Managing Loss of Glycemic Control in Middle-Aged Patients With Diabetes: The Role of GLP-1 Receptor Agonists in Combination-Therapy Regimens

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Middle-aged patients with type 2 diabetes mellitus may have languished on monotherapy or a stable therapy for a substantial period without reconsideration of comorbidities or current control of glycated hemoglobin A$_1c$ (HbA$_1c$). In many patients who lose glycemic control, postprandial hypoglycemia has not been addressed. This is especially true when HbA$_1c$ levels are close to—but not at—goal. Glucagon-like peptide-1 receptor agonists are injectable agents that can be added to oral therapy to address postprandial hyperglycemia. These agents may be a useful alternative to insulin therapy as add-on therapy when dual oral therapy is no longer sufficient and additional glucose lowering is required. Compared with insulin, glucagon-like peptide-1 receptor agonists have provided comparable glucose lowering with less hypoglycemia and without weight gain.

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Osteopathic physicians commonly see middle-aged patients with type 2 diabetes mellitus (T2DM) who lose glycemic control. Approximately 14% of the estimated 26 million adults with diabetes in the United States are between the ages of 45 and 64 years.¹ Almost 60% of the patients with diagnosed diabetes are on oral agents alone,¹ despite the fact that less than 53% of patients are achieving target glycated hemoglobin A₁c (HbA₁c) levels.² Even lower proportions are achieving glycemic and cardiovascular (CV) risk reduction goals and are not smoking (approximately 15%) (Figure 1).²

Glycemic goals for patients with T2DM should be patient-centered and individualized on the basis of disease duration, the patient’s age and life expectancy, comorbid conditions, any known cardiovascular disease (CVD) or advanced microvascular complications, and hypoglycemia unawareness.³ More or less stringent glycemic goals may be appropriate for individual patients. Postprandial glucose can be targeted if HbA₁c goals are not met despite reaching preprandial glucose goals.

The aim of T2DM management is to prevent complications or the worsening of existing complications. Thus, patients must follow a complicated self-management regimen that generally involves several medications and difficult chronic behavioral changes. Such a regimen may be especially true for a middle-aged patient, who is likely to have comorbid hypertension or dyslipidemia (for example, up to 75% of adults with diabetes also have hypertension).⁴

A recent review discusses the rationale, duration, and expected outcomes of intensive glucose control in type 2 diabetes.⁵,6 It focuses on the current role of intensive glucose control in the management of type 2 diabetes and identifies the potential benefits and risks of intensive glucose control in type 2 diabetes.⁵,6

Table 1 summarizes glycemic, blood pressure, and low-density lipoprotein cholesterol (LDL-C) goals for patients with T2DM.³

Blood pressure goals have been revised in the 2014 standards of care from the American Diabetes Association (ADA): The systolic goal has been changed to 140 mm Hg, but the diastolic goal remains 80 mm Hg.³ Lower systolic targets, such as <130 mm Hg, may be appropriate for certain individuals, such as younger patients, but only if they can be achieved without undue treatment burden.³ Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for patients with T2DM who have overt CVD and even those without CVD who are older than 40 years and have one or more other CVD risk factors (eg, family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).³

Another contributing factor to cardiovascular risk that may impact treatment options for glycemic control is patient weight. Obesity and overweight status are risk factors for T2DM and CVD. Furthermore, obesity itself is now considered a disease state.⁶ More than 80% of patients with diabetes are not at a healthy weight (Figure 2).² Cardiovascular safety and effects on weight are important factors in choosing therapeutic options when considering treatment intensification for a middle-aged patient with loss of glycemic control as a result of progressive T2DM.

Pharmacologic Management of T2DM: From Dual Therapy to Triple Therapy

What, then, are the treatment options for patients with T2DM on dual oral therapy that experience loss of glycemic control? It is likely that postprandial hyperglycemia may contribute to a lack of HbA₁c control, especially when fasting plasma glucose levels are close but not at goal (Figure 3).⁷,⁸
Figure 4 shows current treatment recommendations from the 2013 American Association of Clinical Endocrinologists Comprehensive Diabetes Algorithm for triple therapy, which in general highlights agents with a low risk of hypoglycemia and weight gain. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are noted as “use with caution” because there is limited experience with them in clinical practice. Two of these inhibitors (canagliflozin and dapagliflozin) are approved for use in the United States. Both of these oral agents are associated with a low risk of hypoglycemia and some weight loss but carry risks of genitourinary infections. An unexplained adverse effect is an increased LDL-C level.

