 Effective glycemic control is essential to minimize the long-term complications of type 2 diabetes mellitus (T2DM). However, it is well documented that many patients spend prolonged periods outside of the optimal glycemic range. The use of insulin is important to effectively control the disease process in patients with T2DM. Even so, resistance to insulin use among patients and healthcare providers often limits initiation and intensification of insulin therapy. With the increasing prevalence of T2DM across all socioeconomic strata, an expanded viewpoint of early and sustained insulin use is crucial to enhance glycemic control in patients. To manage the effects of T2DM on cardiovascular disease in the aging population, physicians can promote insulin therapy as an affordable and effective treatment option. The author reviews beliefs and myths about the use of insulin in the management of T2DM and discusses strategies to overcome barriers to initiation of insulin therapy in the primary care setting.

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patient resistance to insulin therapy is common, and this attitude often causes delays in initiation of the therapy.\(^7,8\) As many as one-quarter of insulin-naïve patients express unwillingness to take insulin if prescribed, and another 25% are only slightly willing to take insulin.\(^5\) Survey results of insulin-naïve patients with T2DM reveal that attitudinal reluctance to take insulin—which has been termed psychological insulin resistance—derives from multiple physical concerns, including fear of injections and worries about potential weight gain and risk of hypoglycemia (Table).\(^8\) In addition, psychosocial causes of patient resistance include a sense of personal failure and discomfort about administering insulin in public.\(^5\) Psychological insulin resistance may manifest as resistance to initiation of insulin therapy and to escalation of the insulin regimen as the disease progresses.\(^8\)

A sense of personal failure represents one of the strongest obstacles to patient acceptance of insulin.\(^5\) From the patient’s perspective, the need for insulin indicates that his or her inability to control diabetes mellitus through lifestyle changes, weight loss, or adherence to oral therapy has led to a more serious and invasive form of therapy. In the survey by Polonsky et al,\(^5\) the negative attitude that most strongly distinguished unwilling from willing insulin-naïve patients was the sense that they had failed to properly manage their disease (Table).

Several approaches may be useful in addressing, or even averting, such a poor self-image among patients. It remains common clinical practice to use insulin therapy as the proverbial stick. Many practitioners hold the “threat” of insulin over patients to compel better adherence to early-stage interventions.\(^10\) However, it can be useful at the outset of the patient-physician relationship—well before insulin is needed—to explain to the patient that insulin is part of the normal continuum of care as a patient’s disease progresses.\(^7\) When patients understand that the need for insulin represents not a drastic or punitive measure but rather an expected step stemming from the progressive nature of the disease itself, the stigma of insulin therapy fades.\(^5\)

### Healthcare Providers

Research shows that nearly all primary care physicians are aware of appropriate goals for glycemic control in patients with T2DM.\(^10\) Nevertheless, many of these physicians tend to adopt treatment approaches that are inconsistent, or at least inadequate, to achieve glycemic targets. Notable among these approaches is resistance to initiate insulin.\(^7,10\)

The Diabetes Attitudes, Wishes, and Needs (DAWN) study\(^2\) found that many US physicians, especially those in primary care, are inclined to delay initiation of insulin therapy. In fact, US physicians ranked lowest among physicians in all nations except Japan and India in their disposition to initiate insulin.\(^7\) Evidence suggests that, in a typical US primary care practice, insulin initiation is not triggered until a patient’s HbA\(_1c\) level has reached 9% or greater.\(^11\) Some authors have even characterized the current state of T2DM management as collusion between physicians and patients, proposing that there is a dynamic of “implicit and unspoken contracts to continue oral agents for as long as possible.”\(^12\)

Physician resistance to prescribing insulin may originate from either physiologic or practical concerns. Physiologic concerns include apprehension about hypoglycemia or weight gain and the belief that insulin causes adverse metabolic effects. Examples of practical concerns about insulin initiation include patient anxiety, complexity in training patients, and demands on the physician or the physician’s practice to manage the patient’s use of insulin.\(^13\) These concerns, however, are often unfounded or exaggerated. For example, evidence suggests that insulin is actually associated with
beneficial effects on cardiovascular status, particularly on levels of triglycerides and high-density lipoprotein cholesterol.\textsuperscript{10,14} Similarly, although patients do gain weight after insulin initiation, the gain is relatively modest, ranging from 4.4 lb to 8.8 lb (2 kg to 4 kg). Furthermore, weight gain is inversely proportional to body mass index, so that patients who weigh more at the outset of insulin therapy gain less weight as a result of the therapy.\textsuperscript{14}

