



UPDATE ON TYPE 2 DIABETES: Incorporating Incretin-Based Strategies Into Treatment

Learning Objectives

After completing this activity, participants should be better able to:

- Summarize the pharmacologic effects of incretin-based therapies in the treatment of type 2 diabetes
- Specify the glucose-lowering ability of the 2 major classes of incretin-based therapies
- Explain the effects of glucagon-like peptide-1 (GLP-1) analogs on weight and other cardiometabolic risk factors for patients with type 2 diabetes, based on evidence from recent clinical trials
- Develop treatment plans for type 2 diabetes that incorporate incretin-based therapies

Beyond Insulin Resistance and Deficiency: Incretin-Based Therapies for Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and impaired insulin secretion, the latter leading to a state of insulin deficiency. However, other physiologic defects also occur, such as increased pancreatic glucagon production, an impaired incretin effect resulting in increased hepatic glucose production and increased gastric-emptying rates. These can now be addressed by therapies with different mechanisms of action. Recent developments to target these defects have focused on incretins.

Incretins are peptide hormones secreted by endocrine cells in the gastrointestinal tract.¹ In healthy individuals, glucose given orally enhances beta-cell insulin secretion substantially more than glucose administered intravenously.² This difference is the “incretin effect.” It results from the inability of intravenous glucose to stimulate the release of these gut hormones, particularly glucagon-like peptide-1 (GLP-1). GLP-1 and another physiologically relevant incretin hormone, glucose-dependent insulinotropic

GLP-1 is expressed in many tissues, where it may provide additional benefits, including cardioprotection.

What factors are associated with the weight loss observed during GLP-1 agonist therapy?

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polypeptide (GIP), play a significant role in maintaining normal glucose concentrations, especially during the postprandial period.³ Both are also rapidly degraded by the endogenous dipeptidyl peptidase 4 (DPP-4) enzyme.

In patients with T2DM, the incretin response is impaired.⁴ GLP-1 production is reduced in response to a meal and further destroyed by DPP-4. GIP activity is also impaired, although to a lesser extent than GLP-1. GIP stimulates insulin response from beta cells in a glucose-dependent manner, but unlike GLP-1, appears not to inhibit glucagon secretion from alpha cells. GIP has minimal effects on gastric emptying and no significant effects on satiety.⁵ GIP secretion is increased in patients with T2DM, but beta cells are resistant to its effects in the setting of T2DM. Therefore, infusion of exogenous GIP in patients with T2DM is of little help in restoring the incretin effect. However, exogenous GLP-1 retains biologic activity and can control hyperglycemia by various effects in patients with T2DM (Figure 1). These effects lead to reductions in fasting plasma glucose (FPG) and postprandial glucose (PPG) that make it useful for treating hyperglycemia in patients with T2DM.⁵ Targeting fasting glucose and post-meal glucose has physiologic and treatment advantages.

GLP-1 is expressed in many tissues, where it may provide additional beneficial effects. Its actions include⁶:

- Decreasing gastric emptying, thereby slowing the processing of nutrients and increasing satiety
- Suppressing appetite and increasing satiety via direct effects on the central nervous system
- Positively influencing cardiac function

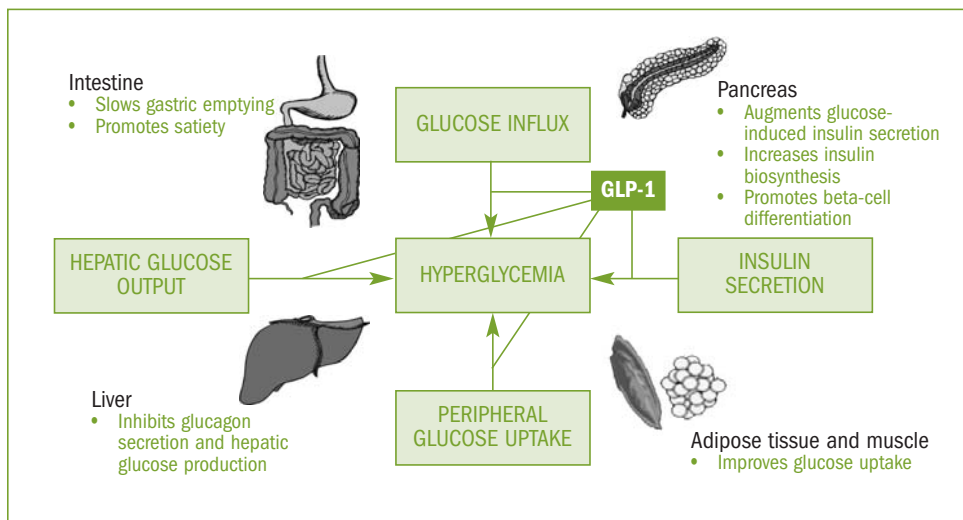


Figure 1. GLP-1 elicits multiple effects in the control of hyperglycemia.

