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Clinical Use of Incretin-Based Therapy in Type 2 Diabetes Mellitus

LEARNING OBJECTIVES

After reviewing this activity, the reader will be better able to:

1. List the pros and cons of incretin-based therapies.
2. Differentiate the clinical effects of glucagon-like peptide-1 receptor (GLP-1R) agonists from those of dipeptidyl peptidase 4 (DPP-4) inhibitors.
3. Address common barriers to GLP-1R agonist therapy so as to improve patient adherence.

TARGET AUDIENCE

This activity is specifically designed for physician assistants and nurse practitioners involved in the treatment of patients with type 2 diabetes mellitus.

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Integrating Incretin-Based Therapy Into Patient Care

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On July 29, 2011, only 60% of the physician assistants and nurse practitioners at the Metabolic and Endocrine Disease Summit (MEDS) in Orlando, Florida, indicated that they intensify glucose-lowering therapy when the glycated hemoglobin (A1c) level has been 7.0% or higher for 3 months or more. This finding suggests that 40% of physician assistants and nurse practitioners practice outside the current American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommendations, which indicate that therapy should be adjusted or advanced every 2 to 3 months if the appropriate glycemic goal has not been achieved.[1] That goal is less than 7.0% for most patients with type 2 diabetes mellitus (T2DM), according to the American Diabetes Association (ADA).[2]

MEDS, which was cosponsored by the Primary Care Metabolic Group and Clinician Reviews, was attended by nearly 300 physician assistants and nurse practitioners. Answers to other questions asked during the summit showed that attendees had a limited understanding of the differences between the glucagon-like peptide-1 receptor (GLP-1R) agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as limited knowledge of simple strategies for promoting patient adherence to therapy with a GLP-1R agonist. This 2-article supplement addresses these 2 central issues.

Role of Incretin System in Glucose Homeostasis

The incretin system is one of several processes that help control blood glucose levels. In healthy individuals, this system may be responsible for up to 70% of insulin secretion in response to ingestion of oral glucose or a meal.[3] Of the principal gut incretin hormones, only GLP-1 has its effects preserved in patients with T2DM. Consequently, GLP-1 is an important therapeutic target in the treatment of patients with T2DM. GLP-1 is rapidly secreted in response to food ingestion. However, as GLP-1 is rapidly cleared through the action of the enzyme DPP-4, GLP-1R agonists and DPP-4 inhibitors have been developed to manage T2DM but not type 1 diabetes mellitus. The GLP-1R agonists (exenatide, liraglutide) resist degradation by DPP-4 and

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bind to the GLP-1 receptor. The DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin) bind to DPP-4, thereby prolonging the activity of endogenous GLP-1.

The several-fold higher level of GLP-1 achieved with use of GLP-1R agonists[4] over DPP-4 inhibitors[5] is thought to contribute to important differences between these classes of agents (Table 1). GLP-1R agonists and DPP-4 inhibitors both increase insulin biosynthesis[6-10] and inhibit glucagon secretion[6,8,9,11-14] in a glucose-dependent manner. However, only GLP-1R agonists have been shown to slow gastric emptying[8,15] and promote satiety.[8,16,17]

Glycemic Efficacy

One of the most important differences between GLP-1R agonists and DPP-4 inhibitors is the magnitude by which they lower blood glucose levels. When used alone or added to other glucose-lowering therapy, GLP-1R agonists lower A1c by 0.5% to 1.5%,[18-20] whereas DPP-4 inhibitors lower A1c by 0.5% to 0.8%.[9,10,21-26] In addition, as add-on therapy, GLP-1R agonists lower fasting plasma glucose (FPG) by 7 to 74 mg/dL, and DPP-4 inhibitors lower FPG by 11 to 29 mg/dL[9,26-32]; postprandial glucose (PPG) is reduced by 41 to 47 mg/dL with use of add-on GLP-1R agonists and by 49 to 68 mg/dL with use of add-on DPP-4 inhibitors.[9,25,26,33]