With regard to practical concerns, initiation of insulin will likely impose additional time demands on the physician or practice. However, many physicians report that these additional demands are not excessive\textsuperscript{10} and can be addressed with small steps in patient education. Although some patients initially experience anxiety about insulin, this attitude often reverses after they begin using insulin. Many patients report less fatigue and an improved sense of well-being, as well as high levels of treatment satisfaction, after beginning insulin therapy.\textsuperscript{15} Thus, early education of patients about the benefits of insulin can reduce burdens on the physician and practice.

Adherence to Insulin Therapy

Rates of adherence to insulin therapy among patients with T2DM range from 63\% to 77\%.\textsuperscript{16,17} Demographic factors associated with poorer adherence include younger age at presentation, younger age at diagnosis, greater social deprivation, higher body mass index, and higher HbA\textsubscript{1c} level.\textsuperscript{17} Not surprisingly, more complex insulin regimens and higher doses of insulin are also associated with poorer rates of adherence. In addition, ethnicity has been linked to differences in insulin adherence, with African Americans demonstrating lower adherence than all other ethnic groups.\textsuperscript{16}

Recognition by medical staff of the high rate of patient nonadherence is important for obvious reasons. Rather than routinely changing a patient’s regimen in response to elevated blood glucose or HbA\textsubscript{1c} levels, physicians should consider that the patient is simply not adhering to the prescribed regimen.

Good patient-physician communication remains a cornerstone of improving insulin acceptance and adherence by patients.\textsuperscript{18} Achieving such effective communication includes efforts by physicians to explore reasons for patients’ resistance.\textsuperscript{9} For example, patients who are fearful of needles may be unaware of improvements in dosing and injection devices that make insulin administration easier and less painful. A simple, in-office demonstration that includes the first injection may be all that is needed to reassure the patient. For patients concerned about the risks of weight gain, providing accurate information about these risks while emphasizing that most patients feel substantially better when using insulin can alleviate their anxiety.

Because patients often take cues from physicians, greater engagement of the patient in disease management can yield considerable improvement in insulin adherence.\textsuperscript{16} Certain novel approaches may help physicians better engage patients. For example, findings from one study\textsuperscript{16} suggest that discussions about prescription refill rates may stimulate dialogue between patients and healthcare providers about conscientious adherence to insulin regimens. For patients who are anxious about the lifelong need for insulin, the use of insulin therapy can be suggested as only a trial intervention lasting several months. After patients begin using insulin and start to feel better, they are likely to continue the therapy.\textsuperscript{19}

Empowering patients with an algorithm to self-titrate their insulin therapy (Figure 1) is another way to improve adherence and, thereby, help patients achieve and maintain glycemic control.\textsuperscript{20} Results from multiple studies—including a Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar (AT.LANTUS)\textsuperscript{21}; the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study\textsuperscript{22}; and the Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation 303 (PREDICTIVE 303) trial\textsuperscript{23,24}—show that good glycemic control with a low incidence of hypoglycemia (ie, <1\%) were achieved with both patient-driven and clinic-directed algorithms.\textsuperscript{20}

Tighter glycemic control yields a longer life expectancy as well as reduced vascular and neuropathic complications of T2DM.\textsuperscript{25,27} Many patients have experienced the ravages of these complications and want desperately to avoid them. Physicians should recommend that patients “parent” themselves. A physician can note, for example, that a patient would never allow his or her child to stray far from adherence to treatment, so why would the patient allow himself or herself to do so by not following an insulin regimen? Physicians should also stress that a patient has many people relying on his or her health and well-being, and these people would suffer if the patient became ill from not adhering to the insulin regimen.

