New Therapeutic Options: Management Strategies to Optimize Glycemic Control

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Management of type 2 diabetes mellitus (T2DM) can be challenging. Patients frequently present with poor glycemic control despite therapy. Other patients may be nonadherent or resistant to continuing their treatment when confronted with undesirable adverse effects, such as weight gain, that are associated with many conventional therapies. Incretin-based therapies developed to treat patients with T2DM, including oral dipeptidyl peptidase-4 inhibitor agents or glucagon-like peptide-1 agonists, offer the potential of sustained glycemic control for many patients without the adverse events associated with other classes of antihyperglycemic medications. Available safety data from clinical trials indicate that incretin-based therapies have weight-neutral or weight-reducing effects, with no apparent adverse impact on other important safety parameters, such as cardiovascular disease. The integration of these therapies into treatment algorithms, as highlighted in three case presentations, will increase treatment options for patients with T2DM.

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Type 2 diabetes mellitus (T2DM) can be challenging to manage. Part of this difficulty arises from limitations associated with traditional antihyperglycemic agents, such as hypoglycemia and weight gain. In addition, with convenient access to various sources of information (or misinformation), such as the Internet, online chat rooms, and support groups, patients may be inquisitive with respect to their disease and treatment. When discussing therapy, clinicians should provide patients with evidence-based treatment options that patients can understand and relate to in the context of their condition.

Treatment guidelines from the American Association of Clinical Endocrinologists (AACE) recommend initiating lifestyle modification at the time of diagnosis, in addition to various pharmacotherapies based on the patient’s glycated hemoglobin (HbA1c) level. The American Diabetes Association goals of antihyperglycemic therapy are to achieve an HbA1c of less than 7.0%, fasting plasma glucose (FPG) range of 70 mg/dL to 130 mg/dL, and a peak postprandial glucose (PPG) of less than 180 mg/dL. The AACE goals are an HbA1c of 6.5% or lower, an FPG of less than 110 mg/dL, and a 2-hour PPG of less than 140 mg/dL.

The current article presents a series of cases highlighting some commonly encountered issues in the treatment of patients with T2DM. Clinical evidence is offered to engage patients in a meaningful discussion of T2DM and treatment options.

Case 1
The patient is a 48-year-old man who was diagnosed as having T2DM 2 years ago. He has been treated with lifestyle changes and increasing doses of metformin, which is currently at 1000 mg twice daily. Available laboratory results show his HbA1c is 7.6% (increased from 7.2% last year), his fasting plasma glucose is 170 mg/dL, and his postprandial glucose is 240 mg/dL.

Comment
This patient has been treated with lifestyle changes and pharmacotherapy with increasing doses of metformin for his diabetes. At least one component of the disease progression in this patient is likely caused by declining β-cell function. Options for further treatment aimed at reducing the patient’s HbA1c level include the use of combination therapy with metformin or a switch from metformin to another therapy.

The natural history of T2DM typically involves progressive pancreatic islet cell dysfunction and worsening glycemic control. Traditional antihyperglycemic agents—thiazolidinediones and sulfonylureas—often fail to maintain glycemic goals long-term, in part, because they do not target the underlying patho-

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physiologic processes of T2DM, which include a progressive decline in \( \beta \)-cell function and impaired incretin response. Incretin-based therapies address these mechanisms and offer the advantage of potentially slowing disease progression by enhancing insulin secretion and suppressing glucagon release.

Evidence from a recent clinical trial\(^3\) involving the glucagon-like peptide-1 (GLP-1) agonist exenatide showed a sustained improvement in \( \text{HbA1c} \) levels in patients with T2DM who completed at least 3 years of treatment. Patients who enrolled in a randomized, double-blind, parallel-group, 30-week study had the option to continue in their open-label extensions; completers were then given the option to enroll in a single, open-ended, open-label extension. During the blinded portion of the study, patients received combination therapy of exenatide with either metformin or a sulfonylurea, or triple therapy with exenatide, metformin, and a sulfonylurea.\(^3\)

Patients who completed 156 weeks of treatment with exenatide reduced \( \text{HbA1c} \) levels by a mean (SD) of \(-1.0\% (0.1\% \) (\( P<.0001 \)) and reduced FPG by 23.5 (3.8) mg/dL (\( P<.0001 \)). These findings demonstrated a sustained and durable control of \( \text{HbA1c} \) in patients completing 3 years of treatment with exenatide (Figure 1).\(^3\)

With other T2DM interventions, an initial improvement in glycemic control is followed by increasing levels of \( \text{HbA1c} \) over time. However, the results of this analysis suggest some stability and durability in the \( \text{HbA1c} \) response when exenatide is used as a component of the combination therapy. When discussing treatment options with patients, physicians should explain that, based on clinical trial evidence, the addition of exenatide to metformin could potentially reduce \( \text{HbA1c} \) levels by a percentage point or more.