Head-to-Head Comparisons

Incretin-based therapies have been compared one with another in several randomized clinical trials. In a 26-week trial, patients with glycemia inadequately controlled with metformin, sulfonylurea, or both received exenatide 10 µg twice daily or liraglutide 1.8 mg once daily.[13] A1c levels were reduced by 0.79% with exenatide and 1.12% with liraglutide, and FPG levels were reduced by 11 mg/dL and 29 mg/dL, respectively. The larger reduction in FPG with use of liraglutide may stem from the longer elimination half-life of that medication (13 hours)[34] compared with exenatide (2.4 hours).[35] Reductions in body weight were similar between the groups, but minor hypoglycemia affected fewer patients in the liraglutide group (26%) than in the exenatide group (34%). During a 14-week extension phase, A1c levels decreased another 0.3% in patients switched from exenatide to liraglutide 1.8 mg once daily and 0.1% in patients who continued with liraglutide.[36]

Two trials have compared exenatide with sitagliptin. In the first, a 6-week crossover trial, patients received either exenatide 5 µg twice daily for 1 week followed by 10 µg twice daily for 1 week, or sitagliptin 100 mg once daily for 2 weeks.[8] From a baseline of 178 mg/dL, FPG levels decreased to 163 mg/dL in patients treated with exenatide and to 159 mg/dL in those treated with sitagliptin. In addition, from a baseline of 245 mg/dL, PPG levels decreased to 133 mg/dL and 208 mg/dL, respectively. After the crossover, PPG levels increased 73 mg/dL in patients switched from exenatide to sitagliptin but decreased 76 mg/dL in patients switched from sitagliptin to exenatide. In the second, 4-week open-label trial, patients receiving insulin glargine and metformin were given exenatide 5 or 10 µg twice daily or sitagliptin 100 mg once daily.[37] A1c levels decreased 1.9% in patients treated with exenatide add-on therapy, 1.5% in patients treated with sitagliptin add-on therapy, and 1.2% in patients treated with insulin glargine and metformin only. The 6-hour PPG excursion was significantly smaller in the exenatide and sitagliptin add-on groups compared with the glargine-and-metformin group ($P < .01$ and $P < .001$, respectively).

Liraglutide has been compared with sitagliptin as add-on therapy in patients with glycemia inadequately controlled with metformin. From a baseline of 8.4% to 8.5%, A1c levels decreased 1.2% and 1.5% in patients treated with liraglutide 1.2 or 1.8 mg once daily, respectively, and 0.9% in patients treated with sitagliptin after 26 weeks.[38] FPG levels decreased 34 mg/dL, 39 mg/dL, and 15 mg/dL, respectively. After another 26 weeks, further reductions were noted. From baseline to

TABLE 1 Actions of GLP-1R agonists and DPP-4 inhibitors in regulating glucose homeostasis.

	Physiologic		Pharmacologic		
	↑ Insulin secretion (glucose-dependent)	↓ Glucagon secretion (glucose-dependent)	Promote satiety	Weight effect	↓ Gastric emptying rate
GLP-1R Agonists	Yes	Yes	Yes	↓ 1-4 kg	Yes
DPP-4 Inhibitors	Yes	Yes	No effect	↔	No effect

52 weeks, A1c levels decreased 1.3% and 1.5% in the liraglutide 1.2 and 1.8 mg groups, respectively, and 0.9% in the sitagliptin group.[39] FPG levels decreased 31 mg/dL, 37 mg/dL, and 11 mg/dL, respectively.

Another head-to-head trial compared sitagliptin 100 mg once daily with saxagliptin 5 mg once daily in patients with A1c levels of 6.5% to 10% on stable doses of metformin.[40] After 18 weeks, A1c levels decreased 0.6% in patients treated with sitagliptin and 0.5% in patients treated with saxagliptin from a baseline of 7.7%.

Nonglycemic Effects

GLP-1R agonists and DPP-4 inhibitors have nonglycemic effects that are clinically important, again with some differences between these classes of agents.

