Abstract

- **Objective:** To outline a simple and evidence-based approach for initiating insulin.
- **Methods:** Algorithms for considering and approaching insulin initiation were derived from extensive literature searches and author experience.
- **Results:** Type 2 diabetes is characterized by progressive loss of beta cell function and peripheral insulin resistance. The initiation of insulin is often a pivotal intervention to avert the exposure to hyperglycemia and prevent diabetic complications. Early use of insulin may mitigate long-term consequences of hyperglycemia and can be done effectively when barriers to initiation are recognized.
- **Conclusion:** Successful insulin initiation requires an ability to elicit and navigate common barriers and misperceptions about insulin. Simple algorithms for starting and titrating insulin can be used by primary providers, with ongoing collaboration with diabetes specialists to ensure optimal management.

The rising prevalence of obesity and increased life expectancy have together contributed to the epidemic of type 2 diabetes mellitus. The pathophysiology of diabetes is characterized by progressive deterioration of pancreatic beta cell function and concomitant peripheral insulin resistance. Prolonged exposure to hyperglycemia resulting from this pathology increases long-term risk for developing micro- and macrovascular complications. Despite earlier diagnosis and management, beta cell exhaustion and the need for insulin therapy are often inevitable [1]. The conventional approach to treating type 2 diabetes has emphasized a stepwise introduction of lifestyle modifications and oral drugs before recommending insulin. To limit protracted exposure to hyperglycemia, consensus opinion increasingly favors the initiation of insulin earlier in the disease course of diabetes, well before failure with other regimens [2,3]. Early initiation of insulin involves adopting an aggressive strategy towards glucose control and requires health care providers and patients alike to recognize the most appropriate time to start insulin, the barriers impeding early initiation, and feel comfortable with available insulin formulations and starting regimens.

**CASE STUDY**

**Initial Presentation**

A 60-year-old man with type 2 diabetes and obesity presents to the primary care office. He was diagnosed with diabetes 6 years ago when fasting blood glucose exceeded 126 mg/dL. Glycosylated hemoglobin (HbA1c) at the time of diagnosis was 78%. He has no known history of cardiovascular disease, retinopathy, nephropathy, or neuropathy. Despite multiple attempts at losing weight, his body mass index remains unchanged at 35 kg/m^2_. He does not routinely exercise and has a sedentary lifestyle. Six months ago, his HbA1c was 8.7% while on metformin 1000 mg twice daily and glyburide 10 mg twice daily. Pioglitazone 30 mg daily was added to his regimen at that time. He now reports morning fasting glucoses using a glucometer between 145 and 185 mg/dL. HbA1c today is 8.5%.

- **When should insulin be initiated in patients with type 2 diabetes?**

**When to Initiate Insulin**

Since its initial discovery in the early 20th century, insulin has been a lifesaving treatment for diabetes. In type 1 diabetes, it serves as vital replacement treatment from the time of diagnosis; however, since insulin deficiency occurs gradually in patients with type 2 diabetes, the optimal time to begin insulin therapy for these patients is not clearly defined or easily recognized. Nevertheless, support for earlier introduction is growing [2,3].

The traditional management paradigm for type 2 diabetes includes a stepwise approach, beginning with lifestyle modifications such as physical activity and dietary education...
Most guidelines recommend that insulin should be prescribed when a patient continues to have elevated glucose levels despite attempts at treatment with oral hypoglycemic drugs; others have recommended insulin initiation as early as the time type 2 diabetes is diagnosed [9,13–15,21]. The introduction of insulin to patients already at their goal HbA1c should also be considered, especially when the pace of disease progression is fast and long-term insulin independence is deemed unlikely. The American Diabetes Association recommends the earliest consideration of insulin when lifestyle modifications with metformin fail to lower HbA1c below a threshold of 7%, and reconsideration when HbA1c remains greater than 7% despite 2 or 3 OADs [22]. Starting insulin when dual-oral therapy has failed is cost-effective and offers benefits on weight, lipid profile, and peripheral edema [23–26]. Adding a third oral hypoglycemic drug is rarely effective, since additional drugs provide diminishing levels of efficacy. Alternative therapies such as incretin agonists or inhibitors of dipeptidyl-peptidase-4 inhibitors are only appropriate if the patient's HbA1c is very close to goal, since both of these drugs have limited efficacy.

