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Incretins & Type 2 Diabetes

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e Patients with type 2 diabetes mellitus (T2DM) who achieve glycemic goals through lifestyle modification and/or pharmacologic therapy experience substantially reduced morbidity and mortality. Those patients who do not achieve glycemic goals remain at high risk for serious complications. Patients may fail to achieve their glycemic goals for several reasons, including suboptimal treatment choices and poor adherence to therapy. Additionally, because T2DM is a progressive disease, patients may achieve initial glycemic control only to see their control deteriorate over time. Health care providers may

also fail to intensify pharmacotherapy to maintain glycemic control as the disease progresses.¹

To help guide health care practitioners in selecting the most appropriate interventions, a recently updated treatment algorithm from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has been published. This algorithm creates three steps and two tiers of therapy and incorporates newer classes of medications with well-validated therapies (Figure 1).^{2,3}

Because so many patients with T2DM are not at hemoglobin A_{1c} (A1C) goal, there is a need to reeval-

Controlling hyperglycemia is critical in order to reduce the morbidity and mortality of type 2 diabetes, and the treatment algorithm calls for therapy to be intensified if A1C goals are not reached within a few months. GLP-1 agonists are an option for treating patients who do not achieve goals with lifestyle modifications plus other antihyperglycemia agents.

uate therapeutic interventions. This article explores the role of the incretin system in T2DM, describes the effects of medications that target the incretin system and discusses a patient case to review the clinical application of these newer agents. Because the ADA/EASD algorithm includes only the glucagon-like peptide-1 (GLP-1) agonists and not the dipeptidyl peptidase-4 (DPP-4) inhibitors, the article focuses on the GLP-1 agonists.

Case Study

Ms. D is 55 years old and has a five-year history of T2DM. Her chief complaints are fatigue, occasional

blurred vision and nocturia twice nightly. Her self-monitoring of blood glucose involves testing her fasting blood sugar three times per week; levels have ranged from 152 mg/dL to 172 mg/dL during the past two weeks.

Ms. D is obese (height, 5'3"; weight, 180 lbs; BMI, 31.9 kg/m²). Her average caloric intake is 1,500 calories daily; she participates in Weight Watchers meetings once weekly. She leads a sedentary lifestyle—she is employed as a school bus driver, and her exercise is limited to walking her dog for 30 minutes twice a week.

In addition to T2DM, Ms. D was diagnosed with hypertension 20 years ago and dyslipidemia 12 years ago. Her family history includes T2DM in both →

Learning Objectives

- Explain the pathophysiology of type 2 diabetes mellitus (T2DM) and how the progressive nature of this disease demands progressive therapeutic interventions to reach and maintain glycemic goals.
- List initial therapy options for T2DM and state the rationale for rapidly progressing to additional interventions, as appropriate.
- Explain the role of incretins in normal physiology and describe the defects of incretin secretion and incretin action that occur in T2DM.
- Discuss the pros and cons of incretin-based therapies and where they fit into the treatment algorithm.
- Discuss how to manage a patient case study according to the most recent treatment algorithm to motivate patients with diabetes to achieve current American Diabetes Association guideline goals.

Target Audience

Primary care physician assistants and clinicians who have an interest in treating patients with diabetes.

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Method of Participation

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Ms. D's Lab Values & Medications

Current Laboratory Values

Random glucose (mg/dL): 158
A1C (%): 7.8
LDL-C (mg/dL): 128
HDL-C (mg/dL): 40
Triglycerides (mg/dL): 215
BP (mm Hg): 128/80

Current Medications

Metformin 1,000 mg twice daily
Irbesartan 300 mg once daily
Atorvastatin 40 mg once daily at bedtime
Aspirin 81 mg once daily

Abbreviations: A1C, hemoglobin A_{1c}; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

parents and two siblings and hypertension in her mother and three siblings. A comprehensive metabolic panel and urinalysis were within normal limits with the exception of her increased serum glucose value. Her most recent laboratory values and current medications are listed in the accompanying table.

Has Ms. D achieved treatment goals?

Treatment Options for T2DM

The A1C goal recommended by current treatment guidelines for nonpregnant adults is generally less than 7%. Achievement of this goal is associated with a significant reduction in the risk for microvascular and macrovascular complications.³ However, data from recent large randomized trials has led some authors to argue that the burdens associated with maintaining tight glycemic control, including costs and risks of hypoglycemia, must be balanced against the potential benefits, and that an A1C goal of 7% to 7.5% is reasonable for some patients.⁴

Lifestyle interventions (e.g., diet and exercise) that reduce overweight and obesity can significantly improve glycemic control.² Such interventions should always be included in the treatment of T2DM unless clinically contraindicated.² However, the majority of patients will also require pharmacologic therapies and, because diabetes is a progressive disease, dosage increases and additional medications are often required to achieve or maintain treatment goals over time. Metformin is recommended as initial therapeutic strategy based on its efficacy, low risk of hypoglycemia,

low risk of weight gain and generic availability.

