Treating Patients With Diabetes of Long Duration: GLP-1 Receptor Agonists and Insulin in Combination
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Patients with long-standing type 2 diabetes mellitus (T2DM) can be clinically challenging for physicians to treat because these patients often lack sufficient β-cell function to respond to some oral glucose-lowering agents, may have profound co-morbidities, and may have renal impairment that limits the use of traditional agents. These complications, in addition to older age, also increase the risk of hypoglycemia, which can be a major barrier to treatment success. Individualizing treatment targets to balance the benefits of glycemic control with risks of hypoglycemia is the first step to successfully treating these patients. Careful selection of combination therapy strategies to address limited β-cell function, renal function, and cardiovascular status, along with attention to selection of agents associated with lower risk of hypoglycemia, is important. Basal insulin analogs are often used in patients with long-standing diabetes to address insulinopenic states. Incretin-based therapies, particularly GLP-1 receptor agonists, provide postprandial control with lower risks of hypoglycemia than prandial insulin. The author discusses the management of patients with long-standing diabetes who may have limited β-cell function and require transition to insulin therapy with gradual intensification.

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The management of long-standing diabetes is a complex and increasingly common clinical challenge in the primary care setting. Type 2 diabetes mellitus (T2DM) is being diagnosed earlier, and patients are living longer. Treatment options have advanced and multiple classes of diabetes therapies are now available, which can add to the complexity of T2DM management. Current guidelines emphasize individualization of treatment goals and patient care.\(^1\)\(^-\)\(^3\) Individualization is especially important for middle-aged and older adults with diabetes, who may be characterized as belonging to 1 of 3 clinical groups: a relatively healthy group, a group having characteristics likely to make diabetes self-management difficult, and a group with poor health status for whom current management targets have uncertain benefit.\(^4\) The concept of higher (or lower) glucose targets, depending on individual patient characteristics, was first widely embraced because of these uncertain benefits.\(^5\) The risk of severe hypoglycemia likely represents the greatest barrier to T2DM care in older patients and in those with diabetes of long duration.\(^6\)

### Setting Treatment Goals

It is not always easy to separate data from patients with long-standing T2DM from that of T2DM in older patients, but the Diabetes in Aging Study showed that in long-standing T2DM, coronary artery disease and hypoglycemia were the most common nonfatal comorbidities (18.98 per 1000 person-years and 15.88 per 1000 person-years, respectively).\(^7\) Setting appropriate treatment goals that take prevalent comorbidities into consideration is the first step in the successful management of T2DM. These goals will likely change over time and with progression of the disease.

#### Patient Management

A decision has been made to start a patient on insulin because they are not achieving their targets.

- Basal insulin analogs have proven efficacy, once-daily dosing, and lower risk of hypoglycemia than alternative insulin therapies.
- Pen devices for insulin delivery are convenient, painless, and discreet.

#### Patient Discussion: Insulin Initiation and Adjustment Recommendations

- Invite the patient to bring a family member or friend for support.
- Show the patient how to use the pen device (needle placement, dialing insulin, discharging dose).
- Ask the patient to self-inject a token amount of insulin (1-2 units) during an appointment.
- Discuss initial insulin dose, timing (dinner, bedtime, or morning) and dose adjustments including titration algorithm, based on agreed upon blood glucose targets.
- Review importance of glucose self-monitoring for insulin self-titration.
- Suggest using a diary to record insulin dose and daily glucose levels.
- Resolve any concerns before the patient leaves.
- Arrange a follow-up after 1 week (visit or phone) to review and adjust therapy.

#### After Metformin, Complicated Choices

Metformin is typically the first line of drug therapy for patients with T2DM. However, the choice of therapeutic agents after metformin becomes more complicated for older patients, and current treatment recommendations do not explicitly discuss this difficulty. Older patients with T2DM are a very heterogeneous group with multiple comorbidities, increased risk of hypoglycemia, and greater susceptibility to adverse effects of antihyperglycemic drugs, making their treatment particularly challenging. Ideally, preferred drugs in older patients should not be cleared by the kidneys and should have a low risk of adverse cardiovascular effects or hypoglycemia. Generally, metformin, incretin-based therapies (ie, glucagon-like peptide-1 [GLP-1] agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors), and long-acting insulin should be preferred over other treatment options (sulfonylureas, glinides, and glitazones).

#### Eventual Need for Basal Insulin

Type 2 diabetes mellitus is a progressive disease characterized by insulin resistance, \(\beta\)-cell dysfunction, and an impaired incretin effect. Chronic hyperglycemia and elevated lipid levels cause glucotoxicity, which in turn leads to further \(\beta\)-cell dysfunction and failure. As a result, exogenous insulin is eventually needed in patients with T2DM of long duration.