In the case patient, insulin therapy could have been discussed when it became clear that lifestyle modification was unlikely to normalize his glucose (Figure 1). Starting insulin when metformin failed to bring HbA1c below the 7% threshold, rather than treatment with pioglitazone, would have been an effective approach.

Case Continued

The patient had expressed concern that administering insulin would unnecessarily complicate his life and commit him to a lifetime of painful daily injections. His mother died 6 months after starting insulin treatment. He is anxious to avoid insulin treatment by being compliant with any other oral treatments and feels that his diabetes is “not so bad” that it warrants treatment with insulin.

- What are barriers to insulin initiation?

Overcoming Barriers to Insulin Initiation

Although the early commencement of insulin is associated with significant clinical benefits, several physical and psychological obstacles constrain both patients and providers from advancing therapy (Table 1 and Table 2). The Diabetes Attitudes, Wishes, and Needs (DAWN) study employed survey assessment to understand patient reticence for beginning insulin injection administration and provider reluctance in prescribing insulin [27]. The DAWN analysis revealed that within the global community, general physicians in the United States were among the most likely to delay insulin
therapy until absolutely needed, while patients in the United States tended to hold a very negative view towards insulin [27]. The perceptions highlighted by the DAWN study group play a considerable role in the underutilization of insulin in the treatment of type 2 diabetes. Data from the Third National Health and Nutrition Examination Survey (NHANES III) reveal that the last decade has witnessed a significant decline in the use of insulin in the United States, with concomitant decreases in achievement of glycemic targets [28].

Fear of insulin is very common. Supportive feedback, sincere empathy, and guided education to empower self-management can help overcome this apprehension [27,29]. Fear of needles and injections is a concern shared by patients with and without diabetes. Some have genuine trepidation regarding the prospect of pain, while others may focus on the perceived stigma of publicly carrying and using a needle [30]. Modern day technology has facilitated the design of needles with very fine gauges (31–32G) and shortened lengths (0.5 in), which minimize pain. Additionally, in-office demonstration of self-injection with sample equipment can reassure patients by illustrating that self-injection is not only minimally invasive but also not as daunting as perceived. For some, the standard vial and syringe can be cumbersome and associated with significant social stigma. Insulin pens can be easily concealed and carried at room temperature and are therefore preferred by a growing number of patients for their ease of use [31,32].

Concerns about weight gain, hypoglycemia, and the relative efficacy of insulin over other therapies is commonly encountered. Since patients with type 2 diabetes, unlike many patients with type 1 diabetes, retain a normal glucagon response to hypoglycemia, severe insulin-induced hypoglycemia is rare [33,34]. Disciplined physical activity and dietary education should be reinforced when starting insulin, as these interventions have been shown to abrogate weight gain [35–37]. Additionally, continuing the use of insulin sensitizers such as metformin following insulin initiation has also been shown to maintain weight neutrality [38].

As expressed by the case patient, initiation of insulin can be interpreted as a personal failure of disease management; this concept is widely endorsed by many patients and...
contributes to the avoidance of insulin. This phenomenon of self-blame and “psychological insulin resistance” is most typical among older U.S. patients [27,39–41]. Clinicians can reinforce this perception if insulin treatment is used as a threat to encourage patients to engage in lifestyle modification. Such threats reinforce the stigma associated with insulin use and make adoption of insulin even more challenging when it becomes necessary.

Early advocacy for insulin therapy well before it is prescribed can mitigate and minimize insulin resistance. Cultivating the understanding that progressive beta cell loss and peripheral insulin resistance may occur even with diligent adherence to therapy can help make insulin more acceptable in future discussions [42]. Clinicians can help patients understand that insulin therapy may improve a patient’s sense of well-being if the alternative is prolonged hyperglycemia: use of insulin and subsequent attainment of glycemic control can increase patients’ physical and mental well-being. Direct empathy followed by a structured discussion regarding the realistic needs for insulin help vitalize patient-physician trust and can galvanize patients to approach insulin therapy as a boon rather than penalty.

When available, a diabetes educator or other dedicated health care professional can maximize the efficiency of insulin initiation in a busy practice. The availability of ancillary staff in the fields of diabetes education and nutrition has been associated with improved adherence to insulin use and glycemic control [43,44]. When such support is absent and the clinician has limited resources to effectively engage his/her patients with insulin, referral to a local diabetes educator or subspecialty diabetes practice with sufficient resources is appropriate [45].