Case Study Assessment

Ms. D's A1C of 7.8% indicates that she is not at goal and that additional interventions are needed. Her diet appears to be well managed, but she would benefit from interventions that increase her level of physical activity. Ms. D is currently receiving step 1 therapy according to the ADA/EASD algorithm; additional step 2 medication is appropriate to assist in lowering her A1C.

Step 2 Treatment Options

Tier 1 recommendations for step 2 therapy include the addition of either a sulfonylurea or basal insulin to metformin and lifestyle modification. These agents increase insulin levels to the tissue, either by enhancing secretion (sulfonylureas) or by providing exogenous supplementary insulin. These agents have been available for many decades and thus are associated with a significant amount of clinical experience.

Thiazolidinediones (TZDs) target insulin resistance and thus are appropriate for use in patients who still have insulin secretory ability (e.g., those with a relatively short duration of disease). A TZD-metformin-based therapy has recently shown greater improvements in insulin resistance-related parameters compared with a sulfonylurea-metformin-based regimen.⁵

TZDs do increase the risk for congestive heart failure and are contraindicated in patients with a history of it.⁶ Recent evidence suggests that long-term use of TZDs may reduce bone mineral density and result in a twofold increase in the risk of distal fractures in women and men with T2DM.^{7,8}

GLP-1 agonists target the incretin system and result in good glycemic control with minimal risk of hypoglycemia and the promotion of weight loss. The treatment algorithm notes that the addition of exenatide or pioglitazone may be considered when hypoglycemia is particularly undesirable (e.g., such as in a hazardous job that requires constant vigilance).²

Case Study Update

Ms. D's occupation as a bus driver makes the addition of medications with a higher risk of hypoglycemia (e.g., insulin or a sulfonylurea) less desirable. Furthermore, because she is obese, medications that are not associated with weight gain may be preferable. She was given a trial of pioglitazone 30 mg daily but experienced significant peripheral edema and weight gain. Despite a dosage reduction, the edema did not resolve after six

weeks of therapy, and pioglitazone was discontinued. At her next visit, her A1C had increased to 8.0%, and a trial of a GLP-1 agonist is considered.

Incretins' Role in T2DM Management

Insulin secretion is significantly higher after oral glucose administration than after an equivalent intravenous glucose infusion, indicating that hormones released in the gut (i.e., enteric hormones known as incretins) stimulate insulin secretion. This response is known as the "incretin effect."⁹

The incretin effect results primarily from the action of two gut peptides—GLP-1 and glucose-dependent insulinotropic peptide (GIP).¹⁰ While both GLP-1 and GIP stimulate insulin secretion and promote beta-cell proliferation, only GLP-1 inhibits gastric emptying, reduces appetite, inhibits food intake and weight gain and suppresses glucagon secretion.^{11,12} Other effects of GLP-1 include actions at receptors in the hypothalamus and the brainstem that lead to appetite suppression, and a direct regulatory effect on hepatic glucose uptake and production.¹³

Blocking DPP-4, which is the enzyme that inactivates GLP-1, is another strategy to maintain physiologic GLP-1 levels. This produces similar GLP-1-mediated pancreatic effects but fails to suppress appetite, slow gastric emptying or assist in weight loss.

GLP-1 Agonists

Currently, only one GLP-1 agonist, twice-a-day exenatide, is approved by the Food and Drug Administration (FDA) for use in the treatment of T2DM. Investigational GLP-1 agonists include once-a-day liraglutide, once weekly taspoglutide and a once weekly long-acting release formulation of exenatide. Each of these agents is administered via subcutaneous injection.^{14,15}

In randomized, controlled clinical trials, patients receiving twice-a-day exenatide for T2DM treatment experienced significantly decreased mean A1C values (−0.3% to −0.98%, $P < 0.001$ to $P < 0.0001$), fasting plasma glucose levels (−7.2 mg/dL to −30.42 mg/dL, $P < 0.05$ to $P < 0.001$) and weight loss (−0.28 kg to −1.6 kg, $P < 0.05$ to $P < 0.0001$).¹⁶⁻¹⁹ These effects were observed when exenatide was administered as a single pharmacologic agent plus diet and exercise, or when it was administered concurrently to patients suboptimally controlled on either metformin, a TZD or a sulfonylurea.