Weight

As already noted, GLP-1R agonists (but not DPP-4 inhibitors) promote satiety, which in turn reduces caloric intake.[8,17,41] Treatment with a GLP-1R agonist over several months is thought to result in a mean weight loss of 1 to 4 kg in most patients.[18,20,27-31,42] Nausea appears to have no impact on weight loss; the amount of weight lost by patients who have nausea for less than 7 days is similar to the amount lost by patients who have nausea for 7 days or more.[20] In addition, weightloss has been sustained for up to 3½ years.[42,43] DPP-4 inhibitors are considered weight-neutral, though some patients treated with these agents experience a slight decrease or slight increase in weight.[14,21-23,44,45]

Blood Pressure and Blood Lipids

The effects of the GLP-1R agonists and DPP-4 inhibitors on cardiovascular biomarkers, specifically blood pressure and the lipid profile, have been investigated in many trials. Although modest, these effects can be considered an attribute, as cardiovascular risk is not adversely affected (as is the case with some other glucose-lowering agents). GLP-1R agonists lower systolic blood pressure 1 to 7 mm Hg but do not change diastolic blood pressure or heart rate.[13,20,28-31,36,38,46-49] The effects of DPP-4 inhibitors on blood pressure are small.[21,45]

The lipid profile, notably the triglyceride level, is often improved with use of GLP-1R agonists; whether this improvement results from a reduction in blood glucose or from another mechanism is unknown. A reduction in the triglyceride level of 0 to 44 mg/dL has been observed with the GLP-1R agonists.[13,28,29,31,38,39,42,47] A change in the triglyceride level ranging from an increase of 16 mg/dL to a decrease of 35 mg/dL has been observed with the DPP-4 inhibitors.[21,45]

Safety and Tolerability

Although the long-term safety of GLP-1R agonists and DPP-4 inhibitors has not been established, it is being actively investigated, and these classes of agents have an important advantage in their safety profiles. Adverse events occurring in 5% or more of patients are generally mild and do not lead to treatment discontinuation. Diarrhea, headache, and dizziness are common adverse events observed with GLP-1R agonists,[34,35] and upper respiratory tract infection, nasopharyngitis, and headache are common with DPP-4 inhibitors.[50-52]

Hypoglycemia

With use of GLP-1R agonists[18,20,46,53] and DPP-4 inhibitors,[21-23,44,54,55] the incidence of hypoglycemia is low—likely the result of the glucose-dependent manner of stimulation of insulin release and inhibition of glucagon secretion observed with both classes of agents. Severe hypoglycemia has not been reported in monotherapy trials of exenatide,[18,46] liraglutide,[20,53] sitagliptin,[21,56] saxagliptin,[22] and linagliptin.[23] In fact, the ADA/European Association for the Study of Diabetes (EASD) recommends use of GLP-1R agonists in patients in whom hypoglycemia is a major concern, such as patients with hazardous jobs.[57] In addition, the US Federal Aviation Administration lists both classes of agents as allowable for aviators.[58] However, when either a GLP-1R agonist or a DPP-4 inhibitor is combined with a sulfonylurea, the incidence of mild to moderate hypoglycemia increases, affecting up to 36% of patients.[14,59] Consequently, when a sulfonylurea is combined with a GLP-1R agonist or a DPP-4 inhibitor, the dose of the sulfonylurea should be reduced by half.

Nausea

Transient nausea is common with GLP-1R agonists,[18,20,46] whereas the incidence of nausea with DPP-4 inhibitors is similar to that with placebo.[22,44,54] Use of a dose-escalation strategy is now recommended when initiating therapy with a GLP-1R agonist.[34,35]

Acute Pancreatitis

Acute pancreatitis has been observed in some patients treated with exenatide,[35] liraglutide,[34] sitagliptin,[50] and linagliptin.[52] However, because the risk for pancreatitis is almost 3 times higher for patients with T2DM than for

TABLE 2 Use in special populations

Population	GLP-1R Agonist		DPP-4 Inhibitor		
	Exenatide	Liraglutide	Sitagliptin	Saxagliptin	Linagliptin
Kidney dysfunction/ decreased creatinine clearance	<30 mL/min: contraindicated 30-50 mL/min: caution 50-80 mL/min: no change in dose	Use with caution; no change in dose	<30 mL/min: 25 mg once daily 30-49 mL/min: 50 mg once daily ≥50 mL/min: no change in dose	<50 mL/min: 2.5 mg once daily	No change in dose
Pregnant	Category C		Category B		
Lactating	Discontinue nursing or medication		Caution		
Elderly	Take care in dose selection based on renal function	No effect of age on pharmacokinetics	Take care in dose selection based on renal function	Take care in dose selection based on renal function	No change in dose

