary as a result of their prior experience. Ultimately, by helping patients achieve glycemic control, short-term therapy can prevent DM-related complications and improve the overall quality of life. However, clinical studies on possible sustained benefits of short-term therapy with basal insulin are needed.

CONCLUSIONS

Achieving and maintaining glycemic control is imperative for patients with type 2 DM to minimize the risk

Table III. Dose titration of basal insulin.*

Start with 10 IU/d bedtime basal insulin and adjust weekly

Mean of Self-Monitored FPG Values from Preceding 2 Days (mg/dL)	Increase in Insulin Dose (IU/d)
\geq 80	8
\geq 40 but < 80	6
> 20 but < 40	4
100–120	2

FPG = fasting plasma glucose.

*The treat-to-target FPG was \leq 100 mg/dL. Exceptions to this algorithm were: (1) no increase in dosage if plasma-referenced glucose <72 mg/dL was documented at any time in the preceding week; and (2) in addition to no increase, small insulin dose decreases (2–4 IU/d per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose <56 mg/dL were documented in the preceding week.

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of DM-related microvascular and macrovascular complications. Unfortunately, most patients with type 2 DM fail to achieve an acceptable level of glycemic control, resulting in an inevitable cycle of sustained hyperglycemia, insulin resistance, and progressive decline in insulin secretion. Furthermore, current treatment algorithms take a stepwise approach and call for initiation of insulin therapy only after intensification of oral therapy and failure to achieve glycemic control over time. For many patients, such a delayed approach to initiation of insulin therapy only increases glucotoxicity and prolongs microvascular and macrovascular disease risk.

In contrast, early addition of insulin therapy to oral therapy regimens can help patients reach glycemic control and slow disease progression. Furthermore, if glycemic control is achieved early in the course of DM progression, it may be possible to restore β -cell function and insulin sensitivity in some patients. Indeed, a number of studies demonstrate the efficacy of short-term insulin therapy as an approach to achieving glycemic control. The initiation of insulin early in the course of disease may help patients achieve long-term glycemic control and improved quality of life.

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