The landmark United Kingdom Prospective Diabetes Study (UKPDS) showed the natural progression of
T2DM and decline in β-cell function, which was already at 50% by time of diagnosis and was virtually nonexistent by 12 years of known T2DM. After 9 years, only 25% of patients in UKPDS had good glycemic control on monotherapy and lifestyle measures, and many of the patients in the study required insulin therapy.

Insulin therapy, particularly basal insulin analog therapy, is relatively simple to start with gradual up-titration by the physician or the patient. Basal insulin analogs are associated with less nocturnal hypoglycemia compared with neutral protamine Hagedorn (NPH) insulin. Longer-acting insulin analogs and more concentrated insulin analogs currently in development are associated with even lower risk of nocturnal hypoglycemia.

Figure 1 and Table 1 provide insights into introducing patients to the concept of insulin therapy and having patients self-inject during the office visit while discussing initial dosing of basal insulin. The initial dose may be a standard 10 units or be weight-based, as suggested by the American Association of Clinical Endocrinologists (AACE) on prevailing glycated hemoglobin A1c (HbA1c) levels (for HbA1c < 8%, a total daily dose of 0.1-0.2 U/kg; for HbA1c ≥ 8%, a total daily dose of 0.2-0.3 U/kg), and suggestions for self-titration algorithm and dose adjustment until fasting plasma glucose reaches the target set for each patient. Multiple self-titration schedules are available in the published literature that can be considered for individual patients. Although the self-titration algorithms differ, the principle remains the same, which is providing a tool to each patient for self-adjustment of the insulin dose that meets their individual needs.

Diminishing Value of Sulfonylureas: Limited Durability and Risks of Hypoglycemia

Sulfonylureas rely on endogenous β-cell function for their action as insulin secretagogues; thus, their usefulness in managing T2DM of long duration is limited. This is borne out by the A Diabetes Outcome Progression Trial, in which patients’ HbA1c levels rose more rapidly over the years (loss of control) with sulfonylureas than with metformin, thiazolidinediones, or insulin (Figure 2). The other issue with sulfonylureas is the risk of hypoglycemia, which increases as patient β-cell reserve decreases. One should not choose a medication on the basis of acquisition costs alone, as the costs of managing hypoglycemia are great and the adverse impact of hypoglycemia on patient’s future adherence to medication is difficult to quantify.

Hypoglycemia is common not only in type 1 diabetes mellitus but also in T2DM. It is underrecognized and undertreated. The fear of hypoglycemia contributes to provider clinical inertia and can lead to patient defensive eating and medication nonadherence. It has also been implicated as a cause in cardiovascular complications of T2DM. The risk of hypoglycemia is greater in T2DM of long duration and in elderly patients. Therefore, when contemplating insulin intensification strategies beyond basal insulin analogs, hypoglycemia is an important consideration.

### Table 1. Self-Titration of Insulin

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose, mg/dL</th>
<th>Action</th>
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<tbody>
<tr>
<td>&gt;90</td>
<td>Aggressive&lt;br&gt; Increase dose 3 units</td>
</tr>
<tr>
<td>70-90</td>
<td>Less Aggressive&lt;br&gt; 80-110&lt;br&gt; Target range; no change</td>
</tr>
<tr>
<td>&lt;70</td>
<td>&lt;80&lt;br&gt; Decrease dose 3 units</td>
</tr>
</tbody>
</table>

* Physicians should discuss and agree on day-to-day blood glucose targets with patients and empower patients to assist in insulin dose adjustment. Self-titration of insulin dose is based on average of fasting plasma glucose levels over 3 days.
Natural History of T2DM: Beta-Cell Dysfunction, Incretin Deficiency

Beyond insulin resistance and decreased insulin secretion, other factors are also involved in the natural history of T2DM. Glucose homeostasis is largely regulated by the incretins, which are gut-derived hormones released in response to nutrient (primarily glucose and fat) ingestion. These hormones elicit several important effects, including stimulation of insulin, a glucose-dependent effect. During the development and progression of T2DM, signals from gut-derived factors are diminished because of defective release of incretin hormones or resistance to their action. Combined beta-cell dysfunction and incretin deficiency aggravate hyperglycemia, which further impairs insulin secretion and action. The reduced incretin effect is a substantial contributor to insulin deficiency. It is estimated that up to 70% of overall postprandial insulin response to glucose is mediated by the incretin hormones.