α-Glucosidase inhibitors (AGIs) are oral antidiabetic drugs used for T2DM that work by preventing the digestion of carbohydrates in the gastrointestinal (GI) tract. These inhibitors lower postprandial glucose by inhibiting the gut enzyme that breaks down complex carbohydrates, thus delaying polysaccharide absorption. They are not associated with a risk of hypoglycemia. The HbA1c-lowering effect of AGIs is modest, around 0.4% to 0.7%. Adverse effects such as bloating, flatulence, and diarrhea have limited the use of AGIs in the United States. α-Glucosidase inhibitors are more popular in Asia, and there are data directly comparing these agents with dipeptidyl peptidase-4 (DPP-4) inhibitors in Japanese patients with T2DM inadequately controlled on sulfonylurea therapy. At 24 weeks of therapy, the HbA1c reduction was almost identical between the groups (−0.091%, P=.47). As expected, GI adverse effects were more common with AGIs.

Table 1. Goals for Patients With Type 2 Diabetes Mellitus as Recommended by the American Diabetes Association

<table>
<thead>
<tr>
<th>Measure</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic</td>
<td></td>
</tr>
<tr>
<td>HbA1c level</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>140 mm Hg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 mm Hg</td>
</tr>
<tr>
<td>Low-Density Lipoprotein Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Without overt cardiovascular disease</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>With overt cardiovascular disease and statin therapy</td>
<td>&lt;70 mg/dL</td>
</tr>
</tbody>
</table>

Incretin-Based Therapies: GLP-1 Receptor Agonists and DPP-4 Inhibitors

Glucagon-like peptide-1 receptor agonists are peptides with substantial similarity to the native incretin hormone, GLP-1. Think of incretin as a hormone that increases insulin. These receptor agonists stimulate insulin secretion from β cells of the pancreas through a G-protein receptor-mediated process that is regulated by the intracellular glucose level (ie, it is glucose dependent). Also, GLP-1 receptor agonists reduce glucagon secretion from α cells and slow gastric emptying.

Dipeptidyl peptidase-4 inhibitors increase endogenous GLP-1 and glucose-dependent insulinotropic polypeptide by inhibiting the enzyme (DPP-4) that breaks down the incretin hormones. The elevated level of GLP-1 increases insulin secretion in a glucose-dependent manner from β cells and reduces glucagon secretion from α cells in the pancreas.

Because the DPP-4 inhibitors rely on endogenous levels of incretin hormones, which may be reduced or impaired in patients with T2DM, and because GLP-1 receptor agonists provide exogenous concentrations of GLP-1, GLP-1 receptor agonists are inherently more effective in reducing HbA1c levels. This effect is supported by clinical trial data13-16 and by a meta-analysis.17 The caveat is that GLP-1 receptor agonists must be given by subcutaneous injection and that higher levels of GLP-1 are also associated with other effects, such as nausea, which (not surprisingly) is dose dependent.
Incretin-Based Therapies as Part of Combination-Therapy Strategies

Incretin-based therapies are associated with a low risk of hypoglycemia because they work only when glucose levels are elevated. Incretin-based therapies are also associated with a low risk of weight gain, and in the case of GLP-1 receptor agonists, may be associated with weight loss that ranges from 1 to 4 kg, as well as improvement in markers of cardiovascular risk factors. These agents are also associated with robust HbA\textsubscript{lc} lowering (0.8% to 2.0%).

Insulin vs Incretin-Based Therapies

Insulin is well known to be the most potent glucose-lowering agent for treating patients with diabetes. Its efficacy is limited only by the risk of hypoglycemia, which also requires the need for self-monitoring of blood glucose levels by patients. Patient concerns that limit the use of insulin include its propensity to cause weight gain. Although its route of administration by injection is often cited as a barrier, the use of pen devices and the availability of very small needles have largely alleviated this concern.