Saxagliptin, a dipeptidyl dipeptidase-4 (DPP-4) inhibitor, has also shown efficacy in lowering \( \text{HbA1c} \) levels in patients with T2DM when used as monotherapy. One 24-week study\(^4\) demonstrated reductions in \( \text{HbA1c} \) of \(-0.79\% \) and \(-0.94\% \) for 100 mg and 200 mg saxagliptin, respectively (\( P<.001 \)) in both vs placebo. In addition, \( 41\% \) and \( 45\% \) of patients in the respective saxagliptin groups achieved an \( \text{HbA1c} \) of less than \( 7.0\% \), compared with only \( 17\% \) in the placebo group (\( P<.001 \)).\(^4\)

Similar results were seen in combination therapy with metformin: at 24 weeks, saxagliptin significantly reduced \( \text{HbA1c} \) by \(-0.65\% \) (\( P<.001 \)). The percentage of patients achieving an \( \text{HbA1c} \) of less than \( 7.0\% \) was \( 47\% \) in the saxagliptin group and \( 18.3\% \) in the placebo group (\( P<.001 \)).\(^5\) As add-on therapy with ongoing pioglitazone, saxagliptin significantly reduced both \( \text{HbA1c} \) (-\( 0.7\% \); \( P<.001 \)) and FPG (-17.7 mg/dL; \( P<.001 \)), and the percentage of patients reaching the target goal was \( 45.4\% \) and \( 23.0\% \) in the saxagliptin and placebo groups, respectively (\( P<.001 \)).\(^5\)

In populations with a baseline \( \text{HbA1c} \) of \( 8.8\% \), saxagliptin also demonstrated moderate efficacy in combination with high-dose metformin. At week 24, the combination of saxagliptin (50 mg twice daily) with high-dose metformin (1000 mg twice daily) resulted in an \( \text{HbA1c} \) reduction of \(-1.9\% \) vs baseline, and \(-2.07\% \) vs placebo.\(^7\) Evidence from a 104-week study also suggested a durable and sustained reduction in \( \text{HbA1c} \) with saxagliptin as add-on therapy to metformin (Figure 2).\(^5\) Results with both exenatide and saxagliptin demonstrated durable and apparently sustainable reductions in \( \text{HbA1c} \) and could theoretically cause islet or \( \beta \)-cell function regeneration or an improvement in viability of \( \beta \) cells. However, further study will be needed to determine whether such increases in \( \beta \)-cell mass or function are occurring.

Results with saxagliptin, another DPP-4 inhibitor, in combination with metformin have also demonstrated significant reductions in \( \text{HbA1c} \) and have shown evidence of durability during a 2-year study (Figure 3). In this case, however, the \( \text{HbA1c} \) pattern did not appear to show a plateau effect, but instead indicated an initial response was followed by a gradual increase between 30 and 102 weeks.\(^8\) Further follow-up may be needed to determine whether the efficacy of saxagliptin is sustainable over the long-term.

**Summary**

Based on available evidence, combination treatment, which includes incretin-based therapy (ie, GLP-1 agonist or DPP-4 inhibitor), may be beneficial in patients with disease progression despite treatment and an increase in metformin dosage. Long-term studies showed that incretin-based therapies can be used in

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combination with metformin, with an expected HbA1c reduction of about 1.2% and with durability of response of at least 1 year.\(^3\)\(^,\)\(^4\)\(^,\)\(^7\)\(^,\)\(^9\)

**Case 2**

The patient is a 50-year-old woman recently diagnosed as having T2DM. She takes 500 mg metformin twice daily. Her height is 5 ft 5 in and her weight is 180 lbs. Her body mass index is 30, which is consistent with obesity. The patient has had difficulty losing weight, despite attempts at lifestyle modification. Her family history is notable for T2DM and insulin resistance in her older sister.

**Comment**

When considering treatment for this patient, weight loss should be a desired goal. Traditional antihyperglycemic agents, including thiazolidinediones and sulfonylureas, are associated with weight gain. In contrast, recent evidence\(^3\)\(^,\)\(^4\) associates incretin-based therapy and GLP-1 agonists combination therapy with weight loss and DPP-4 inhibitors with weight-neutrality.