In a randomized, open-label multicenter study

in 501 patients with T2DM, exenatide produced similar reductions in A1C (−0.07%) as insulin aspart 70/30 (−0.06%); however, patients on exenatide lost 2.5 kg while patients on insulin aspart gained 2.9 kg, for a significant difference of 5.4 kg ($P < 0.001$).²⁰ A similar open-label, multicenter study of 551 patients with T2DM compared exenatide with insulin glargine. Both medications reduced A1C by 1.11%; however, patients on exenatide lost 2.3 kg while those on insulin glargine gained 1.8 kg, for a significant difference of 4.1 kg ($P < 0.0001$).²¹

Long-term treatment for up to 3.5 years with exenatide in combination with other oral antihyperglycemia agents has been shown to result in sustained glycemic control, progressive weight reduction and significant improvements in several cardiovascular risk factors, including triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and systolic and diastolic blood pressure.²²

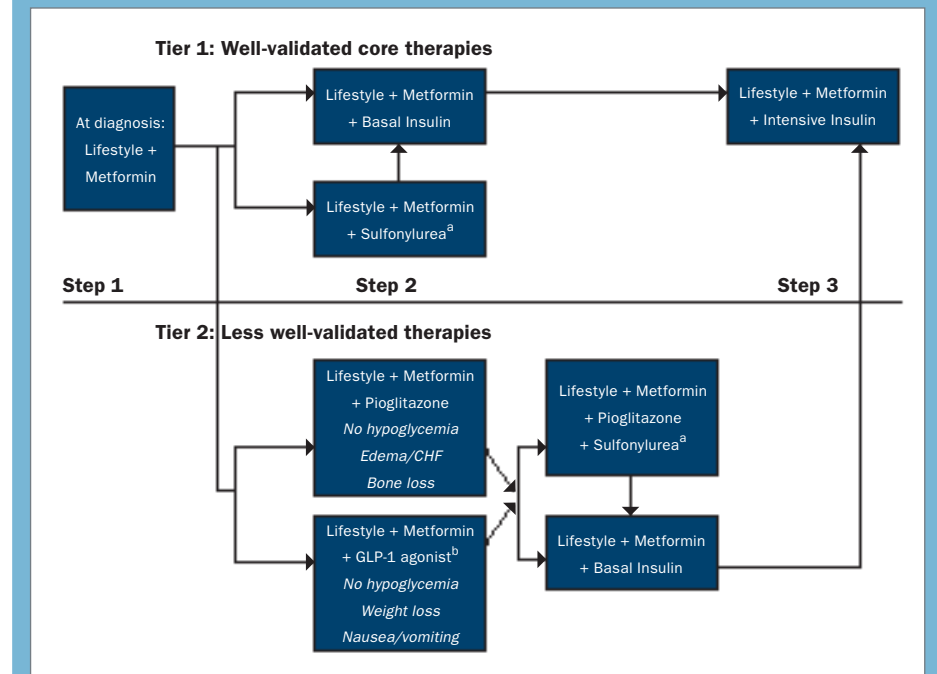
Only one head-to-head trial has compared the effects of GLP-1 agonists. In this recently published study, once-a-day liraglutide was compared with twice-a-day exenatide as add-on therapy in patients receiving metformin and/or a sulfonylurea for 26 weeks. Compared with exenatide, treatment with liraglutide was associated with significantly greater reductions in A1C values (−1.12% vs. −0.79%, $P < 0.0001$) and fasting plasma glucose levels (−1.61 mmol/L vs. −0.6 mmol/L, $P < 0.0001$) and with a comparable degree of weight reduction (−3.24 kg with liraglutide and −2.87 kg with exenatide) (Figure 2).²³

Incidence of the most common adverse event, nausea, was comparable between the two treatment groups but resolved earlier in the liraglutide group (estimated treatment rate ratio 0.45, $P < 0.0001$). Minor hypoglycemia also occurred in both treatment groups, although it was less frequent with liraglutide than with exenatide.²³ However, hypoglycemia may result when GLP-1 agonists are added to other medication regimens. (For example, it is recommended that the dose of a sulfonylurea be reduced 50% to minimize the risk for hypoglycemia when GLP-1 agonists are added to a sulfonylurea regimen in patients with an A1C less than 8%.)

Limitations associated with incretin agonists include comparatively less clinical experience with these agents and lack of a generic equivalent. In addition, some patients may wish to avoid daily injections and may prefer oral therapies when possible. There have been a handful of case reports

Figure 1 ADA/EASD T2DM Management Algorithm

The American Diabetes Association and the European Association for the Study of Diabetes algorithm for metabolic management of type 2 diabetes mellitus.