patients without diabetes,[60] it is not known whether these agents are indeed the cause. Analyses of the health insurance records of almost 350,000 patients have suggested that, compared with other glucose-lowering therapies, these 4 agents do not increase the risk for pancreatitis.[61,62] Exenatide, liraglutide, sitagliptin, saxagliptin, and linagliptin are undergoing further evaluation to clarify this issue.[63-67] In the interim, patients with a history of pancreatitis should not be treated with exenatide, liraglutide, or sitagliptin.[34,35,50] Patients treated with incretin-based therapy should be given information regarding the signs and symptoms of pancreatitis and the actions to be taken should they occur.

Hypersensitivity Reactions

Patients considering therapy with DPP-4 inhibitors should be informed that hypersensitivity reactions have been found with use of these agents. With sitagliptin, the most serious hypersensitivity reaction is Stevens-Johnson syndrome (commonly characterized by fever, itching, bull's-eye sores, bullae, and joint aches); anaphylaxis and angioedema also may occur.[50] With saxagliptin, 1% to 2% of patients develop urticaria and facial edema.[51] Linagliptin may cause urticaria, angioedema, localized skin exfoliation, and bronchial hyperreactivity.[34] The US Food and Drug Administration (FDA) has required that saxagliptin[67] and linagliptin[68] be investigated further.

Medullary Thyroid Cancer

Among the ongoing safety investigations with GLP-1R agonists are those being conducted to determine if there is an association with medullary thyroid cancer (MTC). The possibility of an association surfaced in postmarketing reports for exenatide[64] and during the FDA review of the new drug application for liraglutide.[63,65] Data from rodent and monkey studies suggest that GLP-1R agonists are unlikely to cause MTC.[69] Indeed, thyroid tumors have been found in animals administered native GLP-1.[70] Two-year follow-up data with liraglutide showed no increase in mean calcitonin level, a marker for MTC.[43] The prescribing information for liraglutide includes a boxed warning describing the findings in rodents as well as the risk for MTC. Liraglutide is also contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2.[34] An association between thyroid cancer and DPP-4 inhibitors has not been found.[50-52]

Cardiovascular Events

In December 2008, the FDA adopted new standards for the cardiovascular safety of all antidiabetic medications. As the clinical evaluations of liraglutide, saxagliptin, and linagliptin had already been completed but did not meet these new standards, the FDA required further investigation of cardiovascular events.[65,67,68] It is worth noting that systematic reviews of clinical trials have indicated that, compared with other glucose-lowering agents, GLP-1R agonists and DPP-4 inhibitors are not associated with increased risk for adverse cardiovascular events.[71-75]

Use in Special Populations

Renal Impairment

As renal impairment is common in patients with T2DM and is present in 1 in 8 patients newly diagnosed with T2DM,[76] and as exenatide, sitagliptin, and saxagliptin are cleared predominantly by the kidneys, careful attention must be given to kidney function and medication selection and dosing to reduce the risk for hypoglycemia with these 3 agents[35,50,51] **(Table 2).** As the renal clearance of liraglutide and linagliptin is minor, dosage need not be adjusted in patients with renal impairment, though caution with use of liraglutide and linagliptin is advised.[34,52]

Pregnancy and Lactation

There have been no adequate, well-controlled studies of use of GLP-1R agonists or DPP-4 inhibitors in pregnant women. Given that the potential risk of exenatide and liraglutide to the fetus has not been investigated (category C), use of either medication during pregnancy should be considered only if the potential benefit to the mother justifies the potential risk to the fetus.[34,35] Similarly, exenatide and liraglutide should not be used by a woman who is nursing, or nursing should be discontinued while either medication is used.[34,35]

On the basis of animal data, DPP-4 inhibitors are classified as category B during pregnancy. It has been suggested that sitagliptin, saxagliptin, or linagliptin be used during pregnancy only if clearly needed.[50-52] Similarly, caution should be exercised when administering a DPP-4 inhibitor to a woman who is nursing.[50-52]