Postprandial hyperglycemia has important implications for the treatment of patients with long-standing T2DM. At some point after the addition of basal insulin and its subsequent titration to achieve fasting blood glucose (FBG) targets, glucose control may need to be further intensified because of postprandial hyperglycemia, which is usually a significant contributor as HbA1c levels become closer to 7% (the higher the proportion of postprandial glucose to fasting plasma glucose, the lower the HbA1c level).

Targeting Postprandial Glucose Levels With Incretin Therapy

From a pathophysiologic perspective, the next action should logically be to add a medication that targets postprandial glucose levels. What are the choices? Until now, treatment algorithms have guided physicians toward the addition of prandial insulin to basal insulin regimens. This approach leads to better glycemic control, but at a cost of increased blood glucose monitoring, greater probability of more insulin-associated weight gain, and greater risk of hypoglycemia. Knowing that incretins are responsible for up to 70% of the overall postprandial insulin response to glucose forms a basis for the use of incretin-based therapies as an alternative to the addition of prandial insulin in the most recent version of the AACE Comprehensive Diabetes Treat-
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To minimize gastrointestinal adverse effects. Exenatide twice daily should be given from 0 to 60 minutes prior to a meal. Liraglutide can be given without regard to mealtimes. The long-acting version of exenatide (exenatide extended-release) is given once weekly without regard to mealtimes. The extended-release formulation is a powder that must be reconstituted by the patient and then administered immediately after reconstitution. Exenatide once weekly is now available in a pen. Data from clinical studies support the therapeutic potential of the GLP-1 receptor agonist–insulin combination, typically showing beneficial effects on glycemic control and body weight and with a low incidence of hypoglycemia. In established insulin therapy, the addition of a GLP-1 receptor agonist to insulin may allow for reductions in insulin dose, which may mitigate weight gain or hypoglycemia concerns. Figure 4 shows data from Buse et al, where the mean duration of T2DM was 12 years. Currently a fixed-dose combination of insulin degludec (a longer-acting basal insulin analog with a lower incidence of nocturnal hypoglycemia than insulin glargine) and liraglutide is in development. Other issues to take into account when choosing medications in patients with T2DM of long duration include the effects of medications on cardiovascular risk. The DPP-4 inhibitors are, on the whole, generally well tolerated. Results from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-TIMI trial showed that DPP-4 inhibition with saxagliptin did not increase or...
Linagliptin is the only DPP-4 inhibitor not cleared primarily by the kidney and therefore requires no dose adjustment in renal impairment (Table 2).

Exenatide is eliminated by the kidney. Neither short-acting nor extended-release exenatide is recommended for patients with severe renal impairment (creatinine clearance, <30 mL/min). Both should be used with caution in patients with renal transplantation. No dosage adjustment of short-acting exenatide is required in patients with mild renal impairment (creatinine clearance, 50-80 mL/min). Caution should be applied when initiating or escalating doses of short-acting exenatide from 5 to 10 μg or when using extended-release exenatide in patients with moderate renal impairment (creatinine clearance, 30-50 mL/min). Liraglutide is not heavily metabolized by the kidney, and therefore no dosage adjustment is necessary in patients with renal impairment. Caution is recommended, however, in cases where drug-induced nausea and vomiting may result in dehydration and affect patients with renal impairment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism/Clearance</th>
<th>Dose Adjustment</th>
</tr>
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<tbody>
<tr>
<td>Sitagliptin</td>
<td>Renal</td>
<td>50 mg/d if GFR 30 to 60 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg/d if GFR &lt;30 mL/min</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Hepatic/renal</td>
<td>2.5 mg/d if GFR &lt;30 mL/min</td>
</tr>
<tr>
<td>Liraglutin</td>
<td>Hepatic</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Renal</td>
<td>12.5 mg/d if GFR &gt;30 to &lt;60 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.25 mg/d if GFR &lt;30 mL/min</td>
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**Abbreviations:** DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate.
Summary

In patients with long-standing T2DM, combination therapy that works in complementary fashion to address basal and prandial hyperglycemia is often required. Basal insulin is often necessary in a state of relative β-cell absence to meet basal insulin needs. Postprandial hyperglycemia can be addressed by prandial insulin, but it can now be conquered by agents that work in glucose-dependent manners, with a low risk of hypoglycemia and a low risk of weight gain. Addition of oral DPP-4 inhibitors offers modest glucose lowering with weight neutrality and good tolerability. Glucagon-like peptide-1 receptor agonists, given by subcutaneous injection, offer more robust glucose lowering, a low risk of hypoglycemia, and the possibility of lower insulin needs and weight loss.

References


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