Recommendations for Earlier Implementation of Insulin Therapy

Clinical practice has long focused on managing T2DM first with lifestyle changes and later with addition of an oral hypoglycemic agent. Early guidelines recommended delaying insulin therapy for as long as possible.\textsuperscript{10} However, such an approach leaves many patients with inadequate long-term glycemic control. Research has shown that by the time insulin therapy is initiated, many patients have lived 5 years with an HbA\textsubscript{1c} level greater than 8\% and 10 years with an HbA\textsubscript{1c} level greater than 7\%.\textsuperscript{11}

This realization has led to revised thinking about treatment. The most recent standard-of-care guidelines by the ADA\textsuperscript{2} and the European Association for the Study of Diabetes (EASD)\textsuperscript{14} recommend earlier initiation of insulin in patients for whom glycemic targets are not being achieved. Although an HbA\textsubscript{1c} level of less than 7\% is recommended for most patients with T2DM,\textsuperscript{4,14} treatment goals should be individualized based on patient status and medical history. Higher HbA\textsubscript{1c} levels may be appropriate for some patients, including those who are especially vulnerable to hypoglycemia, those who have severe microvascular complications or comorbid conditions, and those who have short life expectancies.\textsuperscript{2}

Glycosylated hemoglobin is an index of glycemic control during the preceding 2 to 3 months. To achieve an HbA\textsubscript{1c} level of less than 7\%, targets for fasting plasma glucose (FPG) and peak postprandial glucose (PPG) are, respectively, 70 mg/dL to 130 mg/dL and less than 180 mg/dL.
Start with bedtime intermediate-acting insulin or bedtime or morning long-acting insulin (can initiate with 10 units or 0.2 units per kg)

Check fasting glucose (fingerstick) usually daily and increase dose, typically by 2 units every 3 days until fasting levels are consistently in target range (3.9-7.2 mmol/L [70-130 mg/dL]). Can increase dose in larger increments, eg, by 4 units every 3 days, if fasting glucose >10 mmol/L (180 mg/dL)

If hypoglycaemia occurs, or fasting glucose level <3.9 mmol/L (70 mg/dL), reduce bedtime dose by 4 units or 10%, whichever is greater

HbA1c ≥7% after 2-3 months

No

Yes

If fasting bg in target range (3.9-7.2 mmol/L [70-130 mg/dL]), check bg before lunch, dinner, and bed. Depending on bg results, add second injection as below. Can usually begin with ~4 units and adjust by 2 units every 3 days until bg in range

Pre-lunch bg out of range. Add rapid-acting insulin at breakfast a

Pre-dinner bg out of range. Add NPH insulin at breakfast or rapid-acting at lunch

Pre-bed bg out of range. Add rapid-acting insulin at dinner a

HbA1c ≥7% after 3 months

Recheck pre-meal bg levels and if out of range, may need to add another injection. If HbA1c continues to be out of range, check 2 h postprandial levels and adjust preprandial rapid-acting insulin

Figure 1. Algorithm for initiation and adjustment of insulin therapy. Insulin regimens should take a patient’s lifestyle and meal schedule into account. Although premixed insulins are not recommended during dose adjustment, they can be used conveniently—usually before breakfast or dinner—if the proportion of rapid-acting and intermediate-acting insulins is similar to the fixed proportions available. Abbreviations: bg, blood glucose; HbA1c, glycosylated hemoglobin; NPH, neutral protamine Hagedorn. With kind permission from Springer Science+Business Media: Diabetes, Medical management of hyperglycaemia in type 2 diabetes mellitus: 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, Vol 52, 2009, 17-30, Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for the Study of Diabetes, Figure 1.
(which, for self-monitoring patients, corresponds to a value of <140 mg/dL 2 hours after beginning a meal).14

**Newly Diagnosed T2DM Cases**

In recent years, short-term intensive insulin therapy in patients newly diagnosed as having T2DM has drawn increasing attention. Ryan et al28 reported that in patients newly diagnosed as having T2DM, a 2-week to 3-week course of intensive insulin therapy, including multiple daily injections, could successfully lay a foundation for prolonged good glycemic control.29 More recently, investigators have reported that early intensive insulin therapy in patients newly diagnosed as having T2DM could contribute to improved recovery and maintenance of β-cell function, protracted glycemic remission, and improved glycemic control, compared with oral antihyperglycemic treatment.29,30