^a Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide
^b Insufficient clinical use to be confident regarding safety.

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of hemorrhagic or necrotizing pancreatitis with exenatide, but causality has not been established.²⁴ The FDA states that clinicians should consider antihyperglycemia agents other than exenatide in patients with a history of pancreatitis.²⁵

DPP-4 Inhibitors

Sitagliptin and saxagliptin are administered orally and are currently the only DPP-4 inhibitors approved by the FDA. Investigational DPP-4 inhibitors include vildagliptin and alogliptin.²⁴ Several studies have demonstrated that treatment with either sitagliptin or saxagliptin, either as monotherapy or in combination with metformin, a sulfonylurea or a TZD, results in reduced A1C values and fasting plasma glucose levels.^{26,27}

No characteristic pattern of adverse events has been associated with the use of DPP-4 inhibitors. Unlike the GLP-1 agonists that promote weight

loss, DPP-4 inhibitors are weight neutral.^{14,26} In addition, sitagliptin does not appear to affect lipid profiles.²⁶ These agents are not currently included in the ADA/EASD treatment algorithm.

Patient Case Assessment

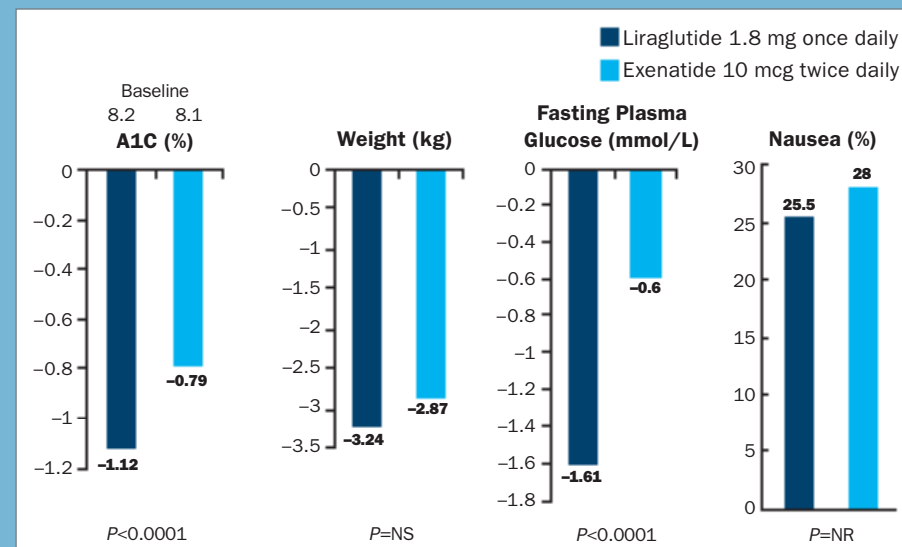
Let's return to the question of whether a GLP-1 agonist would be an appropriate choice for Ms. D.

- Ms. D is obese. She may benefit from the addition of a GLP-1 agonist that produces weight loss in addition to improving glycemic control.
- Exenatide, for example, has the potential to positively affect Ms. D's dyslipidemia and assist with blood pressure control.
- GLP-1 agonists have minimal risk for hypoglycemia, making them less likely to interfere with her occupation.

Based on these factors, a trial of a GLP-1 agonist is recommended. Following treatment initiation, Ms. D requires continuous management to assess →

Figure 2 Liraglutide vs. Exenatide

Liraglutide vs. exenatide when added to metformin and/or a sulfonylurea in type 2 diabetes mellitus



From: Buse JB, Rosenstock J, Sesti G, et al; for LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374(9683):39-47.

her response to therapy. If Ms. D does not achieve her diabetes treatment goal (i.e., A1C less than 7%) within two to three months, reassessment and intensification of her treatment is required until goals are achieved. If the treatment goal is achieved, ongoing follow-up is necessary to successfully manage her advancing T2DM.

Conclusions

The 2009 ADA/EASD treatment algorithm for the management of T2DM highlights the importance of controlling hyperglycemia to reduce morbidity and mortality and calls for clinicians to intensify therapy within two to three months of treatment initiation if A1C goals are not achieved.

GLP-1 agonists are incorporated in the treatment algorithm as an option for treating patients who do not achieve goals with lifestyle modifications plus other antihyperglycemia agents. GLP-1 agonists target multiple aspects of T2DM pathophysiology while concurrently producing weight loss and may have beneficial effects on certain cardiovascular risk factors. GLP-1 agonists have a low risk of hypoglycemia. The most common adverse event associated with GLP-1 agonists is mild to moderate nausea. Patient education is critical to the success of any diabetes

treatment strategy. Discussion about the administration of GLP-1 agonists, as well as potential side effects, their likely time course and strategies to manage them, may help improve patient adherence with this class of agents.