Direct comparisons of basal insulin with DPP-4 inhibitors in patients with glycemia uncontrolled on metformin showed that the mean reduction in HbA\textsubscript{lc} levels was greater for patients on insulin glargine (−1.72%) than for those on sitagliptin (−1.13%), with a mean difference of -0.59% (P<.0001). Not surprisingly, the estimated rate of all symptomatic hypoglycemic episodes was greater with insulin than with the DPP-4 inhibitor (4.21 vs 0.50 events per patient-year; P<.0001). Comparisons of sitagliptin with the investigational very-long-acting basal insulin degludec showed no differences in nighttime hypoglycemic rates between agents but greater improvements in HbA\textsubscript{lc} reduction and fasting plasma glucose levels. However, degludec resulted in higher overall hypoglycemia rates and greater weight gain. Overall, DPP-4 inhibitors are less effective than insulin in reducing HbA\textsubscript{lc} levels but are associated with less hypoglycemia and less weight gain.

In comparisons of GLP-1 receptor agonists and insulin, comparable rates of HbA\textsubscript{lc} lowering can be achieved without increased risks of hypoglycemia and without weight gain—even with some potential for weight loss. A meta-analysis showed that GLP-1 receptor agonists are associated with a greater reduction in postprandial glucose than insulin. Despite a similar decrease in HbA\textsubscript{lc} level, the risk of hypoglycemia was 35% lower (P=.001) with GLP-1 receptor therapy compared with insulin.

In addition, GLP-1 analogs cause a statistically significant decrease in systolic blood pressure compared with insulin.
However, a significantly higher number of GI adverse events were reported with the GLP-1 group compared with insulin. The number of GI adverse events can be minimized with appropriate dose titration and patient counseling (especially in the case of exenatide twice a day—take it 0 to 60 minutes prior to a meal; more time before the meal increases the likelihood of nausea).

**Selecting Triple Therapy**

A systematic review and meta-analysis recently evaluated the comparative safety and efficacy of available classes of antihyperglycemic therapies in patients with T2DM inadequately controlled with metformin and sulfonylurea combination therapy.

Insulins (basal, biphasic, bolus), DPP-4 inhibitors, GLP-1 receptor agonists, and thiazolidinediones (TZDs) all produced statistically significant reductions in HbA1c levels in combination with metformin and a sulfonylurea (-0.89% to -1.17%), whereas meglitinides and AGIs did not (Table 2). Biphasic insulin, bolus insulin, and TZDs were associated with weight gain (1.85-5.00 kg), whereas DPP-4 inhibitors and AGIs were weight-neutral and GLP-1 receptor agonists were associated with modest weight loss (Table 2). Severe hypoglycemia was rare across all treatments; regimens containing insulin were associated with increased hypoglycemia relative to comparators.

**Other Third-Line Agents**

Thiazolidinediones have been accepted treatment options for many years, but recently they have been the subject of greater scrutiny. These agents reduce insulin resistance in skeletal muscle and other tissues. Adverse effects such as weight gain and fluid retention, which may contribute to chronic edema or heart failure, and adverse metabolic effects on bone, which may increase risk of fracture, have limited the use of TZDs. However, of note, in November 2013, the FDA announced lifting some prescribing and dispensing restrictions for rosiglitazone that were put in place in 2010.

Pioglitazone is the only other TZD available for general use. Pioglitazone has many positive attributes, including HbA1c lowering of 0.7% to 1.2%, low hypoglycemia risk, and possible cardiovascular benefits. The reported association of pioglitazone and bladder cancer is an unresolved issue. The benefits and risks of pioglitazone should be weighed when considering it for long-term management of T2DM.

The bile acid sequestrant colesevelam had as its first indication an adjunct to statin therapy for decreasing LDL-C levels in patients with elevated cholesterol levels. It also is indicated as adjunct therapy to other glucose-lowering agents for patients with T2DM. It lowers glucose modestly (HbA1c reductions of 0.4% to 0.6%) through an unknown mechanism. Colesevelam does not cause hypoglycemia or increase hypoglycemia risk when used with other agents. Increased triglyceride levels can be problematic for some patients. The major adverse effect is GI intolerance, which limits its use.

The quick-acting formulation of the dopamine receptor agonist bromocriptine mesylate has glucose-lowering properties and reduces HbA1c levels by about 0.5% through unknown mechanisms of action. Bromocriptine QR (quick-release) formulation needs to be given shortly after waking. Nausea and orthostasis can be treatment-limiting adverse effects, and bromocriptine QR should not be used in patients who are taking antipsychotic drugs.