**Insulin Preparations**

Numerous insulin preparations, with a range of pharmacodynamic properties, are available (Figure 2).31 These preparations include insulin analogs that offer certain advantages over nonanalog (ie, human insulin) alternatives. Among these advantages are improved physiologic time-action profiles and lower incidence of hypoglycemia.32 Insulin analogs include rapid-acting analogs (for prandial insulin coverage), long-acting analogs (for basal coverage), and premixed insulin analogs (which combine both a rapid-acting and an extended-duration component in a single formulation).33

**Insulin Regimens**

Strategies for initiating insulin therapy have been widely studied, with the goal of determining the relative safety and effectiveness of basal, bolus, or basal-bolus regimens.34,35 The APOLLO (A Parallel design comparing an Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetes patients failing Oral treatment) trial34 was designed to compare basal insulin vs prandial insulin administration in patients with T2DM inadequately controlled by oral therapy. Patients were randomly assigned to receive either basal insulin glargine once daily at the same time each day or insulin lispro 3 times daily at mealtimes. At 44 weeks, the basal regimen was found to be as effective as prandial administration with regard to controlling glycemic levels. The basal regimen was also associated with lower risk of hypoglycemia and greater treatment satisfaction.34

The Treating to Target in Type 2 Diabetes (4-T) study36,37 examined the question slightly differently but reached similar conclusions. In the 4-T study, patients who had failed to reach glycemic targets with combination therapy of metformin and a sulfonylurea were randomly assigned to 1 of 3 insulin regimens: biphasic insulin aspart twice daily, prandial insulin aspart 3 times daily, or basal insulin detemir 1 to 2 times daily.38 At 3 years, glycemic efficacy was similar across the 3 groups, but the basal insulin group experienced statistically significant fewer hypoglycemic events and less weight gain than the other groups (P<.001). These and other data form the basis for present recommendations that the initial insulin regimen for patients with T2DM should consist of basal administration.14

**Insulin Dose**

Various algorithms are available to guide insulin initiation,36,37 and physicians are encouraged to choose 1 algorithm with which they are comfortable. Furthermore, no single approach should be used. Drug

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
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</thead>
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<td></td>
<td></td>
</tr>
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<td></td>
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<td></td>
</tr>
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<td>2-4</td>
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<td>20-26</td>
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<tr>
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<td>1</td>
<td>peakless</td>
<td>22-26</td>
</tr>
<tr>
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<td>3-5</td>
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</tr>
<tr>
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<td>30-60 min</td>
<td>varies</td>
<td>10-16</td>
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<td>30 min</td>
<td>1:5-2</td>
<td>24</td>
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<td>5-15 min</td>
<td>varies</td>
<td>10-16</td>
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<tr>
<td>□ insulin lispro protamine/insulin lispro 50/50</td>
<td>10-15 min</td>
<td>varies</td>
<td>10-16</td>
</tr>
</tbody>
</table>

Figure 2. Time action profiles of insulins and insulin analogs. *Units are in hours unless otherwise indicated. Abbreviations: NPH, neutral protamine Hagedorn; RHI, regular human insulin. Adapted from the National Diabetes Information Clearinghouse.32

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therapy should be tailored to the needs of individual patients based on such factors as age, concomitant disorders, and ability to adhere to medical instructions.\textsuperscript{14}

A common starting dose of insulin in patients with T2DM is either 10 U daily or 0.2 U/kg daily of an intermediate-acting or long-acting insulin.\textsuperscript{5} However, because more than 90% of patients with T2DM are resistant to insulin, higher doses are often required to achieve adequate glycemic control.\textsuperscript{5} Many patients with T2DM may require relatively large doses of insulin compared to patients with type 1 diabetes mellitus—sometimes exceeding 1 U/kg daily—to bring their HbA\textsubscript{1c} levels into the target range.\textsuperscript{14}

A patient-driven algorithm developed by the ADA and the EASD (Figure 1) is widely used because it is relatively simple and can be applied to initiating, titrating, and intensifying insulin therapy.\textsuperscript{14} This algorithm recommends increasing the basal insulin dose by 2 U every 3 days until the FPG target is achieved, or by 4 U every 3 days if the FPG level remains above 180 mg/dL. If hypoglycemia occurs or if FPG falls below 70 mg/dL, the basal dose should be reduced by either 4 U or by 10% of the dose, whichever is greater.\textsuperscript{14}