To actively engage the case patient in the insulin initiation plan that he needs, his fears must be acknowledged and misperceptions clarified. Firm reiteration that his prolonged hyperglycemia will contribute to microvascular and macrovascular disease is a reasonable prologue to recommending insulin initiation at this time. He should be reminded of the

### Table 1. Health Care Provider Barriers to Initiating Insulin

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived risk of causing hypoglycemia</td>
<td>Risk of insulin-induced hypoglycemia in type 2 diabetes is very low and comparable with that induced by oral insulin secretagogues (&lt; 3% per patient-year) Long-acting insulin analogues provide even lower rates of hypoglycemia than traditional basal insulins</td>
</tr>
<tr>
<td>Reinforcing feelings of failure</td>
<td>Help patients disconnect individual behaviors from the natural progression of disease Gradual beta cell loss is inevitable, but early insulin use can mitigate unnecessary exposure to hyperglycemia</td>
</tr>
<tr>
<td>Competing array of treatment choices</td>
<td>Studies continue to support the association between early initiation of insulin and improved glycemic control and cost-effectiveness</td>
</tr>
<tr>
<td>Resource limitations</td>
<td>The American Association of Diabetes Educators provide information for locating local diabetes educators at <a href="http://www.diabeteseducator.org">www.diabeteseducator.org</a> Patients can be instructed to titrate their insulin doses themselves using simple available algorithms</td>
</tr>
</tbody>
</table>

### Table 2. Patient Barriers to Initiating Insulin

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of self-injection</td>
<td>Ultrafine (31–32G) and ultrashort (0.5 in) needles provide little to no pain In-office injection demonstrations can overcome initial apprehension</td>
</tr>
<tr>
<td>Social stigma</td>
<td>Insulin pens provide more discretion and ease of use than vials and syringes The use of insulin is more common in the community than perceived by most patients</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Dietary counseling at initiation of insulin helps mitigate weight gain Concurrent use of metformin protects against weight gain</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Hypoglycemia in type 2 diabetes is an uncommon adverse event The use of insulin does not increase this risk significantly more than the use of sulfonylureas Long-acting insulins impart very low risk of hypoglycemia</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Insulin is the most studied and most potent glucose-lowering medication available</td>
</tr>
<tr>
<td>Misperceptions linking insulin with poor prognosis</td>
<td>Insulin actually improves prognosis. Poor outcomes usually occur when insulin therapy is delayed or avoided</td>
</tr>
<tr>
<td>Feelings of failure</td>
<td>Type 2 diabetes pathophysiology is progressive, typically irrespective of personal behavior Addition of insulin can impart significant success in achieving glucose goals</td>
</tr>
<tr>
<td>Complexity of treatment regimen</td>
<td>Insulin regimens can be tailored to patient needs Use of insulin pens can simplify administration Long-acting insulins and premixed insulin can minimize daily injections</td>
</tr>
<tr>
<td>Cost</td>
<td>Insulin preparations are available at lower cost than many oral agents</td>
</tr>
</tbody>
</table>
safety, history, and reliability of insulin, with a demonstration of insulin use offered to illustrate its feasibility.

**Case Continued**

The patient is counseled on the adverse effects of prolonged hyperglycemia and reminded that insulin is a safe and effective agent, capable of decreasing complications akin to those his mother suffered. He is reassured that injections with ultrafine needles elicit very little pain, and an in-office demonstration with insulin pens reinforces this discussion. He is amenable to start treatment with insulin but still apprehensive that this new therapy will be too complex.

- Which insulin regimen should be selected?

**Selecting the Appropriate Insulin Regimen**

When agreement to begin insulin has been reached, selecting the most appropriate insulin type and schedule becomes the next priority. The goal is to mimic normal physiology while maintaining patient compliance with an administration protocol that can be realistically maintained. Fortunately, insulin regimens can be more flexible now that clinicians have an ever-expanding array of insulin formulations available.

Newer long-acting insulin analogues such as glargine and detemir provide basal insulin needs for up to 24 hours and are therefore used commonly as once daily basal formulations [46,47]. Neutral protamine Hagedorn (NPH) is a well-known intermediate-acting insulin used to provide basal coverage with either once- or twice-daily administration. To date, newer long-acting analogues have not shown greater HbA1c-lowering effects when compared with established intermediate insulins such as NPH but are associated with less weight gain and nocturnal hypoglycemia [48–51].