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**Figure 3.** The contribution of fasting vs postprandial plasma glucose in relation to glycated hemoglobin A1c (HbA1c) levels.
Comparing the Available GLP-1 Receptor Agonists

Currently, 3 GLP-1 receptor agonists are available. Exenatide is available in 2 formulations: a short-acting drug that needs to be administered twice daily 0 to 60 minutes before meals with a dose-escalation schedule, and exenatide extended release, which is administered once weekly on the same day each week with no dose escalation. Liraglutide, a once-daily drug with a structure most similar to that of human GLP-1, does not need to be given with regard to mealtime. The short-acting exenatide has the most profound effects on postprandial glucose levels, whereas both of the longer-acting agents affect both fasting and postprandial glucose levels and reduce HbA1c levels more than short-acting exenatide (as shown in clinical trials). Both longer-acting agents are also associated with less nausea than shorter-acting exenatide. All 3 agents are relatively comparable with regard to their weight-loss profiles.

Cardiovascular Safety of GLP-1 Receptor Agonists

The US Food and Drug Administration (FDA) requires new drugs for T2DM to demonstrate cardiovascular safety. An analysis of 58 trials that included more than 10,000 patients receiving GLP-1 receptor agonists and more than 7000 patients receiving comparator GLP-1 agonists do not seem to show any increased risk of cardiovascular events with this class of drugs. Overall, the odds ratio for cardiovascular events with GLP-1 receptor agonists was 0.52 (95% confidence interval [CI], 0.27-0.99) compared with placebo and 0.84 (95% CI, 0.52-1.36) with active controls. Data from clinical trials exploring their antihyperglycemic effects have suggested beneficial effects on some cardiovascular risk factors, notably systolic blood pressure and some aspects of lipid profiles. Specific cardiovascular outcome trials are ongoing, but to my knowledge no results are yet available.

Lifestyle Recommendations

The role of medical nutritional therapy and physical activity as part of T2DM self-management should never be neglected and requires constant reinforcement with the patient and positive coaching. For example, data show that regardless of what diet is used (eg, Zone, Ornish, South Beach), it is the nutritional program that a patient can persist with that will have the greatest success. Recent evidence continues to support the use of the Dietary Approaches to Stop Hypertension diet in managing risk factors for T2DM and has recently been shown to be of specific benefit in women with gestational diabetes. New nutritional guidelines from the ADA focus on overall eating patterns without recommending any one form of diet while reviewing the evidence for several popular eating plans. The American College of Sports Medicine and the ADA have issued a joint position statement on exercise and T2DM that may be useful. In general, the ADA recommends that adults perform at least 150 minutes per week of moderate-intensity aerobic physical activity (at 50%-70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without physical activity.

Summary and Patient-Centered Considerations

The middle-aged patient who is not at HbA1c treatment goal is probably not achieving blood pressure or lipid goals either, and thus presents the osteo-
Table 2. Mixed Treatment Comparison: Adding Third-Line Antihyperglycemic Agents vs Placebo in Adults Taking Metformin and a Sulfonylurea^{26}

<table>
<thead>
<tr>
<th>Treatment + Met + SU</th>
<th>Change From Baseline</th>
<th>Body Weight, kg (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin</td>
<td>−1.17 (−1.57 to −0.81)</td>
<td>1.85 (0.54 to 3.09)</td>
</tr>
<tr>
<td>Biphasic insulin</td>
<td>−1.10 (−1.59 to −0.67)</td>
<td>3.35 (1.65 to 5.03)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>−0.96 (−1.35 to −0.59)</td>
<td>3.01 (1.73 to 4.43)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>−0.89 (−1.51 to −0.26)</td>
<td>1.11 (−1.36 to 3.57)</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>−0.46 (−0.96 to 0.03)</td>
<td>−0.43 (−2.20 to 1.44)</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>−1.06 (−1.45 to −0.69)</td>
<td>−1.59 (−3.01 to −0.20)</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>−1.01 (−1.71 to −0.35)</td>
<td>5.00 (2.52 to 7.43)</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>−0.18 (−2.08 to 1.71)</td>
<td>2.67 (−0.94 to 6.32)</td>
</tr>
</tbody>
</table>

^ Treatment favored vs placebo for both HbA\textsubscript{c} reduction and lack of weight gain.

Abbreviation: CrI, credible interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA\textsubscript{c}, glycated hemoglobin A\textsubscript{c}; Met, metformin; SU, sulfonylurea.