Pediatrics

The safety and effectiveness of GLP-1R agonists and DPP-4 inhibitors have not been established in pediatric patients.[34,35,50-52]

Drug Interactions

Some drug interactions with GLP-1R agonists or with DPP-4 inhibitors are possible. GLP-1R agonists slow gastric emptying, which may alter absorption of oral medications. Therefore, medications that have a narrow therapeutic index or that require rapid gastrointestinal absorption should be used cautiously with GLP-1R agonists and should be closely monitored.[34,35] Although sitagliptin has been noted to slightly increase the peak concentration of digoxin, no dosage adjustment of digoxin or sitagliptin is recommended.[50] The dosage of saxagliptin should be reduced to 2.5 mg once daily when administered with a strong cytochrome P450 3A4/5 inhibitor, such as ketoconazole, itraconazole, clarithromycin, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir, or nefazodone.[51] Conversely, the clearance of linagliptin is increased when administered with a strong P-glycoprotein or cytochrome P450 3A4 inducer, such as rifampin; thus, the combination should be avoided.[52]

Conclusion

GLP-1R agonists and DPP-4 inhibitors can be effective in treating T2DM. These medications have several advantages over other classes of diabetes medications—such as lowering blood glucose levels without increasing the risk for hypoglycemia—and have favorable or neutral effects on body weight. In clinical trials, they have been shown to be effective as monotherapy, in combination with other agents, and, in the case of DPP-4 inhibitors, in combination with basal insulin. GLP-1R agonists are more potent than DPP-4 inhibitors in lowering glucose levels and are associated with weight loss; therefore, use of GLP-1R agonists is preferred in patients with high levels of A1c and in patients who would benefit from weight loss. On the other hand, DPP-4 inhibitors are oral agents and usually do not cause nausea, which occasionally is significant in patients treated with GLP-1R agonists. Both GLP-1R agonists and DPP-4 inhibitors are good choices when hypoglycemia is a particular concern. ■

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Clinician Reviews

Improving Adherence to Glucagon-Like Peptide-1 Receptor Agonist Therapy

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Determining whether a medication is appropriate for a patient requires understanding the benefits and limitations of the medication as well as the needs, interests, and capabilities of the patient. Having an open dialogue based on mutual trust is essential to understanding any barriers the patient has and determining how to address them. Failure to take this important step is likely to lead to poor medication adherence. With respect to glucagon-like peptide-1 receptor (GLP-1R) agonists, this article describes some of the more common barriers, and how clinicians might help patients with type 2 diabetes mellitus (T2DM) to overcome these barriers.

Psychological Concerns

In the international Diabetes Attitudes, Wishes, and Needs (DAWN) study, psychological concerns were common in patients with diabetes, even 15 years after diagnosis, and these concerns negatively affected treatment adherence.[1] Some of these concerns relate to diabetes-related stress and burnout and worsening diabetes. It is imperative, therefore, that these concerns be addressed through the course of the disease. Before initiation of GLP-1R agonist therapy, several steps can be taken to reduce patient concerns and improve motivation. The involvement of other health care team members, such as certified diabetes educators and pharmacists, may be helpful.

Weight and Hypoglycemia

First, the patient should be educated regarding the effects of GLP-1R agonists on weight and hypoglycemia. The 1- to 4-kg weight loss experienced by most patients[2-5] has been reported to contribute to improved quality of life in those treated with exenatide[6] or liraglutide in comparison with glimepiride[7] or sitagliptin.[8] Informing the patient that the risk for hypoglycemia, particularly severe hypoglycemia, is low with GLP-1R agonist monotherapy may also reduce concerns, especially because hypoglycemia is a common complication with sulfonylureas and glinides. Conversely, sensing that glycemic control is improved and that hyperglycemia is occurring less frequently increases satisfaction levels in patients treated with liraglutide.[7-9] Hypoglycemia is more common when a GLP-1R agonist is added to a sulfonylurea or glinide; it is therefore recommended that the dose of the sulfonylurea or glinide be reduced when a GLP-1R agonist is used as add-on therapy.[10,11]

Cardiovascular Markers

Concerns also may be reduced by educating the patient about the effects of GLP-1R agonists on systolic blood pressure and the lipid profile, particularly the triglyceride level. Although GLP-1R agonists are not used as primary therapy to lower blood pressure or to improve the lipid profile, and their long-term effects on cardiovascular endpoints, such as myocardial infarction and stroke, are not known, the blood pressure and lipid effects of these medications support the overall effort to reduce cardiovascular risk.