The addition of prandial rapid-acting insulin (lispro, aspart, or glulisine) to a basal insulin regimen is the foundation of basall-bolus therapy. While this approach is tailored to replicate physiologic pancreatic action, it is generally too complex to be used at the time of insulin initiation.

Although several reasonable permutations to begin insulin exist, the general consensus still favors initiating once-daily basal insulin therapy, with either a long-acting analogue or NPH once nightly before bed (Figure 2). This approach targets elevated fasting blood glucose, and with the addition of a single injection, can provide significant reductions in HbA1c [51,52]. This strategy allows providers to recommend a simple and effective insulin regimen and sets the stage for future modifications that will likely be less challenging to implement. Commencing with 10 units per day as an initial insulin dose is generally safe. In heavier patients, this can be preferentially tailored by using a starting dose of roughly 0.2 units per kg. This injection can be given in the evening if using NPH or either evening or morning when using long-acting analogues. Patients should be instructed to record morning fasting blood glucose, as future titrations to basal insulin will rely on these values as a proxy for insulin action. Several major studies have demonstrated the achievement of HbA1c of less than 7% when patients are given algorithms and appropriate instructions to titrate doses of their basal injections themselves [33,51–55]. This strategy is valuable because it empowers patients to take control of their disease, while decreasing a portion of management burden from primary health care providers. The Treat-to-Target study demonstrated the efficacy of a strategy that initiated glargine or NPH at 10 units before sleep, with patient instructions to increase their dose by 2 units every 3 days until a target fasting glucose of 70 to 130 mg/dL was achieved; up-titration was temporarily halted with any hypoglycemic readings [51]. Using this approach, more than half of the treated patients achieved a HbA1c of less than 7% within 24 weeks. Depending on the comfort level of the patient and provider, more conservative or aggressive algorithms can also be used. If HbA1c has not declined below 7% after 2 to 3 months of titrating basal insulin to target fasting glucose, the addition of prandial insulin should be considered.

Although some advocates support starting with basal-bolus treatment rather than single injection when baseline HbA1c is higher than 8.5%, we prefer starting with a single daily injection, with subsequent alterations to the number of injections as insulin-naive patients acclimatize to their regimen [56].

The use of premixed insulin may provide an alternative solution as an initial regimen when starting HbA1c levels are greater than 8.5%. Premixed formulations are available in a variety of compositions containing part intermediate-acting insulin and part rapid-acting insulin, often in a ratio of 70:30 [57]. These preparations meet basal insulin requirements in addition to mitigating postprandial glucose excursions and have been shown to be superior at lowering HbA1c when compared with long-acting analogues in some studies [58,59]. While the postprandial action of premixed insulins is theoretically advantageous, because their formulations are restricted to fixed ratios of short- and long-acting insulin and contain only NPH as the basal formulation, the incidence of hypoglycemia and erratic glucose levels can limit their effectiveness [60]. Premixed insulins can serve as effective and uncomplicated initial regimens for patients with markedly dysregulated glycemic control; however, achievement of long-term fasting and postprandial glucose control will frequently require gradual transition to a basal-bolus strategy.
Glargine insulin is started at a conservative dose of 20 units before sleep, and the patient is advised to discontinue glyburide. A glucometer is provided, and he is instructed to measure fasting blood glucose daily and to increase his daily glargine dose by 2 units every 3 days until fasting glucose declines below 130 mg/dL. He is advised to call the office to relay his morning glucose values weekly to ensure safety and answer questions. A prescription for a glucagon home injection kit is provided for safety, with instructions on recognizing and treating hypoglycemia and a recommendation to obtain a medical alert bracelet or pendant.

Two months later, he returns to the office. He is currently taking glargine 34 units nightly, and fasting blood glucose measurement have consistently been been between 105 and 130 mg/dL. He reports periodic measurements of preprandial glucose values through the day ranging from 110 to 230 mg/dL. His HbA1c at this visit has declined from 8.5% to 7.4%.

**Case Continued**

- How should the insulin regimen be modified if glycemic targets are not being met?