Ongoing experience with incretin-based therapies will further define their role in treating T2DM and in slowing the progression of this progressive yet manageable disease. □

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Axial-Flow Ventricular Assist Devices

Axial-flow VADs have a number of potential advantages over pulsatile-flow VADs, including standardization, smaller size, ease of implantation and mechanical reliability. But since axial-flow devices are relative newcomers, more research is needed to determine whether the standard of care for patients with heart failure will shift away from time-tested pulsatile-flow devices.

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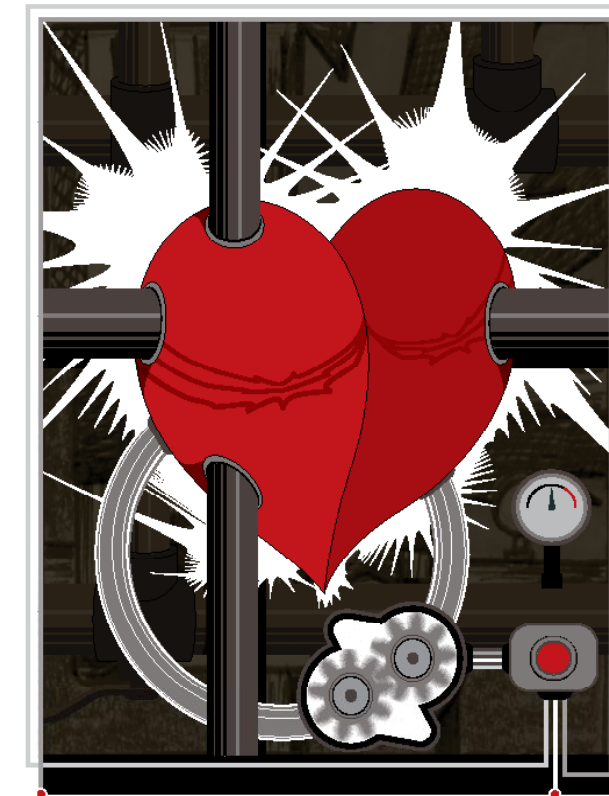


Heart disease is the leading cause of death in the United States, and together with cancer it accounted for nearly half of all U.S. deaths in 2005.¹ Severe heart disease can progress to heart failure (HF), and incidence of new HF cases has been rising slowly but steadily in recent years.^{2,3} Underlying causes vary, but in the United States and other developed countries, it is widely understood that the majority of cases can be attributed to coronary artery disease.⁴ Hypertension, although usually not the primary cause, complicates a majority of HF cases.⁴

HF is the inability of the heart to pump blood at an output that adequately meets the requirements of metabolizing tissues or the ability to do so only at abnormally elevated diastolic pressures or volumes.⁴ HF can occur during the systolic or diastolic phases of contraction. Using the New York Heart Association (NYHA) functional classification system, HF is classified classes I (mildest) through IV (severe). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is an assessment tool used to measure the effects of HF and its therapy on a person's quality of life. Studies have shown a strong correlation between MLHFQ scores and NYHA functional classifications.⁵

The Development of VADs

The first successful human heart transplant was performed by Christiaan Barnard, MD, in Cape Town, South Africa, in 1967. His success brought several further attempts but with few patients



surviving. The discovery of cyclosporine in the early 1980s dramatically improved survival rates by preventing rejection of newly transplanted hearts. It is estimated that more than 100,000 people have undergone successful heart transplantation; as medications continue to improve, so do outcomes. Nevertheless, the demand for donor hearts far exceeds the supply, and this remains the single biggest limiting factor to transplantation.^{6,7}

The first device created to assist the heart in pumping can be traced back to 1966 when Michael E. DeBakey, MD, implanted a booster pump to serve as a temporary assist device.⁶ This device laid the foundation for modern ventricular assist devices (VADs), which serve a variety of functions ranging from bridge-to-transplant therapy to destination therapy (long-term mechanical circulatory support for heart failure without the intention transplantation).⁸ Today's VADs can be broadly categorized based on how blood flows through the device: pulsatile-flow VADs and axial-flow VADs (Table 1).

Pulsatile-flow VADs were developed first and thus are the more researched of the two device classes. With pulsatile-flow VADs, blood flows through the body in a pulsatile fashion similar to the mechanism provided by the biological heart. In newer