In a 3-year follow-up study of patients who completed treatment with exenatide (n=217), the overall weight loss was -5.3 kg (\(P<.0001\) vs baseline), or approximately 10 lbs (Figure 4).\(^3\) Although this decrease may not be substantial as a weight-loss intervention for some patients, the key point in this long-term follow-up study is that the patients did not gain weight during the 3 years. At present, because the study lasted only 3 years, it may be too soon to ascertain whether this weight loss will continue or reach a plateau over the longer-term. The relevant results to consider are an effective HbA1c reduction with some degree of durable weight loss over time.

By comparison, available data with DPP-4 inhibitors indicate a weight-neutral impact. A number of trials have examined the use of sitagliptin alone and in combination with other therapies. Findings were as follows:

- sitagliptin 100 mg monotherapy vs placebo for 24 weeks: -0.2 and -0.1 kg vs -1.1 kg, respectively (\(P<.01\))\(^4\)
- sitagliptin 100 mg monotherapy vs placebo for 18 weeks: -0.6 vs -0.7 kg, respectively\(^10\)
- add-on sitagliptin therapy with metformin for 24 weeks: between-group difference change in body weight (\(P=.835\))\(^5\)
- sitagliptin with ongoing pioglitazone for 24 weeks: no statistically significant difference\(^6\)
- sitagliptin initial combination therapy with high-dose metformin for 24 weeks: small reductions (-0.6 to -1.3 kg)\(^7\)
- sitagliptin alone for 24 weeks: no change

These findings are also highlighted in Figure 5.\(^4\)\(^,\)\(^7\)\(^,\)\(^10\)

These trials either reduced the weight by approximately 1 kg or had no effect on weight, regardless of the combination used. Therefore, patients treated with sitagliptin combination therapy may achieve better glycemic control than those treated with metformin or a sulfonylurea monotherapy while maintaining weight-neutrality.

**Summary**

Based on the available clinical results, treatment options for patients with T2DM who desire to lose weight or to maintain weight are either GLP-1 agonists such as exenatide or DPP-4 inhibitors such as sitagliptin.
cholesterol; and an improvement in blood pressure. All changes were statistically significant. Clearly, such improvements would have a positive impact on long-term outcomes. A key question, however, that is not addressed by these data is whether these lipid effects are mediated directly by exenatide or by the secondary effect of weight loss in these patients. Based on these data, cardiovascular risk factors, including lipid parameters and blood pressure, may improve while on exenatide, but they may also be contingent upon weight reduction while on the therapy.

An unpublished meta-analysis examined cardiovascular end points in patients enrolled in 12 completed, long-term (between 3 and 12 months), randomized, placebo- and insulin-comparator–controlled trials using exenatide twice daily. The intent-to-treat population consisted of 3945 subjects: 2316 were exposed to exenatide and 1629 were not exposed to exenatide (comparator including incretin-based therapies. However, he is concerned about their cardiovascular disease safety profiles. He asks if there have been any studies that have evaluated cardiovascular disease safety and lipid-lowering benefits.

Comment
In the case of cardiovascular disease risk with incretin-based therapies, there is currently evidence for up to 3.5 years of treatment without a statistically significant signal for concern. The effect of exenatide treatment on cardiovascular risk factors was shown in a subgroup of 151 patients in a 3-year extension analysis (Table). Study data demonstrated an HbA1c reduction of approximately 0.8%; an improvement in lipid profile, with reductions in total cholesterol and low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol; and an improvement in blood pressure. All changes were statistically significant. Clearly, such improvements would have a positive impact on long-term outcomes. A key question, however, that is not addressed by these data is whether these lipid effects are mediated directly by exenatide or by the secondary effect of weight loss in these patients. Based on these data, cardiovascular risk factors, including lipid parameters and blood pressure, may improve while on exenatide, but they may also be contingent upon weight reduction while on the therapy.

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reduce a patient’s overall cardiovascular risk. In the case of the DPP-4 inhibitors, studies such as TECOS will evaluate cardiovascular outcomes for patients on sitagliptin.

Other Considerations in Choosing Therapy

- Have the results of comparative studies between GLP-1 agonists and DPP-4 inhibitors been published? The two classes of incretin-based therapy have been compared in a recent double-blind, randomized, double-dummy, crossover, multicenter study. Patients received the GLP-1 agonist exenatide or the DPP-4 inhibitor sitagliptin during an initial treatment period, followed by a crossover to the other therapy during a second treatment period.

  In the study, 61 patients with T2DM who had been treated with a stable regimen of metformin were randomized to either an exenatide-to-sitagliptin or a sitagliptin-to-exenatide treatment sequence. The primary study end point was the effect of sitagliptin and exenatide on 2-hour PPG. Results showed that, for patients in the exenatide-to-sitagliptin sequence, 2-hour PPG decreased to a mean (SD) value of 133 (10) mg/dL from a baseline value of 245 mg/dL while on exenatide. The subsequent sitagliptin treatment in period 2 increased the 2-hour PPG to 205 (12) mg/dL. By comparison, for patients in the sitagliptin-to-exenatide sequence, 2-hour PPG decreased to 208 (6) mg/dL while on sitagliptin. Subsequent exenatide treatment further reduced the 2-hour PPG to 133 (9) mg/dL.