**Intensification of Insulin Regimens**

When goal HbA1c is not achieved with adjustment of once-daily injections, attention should be directed to controlling postprandial glucose variations. Intensification of insulin regimens to control postprandial glucose excursions has been shown to improve glucose control and has been associated with a reduction in markers of atherosclerosis [61–66]. Postprandial hyperglycemia contributes fractionally more

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**Figure 2.** Initiating insulin. HbA1c = glycosylated hemoglobin; NPH = neutral protamine Hagedorn.
to the HbA\textsubscript{1c} at lower HbA\textsubscript{1c} concentrations, thus control of postprandial glucose is necessary if recommended glycemic targets are to be attained.

For patients on a once-daily basal injection, the addition of a rapid-acting insulin with 1 meal a day (usually the largest meal) is a reasonable start, as introducing 3 rapid injections at once can overwhelm many patients (Figure 3). A prandial rapid-acting insulin dose of roughly 4 to 6 units is a good initial approximation (or approximately 30\% of the total basal dose at the time of initiation), and this can be increased by titrating to either a 2-hour postprandial glucose of less than 140 to 180 mg/dL or the next preprandial glucose less than 130 mg/dL. The dose of basal insulin does not generally need to be reduced when starting a prandial insulin for the first time in a patient who is not at his/her goal HbA\textsubscript{1c}. Gradually, prandial injections can be added to other meals as needed. Fixed doses of mealtime insulin can be prescribed, but carbohydrate-adjusted prandial insulin regimens can also be developed with the assistance of dietary specialists. Theoretically, carbohydrate counting provides a more physiologic approach than fixed basal-bolus injections; however, both fixed dosing and carbohydrate counting approaches have been shown to be equally effective in patients with type 2 diabetes when practiced correctly and can be safely managed by patients with home adjustment algorithms based on their preference [67].

When the addition of individual mealtime injections is perceived as overly complex, an intensive regimen of pre-mixed insulin can provide modest coverage of both basal and prandial insulin needs, with fewer injections. Individuals on once-daily dosing of premixed insulin can be escalated to twice or even thrice daily, with significant HbA\textsubscript{1c}-lowering effects, but this can be associated with a higher hypoglycemia risk than basal-bolus strategies [59,68]. As with basal-bolus therapies, simple titration algorithms for intensification exist for premixed insulins [60]. Because premixed insulins contain fixed ratio of both basal and short-acting insulin, as additional premixed injections are added, each individual dose may need to be reduced to prevent hypoglycemia.

While the transition from OAD therapy to initiating single injection insulin treatment can be simple, coordinating the addition of multiple injections based on basal and prandial needs can be daunting, both for provider and patient. In these situations, referral to a local diabetes educator or endocrine specialist can help foster multidisciplinary care and safely steward intensive insulin management.

**Case Continued**

The patient is advised to check his preprandial and bedtime glucose values in addition to fasting levels. His bedtime glucose levels are routinely greater than 200 mg/dL, consistent with his dietary habit of eating a large dinner. Five units of aspart insulin to be taken with dinner is added to his regimen. In the subsequent months, his home measurements show prelunch and predinner glucose levels greater than 140 mg/dL, prompting the addition of breakfast
and lunchtime aspart insulin as well. He initially gains 5 lb after starting prandial insulin, but returns to his baseline weight with dietary management. He reports no glucose readings below 60 mg/dL. Most recently, his regimen has consisted of glargine 35 units at bedtime, 8 units of aspart with breakfast and lunch, and 12 units of aspart with dinner. His HbA1c is now 6.8%.

CONCLUSION

Insulin replacement therapy is ultimately necessary in most patients with type 2 diabetes. The initiation of insulin represents a pivotal intervention to avert the exposure to hyperglycemia and prevent diabetic complications. Earlier introduction of insulin is steadily gaining credence, usually in combination with continued use of metformin. Successful insulin initiation requires an ability to elicit and navigate common barriers and misperceptions about insulin. A myriad of insulin formulations capable of meeting the needs of almost any patient are available, accompanied by advances in administration modalities addressing comfort, discretion, and simplicity. Home titration of a basal insulin formulation followed by addition of prandial insulin before the largest meal is an effective evidence-based approach. Collaboration with diabetes educators, nutritionists, and endocrinologists can help ensure success but should not delay therapy. Most importantly, ongoing collaboration with patients can ensure they achieve the best possible health and enjoy the benefits of the most effective diabetes treatment available.

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INITIATING INSULIN


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