Pancreatic β-Cell Function

Educating the patient regarding the pathophysiology of T2DM and the progressive nature of the disease, which ultimately leads to progressive pancreatic β-cell failure, should begin at the time of diagnosis. It is important, when modifying therapy, to provide education about the treatment, about its impact on disease pathophysiology, and about the durability of its effect so that the patient can establish realistic goals and understand the likely need for further treatment modification. In the case of GLP-1R agonists, the patient should be told about the preliminary evidence suggesting a benefit for pancreatic β-cell function.[12,13] In addition, the sustained glycemic benefits of exenatide (up to 3 years[14-17]) and liraglutide (up to 2 years)[18] should be described.

Needle Phobia

Fear of needles and fear of self-injection are often thought to be major barriers to insulin therapy.[1,19-21] In most cases, these barriers can be overcome by educating the patient and individualizing therapy.[22] One investigation found that barriers to insulin therapy were overcome simply by initiating insulin therapy with appropriate patient support.[19] As GLP-1R agonists are administered subcutaneously, concerns regarding self-injection should be identified and discussed. Concerns about self-injection can be allayed by demonstrating use of one of the pen devices while emphasizing its user-friendly features and the ultra-fine needles that enable near painless injections. In addition, patient concerns about self-injection can often be eased by having the patient self-inject a dose while in the office.

Complexity

Self-injection often elicits reluctance, anxiety, or fear owing to the perceived complexity of the dosing and treatment schedule. Beyond addressing issues related to needle phobia, it is helpful to inform the patient that the dosing regimen of GLP-1R agonists may be more flexible than that of insulin. For example, exenatide is adminis-

tered twice daily, within an hour of eating, and liraglutide is administered once daily, without regard to meals.

Cost

Cost is an important consideration for most patients and should be discussed before selecting any glucose-lowering therapy, including GLP-1R agonist therapy. As copayments and out-of-pocket costs vary among health insurance plans, determining the actual cost to the patient and openly discussing affordability can eliminate or reduce a common barrier to medication adherence. This discussion is especially important for the patient who does not have insurance or who has a plan with a high deductible. For the patient who meets the requirements, assistance from the drug manufacturer or from the Partnership for Prescription Assistance is available. The patient can be directed to these web sites for information:

- Exenatide: http://www.amylin.com/products/patient-assistance-program.htm
- Liraglutide: http://www.novomedlink.com/diabetes/patient-assistance-program.aspx
- Partnership for Prescription Assistance: http://www.pparx.org

Nausea and Vomiting

As noted in the first article in this supplement, transient nausea is common with GLP-1R agonists, but its incidence can be reduced with use of a dose-escalation strategy. For exenatide, the initial dose should be 5 µg twice daily, given within 60 minutes of the morning and evening meals. Taking exenatide closer to mealtime may also minimize nausea. The dose of exenatide can be increased to 10 µg twice daily after 1 month, if needed, to further lower blood glucose levels.[10] For liraglutide, the initial dose should be 0.6 mg once daily. After 1 week, the dose should be increased to 1.2 mg once daily. If after several weeks glucose goals are not achieved, the dose can be increased to 1.8 mg once daily.[11] Anecdotal reports suggest another strategy for reducing nausea and vomiting: eat smaller portions and reduce the fat content of meals.

Summary

Psychological concerns are some of the possible barriers to treatment adherence for patients with T2DM. Identifying factors that may account for these concerns and identifying possible solutions in collaboration with the patient are crucial in improving treatment adherence. Citing the many benefits of GLP-1R agonist therapy—its glucose-lowering efficacy, the weight loss, the low incidence of hypoglycemia, and the impact on cardiovascular biomarkers and pancreatic β-cell function—may ease patient concerns and promote treatment adherence. Simple strategies can be used to address other potential barriers associated with GLP-1R agonist therapy, such as needle phobia, perceived treatment complexity, cost, and nausea and vomiting. ■

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