Regardless of the dosing approach used, timely assessment and adjustment of insulin is crucial. As they do with oral medications, physicians often wait too long before intensifying insulin therapy, leaving patients exposed to excessive glycemia and at increased risk of long-term complications.\textsuperscript{5} Another reason that delay in using insulin is detrimental is that glycemic control becomes more difficult to achieve with increasing delays in intensification of treatment.\textsuperscript{38}

**Patient Self-Monitoring**

Self-monitoring of blood glucose (SMBG) is an important component of successful use of insulin in patients with T2DM. Education of patients is essential to stress the importance of SMBG in avoiding hyperglycemia or hypoglycemia and to ensure that patients understand proper techniques and timing for self-monitoring.

At initiation of insulin therapy (assuming that basal therapy is prescribed), once-daily SMBG may be adequate. If patients are engaged in self-adjustment of insulin doses, SMBG should always be performed before administering the daily dose, and the results should be used to increase or decrease the dose as necessary.

**Approaches in Primary Care**

As primary care physicians assume a greater role in managing insulin therapy, it is important to identify particular practices that can be effectively implemented in such settings. One trend in this regard is a shift toward more patient-centered insulin management.

Recent research has examined if patients can safely and effectively self-titrate insulin levels by following easy-to-use dosing guidelines.\textsuperscript{23,39-41} One such study is the PREDICTIVE 303 trial,\textsuperscript{23,24} which prospectively evaluated the use of insulin detemir in primary care practices in the United States. This study sought to determine the feasibility and utility of simple, patient-directed insulin guidelines (ie, the “303 Algorithm,” shown in Figure 3) for administration of insulin detemir, compared with the standard practice of physician monitoring and dose adjustment.\textsuperscript{24} The PREDICTIVE 303 trial\textsuperscript{23,24} showed that the patient-directed intervention was at least as effective as standard clinical management. The HbA\textsubscript{1c} levels decreased from a baseline of 8.5% in both groups to 7.9% in the algorithm group and 8.0% in the standard management group (\(P<.001\)). The mean reduction in FPG level was 1.8 mmol/L in the algorithm group and 1.2 mmol/L in the standard management group (\(P<.001\)). No increased risk of hypoglycemia was observed in the patient-directed group compared to the physician-directed group.\textsuperscript{23,24}

The PREDICTIVE 303\textsuperscript{23,24} findings suggest that a patient-driven approach to insulin dose adjustment is a safe and effective alternative to physician-directed management. The implications for such a patient-centered model may extend even further. When involved and empowered to play a greater role in their own care, patients may take more personal responsibility for their health, achieving results that meet or exceed those observed in physician-directed situations.\textsuperscript{24,39}

**Conclusion**

Despite vast expenditures of healthcare resources, management of T2DM remains woefully inadequate, and many patients spend a long time well outside the recommended glycemic range. New standard-of-care practice guidelines entail initiating insulin therapy much earlier in the treatment continuum than did previous guidelines. However, resistance to initiation of insulin therapy, both from patients and physicians, is widespread. Furthermore, as much as one-third of patients who use insulin therapy do not adhere to their prescribed regimen.

For patients with deteriorating physiologic function, the importance of insulin therapy in controlling glycemia and minimizing diabetes-related complications cannot be overstated. As the principal responsibility for managing T2DM continues to shift to the primary care setting, primary care physicians must rise to the challenge of overcoming their own resistance and that of their patients to effectively implement insulin therapy.

**Fasting Plasma Glucose, mean, mg/dL (mmol/L)**

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose, mean, mg/dL (mmol/L)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 (&lt;4.4)</td>
<td>Decrease by 3 units</td>
</tr>
<tr>
<td>80–100 (4.4–6.1)</td>
<td>No change</td>
</tr>
<tr>
<td>&gt;100 (&gt;6.1)</td>
<td>Increase by 3 units</td>
</tr>
</tbody>
</table>

Figure 3. Simplified, patient-directed insulin guidelines (ie, the “303 Algorithm”) used in the Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation 303 (PREDICTIVE 303) trial.\textsuperscript{24} The algorithm was used for basal insulin analog (insulin detemir) dosing, based on the mean of 3 fasting plasma glucose levels self-measured for 3 consecutive days.

**References**