  A reduction in PPG was thus observed with either agent when used as an initial therapy, albeit with a greater reduction observed with exenatide. However, when the exenatide group crossed over to therapy with sitagliptin, there was an apparent deterioration in PPG control, whereas sitagliptin-treated patients who crossed over to exenatide continued to maintain control over 2-hour PPG. The two drugs were similar in their effects on FPG, with no significant difference observed (FPG with exenatide: -15 mg/dL vs sitagliptin: -19 mg/dL; P=.3234). Overall, these results suggest that patients receiving incretin-based therapy with GLP-1 agonists such as exenatide may experience a more robust decrease in 2-hour PPG compared with an oral DPP-4 inhibitor such as sitagliptin.

- Are there benefits of incretin-based therapy on congestive heart failure? There is evidence that incretin-based therapies may have beneficial effects on cardiac function in patients with congestive heart failure. In one study of patients with New York Heart Association class III or IV heart failure, a 5-week continuous infusion of GLP-1 was shown to significantly improve multiple functional status parameters, including left ventricular ejection fraction (LVEF), maximum myocardial ventilation oxygen consumption, Minnesota Quality of Life score, and 6-minute walk test compared to control patients receiving standard therapy alone. Moreover, the observed changes in LVEF could not be accounted for by changes in blood pressure and were observed in patients.

### Table

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Change From Baseline, mean (SD)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Body Weight, kg</td>
<td>-5.3 (0.5)</td>
<td>&lt;.0001</td>
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<tr>
<td>HbA1c, %</td>
<td>-0.8 (0.1)</td>
<td>&lt;.0001</td>
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<tr>
<td>Total Cholesterol, mg/dL</td>
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<tr>
<td>Triglycerides, mg/dL</td>
<td>-44.4 (12.1)</td>
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<td>LDL-C, mg/dL</td>
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<tr>
<td>HDL-C, mg/dL</td>
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<td>SBP, mm Hg</td>
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<tr>
<td>DBP, mm Hg</td>
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<td>&lt;.0001</td>
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Exenatide therapy was administered at 10 μg twice daily for 3.5 years. The study design was an open-ended, open-label extension study.

Abbreviations: DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

When sitagliptin was used as monotherapy, 

\[ HbA_1c \] levels, FPG levels, and 2-hour PPG decreased ( -0.7%, -27 mg/dL, and -61 mg/dL, respectively) in the sitagliptin arm compared to the placebo arm (P<0.001). Importantly, the incidence of hypoglycemia and gastrointestinal distress was not different in the sitagliptin group compared to placebo. Results of this study suggest that sitagliptin is safe and effective to use in individuals aged 65 years or older.

**What are the risks of hypoglycemia associated with incretin-based therapies?**

Hypoglycemia is a concern with many conventional T2DM therapies. Available evidence with DPP-4 inhibitors and GLP-1 agonists has shown the overall incidence of hypoglycemia is fairly low. In a study of patients with T2DM inadequately controlled with diet and exercise, patients treated with the DPP-4 inhibitor saxagliptin as monotherapy had a similar incidence of mild-to-moderate hypoglycemic events (5.2%) compared with those treated with placebo (6.3%). Rates of hypoglycemia were also similar between treatment and placebo groups when sitagliptin was used as monotherapy among patients with inadequately controlled T2DM.

**Conclusion**

When choosing optimal therapies for patients with T2DM, considerations include the patient’s stage and progression of disease, the viability of their β cells, comorbid conditions, predisposition for weight gain, renal function, possible aversions to injectable treatments, and cost of therapy. Ultimately, many patients will require insulin therapy as their T2DM progresses. In choosing the best therapies for a patient, insulin secretion, insulin resistance, and glucagon suppression should be considered. Incretin-based therapies can effectively target these key pathogenic processes of T2DM and offer the potential for durable and sustainable improvement in glycemic control, along with long-term safety and tolerability.

**References**


15. Barzilai N, Mahoney EM, Guo H, Lu K, Golm GT, Williams-Herman D, et al. Sitagliptin is well tolerated and leads to rapid improvement in blood glucose in the first days of monotherapy in patients aged 65 years and older with T2DM. Presented at: 69th Scientific Sessions of the American Diabetes Association; June 5-9, 2009; New Orleans, LA. Abstract 587-P.