- Increasing beta-cell proliferation and decreasing beta-cell apoptosis in human in vitro models

There are 2 classes of agents that improve incretin effects in humans (Figure 2):

- GLP-1 receptor agonists: injectable peptides that act as agonists of the GLP-1 receptor, which are more resistant to DPP-4 and so have longer action than human GLP-1
- DPP-4 inhibitors: oral agents that prolong the activity of endogenously released GLP-1 and GIP by inhibiting the DPP-4 enzyme

The major differences between GLP-1 agonists (also called incretin mimetics) and DPP-4 inhibitors are summarized in Table 1. GLP-1 agonists have more potent blood glucose-lowering abilities than DPP-4 inhibitors because they provide exogenous supraphysiologic replacement of the active GLP-1

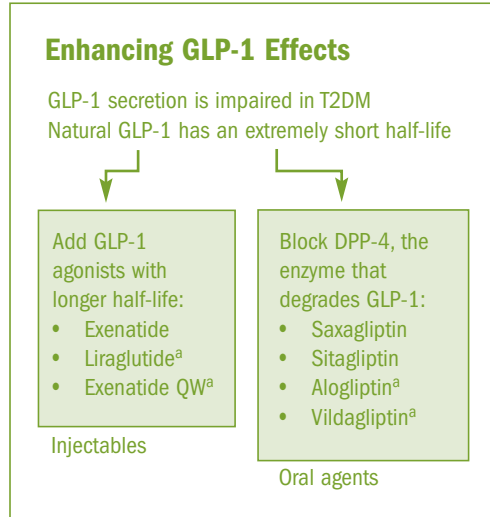


Figure 2. Incretin effects are improved by GLP-1 receptor agonists and DPP-4 inhibitors. ^aInvestigational.

Table 1. Incretin Therapies: Major Differences Between DPP-4 Inhibitors and GLP-1 Receptor Agonists

Properties/Effect	DPP-4 Inhibitors	GLP-1 Receptor Agonists
Glucose-dependent stimulation of insulin secretion	Yes	Yes
Glucose-dependent reduction of increased glucagon	Yes	Yes
Slows gastric emptying	No	Yes
Effect on body weight	Weight neutral	Weight loss
Side effects	Well tolerated	Nausea, vomiting
Hypoglycemia	No	No
Administration	Oral, once daily	Subcutaneous, twice daily

hormone. DPP-4 inhibitors block the active site of DPP-4, thereby preventing inactivation and prolonging the action of endogenous incretins. GIP levels are increased in patients with T2DM, but levels of GLP-1 (which has more significant pharmacologic effects) are decreased.

GLP-1 receptor agonists include exenatide (approved in 2005), a long-acting formulation of exenatide (exenatide QW, currently investigational), and liraglutide (under review by the US Food and Drug Administration [FDA]). DPP-4 inhibitors include sitagliptin (approved in 2006), saxagliptin (approved July 2009), alogliptin (investigational), and several others. Vildagliptin is currently available only in Europe.

Because incretin-based therapies work in a glucose-dependent manner, they cannot lower blood glucose levels in the absence of hyperglycemia. Therefore, they are associated with a very low risk of hypoglycemia. Unlike other classes of antidiabetic medications, these agents do not cause weight gain (GLP-1 agonists) or are weight neutral (DPP-4 inhibitors).

Exenatide is a synthetic version of the GLP-1 protein identified in the saliva of the Gila monster. Exenatide has >50% amino acid–sequence identity with human GLP-1 and is resistant to DPP-4 inactivation. Its primary pharmacologic effect is reduction of postprandial hyperglycemia. An extended-release formulation is being investigated. Poly (D,L-lactide-co-glycolide) (PLG), probably the most popular biodegradable polymer in polymeric controlled-release formulations, is being used to extend the action of exenatide so it can be used as a once-weekly injectable agent (rather than a twice-daily injectable).

Liraglutide is a human GLP-1 derivative, with 97% homology to human GLP-1. This investigational agent is being used subcutaneously once daily. Creating a longer acting molecule for liraglutide involves use of a fatty-acid chain that improves albumin binding and self-association to extend the duration of action. Both longer acting formulations appear to lower postprandial and fasting hyperglycemia and appear to have more potent antihyperglycemic effects than the shorter acting exenatide.

Clinical Applications of Incretin-Based Therapies to Improve Glucose Control: Data for Monotherapy and Combination Therapy Efficacy

DPP-4 inhibitors are oral once-daily agents. They can be used as monotherapy or in combination therapy. These agents do not appear in the current version of the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus statement on the management of hyperglycemia in T2DM (Figure 3),⁷ primarily because of their cost and modest glucose-lowering potential. However, they are extremely well tolerated, have a very low risk of hypoglycemia, and are weight neutral. The American Association of Clinical Endocrinologists Roadmap does include DPP-4 inhibitors. Thus, they may be appropriate for patients who cannot tolerate metformin, sulfonylureas, thiazolidinediones (TZDs), or insulin; or are near (but not at) goal on more established therapies.

In monotherapy trials, 100 mg of sitagliptin resulted in A1C lowering of approximately 0.8%.⁸ A1C reductions of approximately 1.6% to 2.0% were observed when sitagliptin was

added to metformin,⁸ although Nauck et al⁹ demonstrated more modest reductions with the metformin/sitagliptin combination (0.6%). A1C reductions observed with sitagliptin and pioglitazone were approximately 0.7%.¹⁰ Saxagliptin was approved by the FDA on July 31, 2009. Published data are limited, but a recent study showed saxagliptin to be efficacious in drug-naïve patients with T2DM; the A1C reduction was approximately 0.5%.¹¹ Alogliptin also is being reviewed by the FDA. Several studies support its safety and efficacy as monotherapy¹² and in combination with metformin,¹³ pioglitazone,¹⁴ glyburide,¹⁵ or insulin.¹⁶

In contrast to DPP-4 inhibitors, GLP-1 agonists do appear in the current ADA/EASD algorithm as a treatment option for patients with T2DM who are not at treatment goals despite lifestyle modification and metformin therapy (Figure 3).⁷ Exenatide is approved for combination use with metformin, a sulfonylurea, and/or a TZD. Exenatide is not approved for use in combination with insulin. Although not indicated for monotherapy, exenatide has been shown in a clinical study to be effective in drug-naïve patients with type 2 diabetes.¹⁷ Further safety and efficacy data are needed to support such use. Compared with short-acting

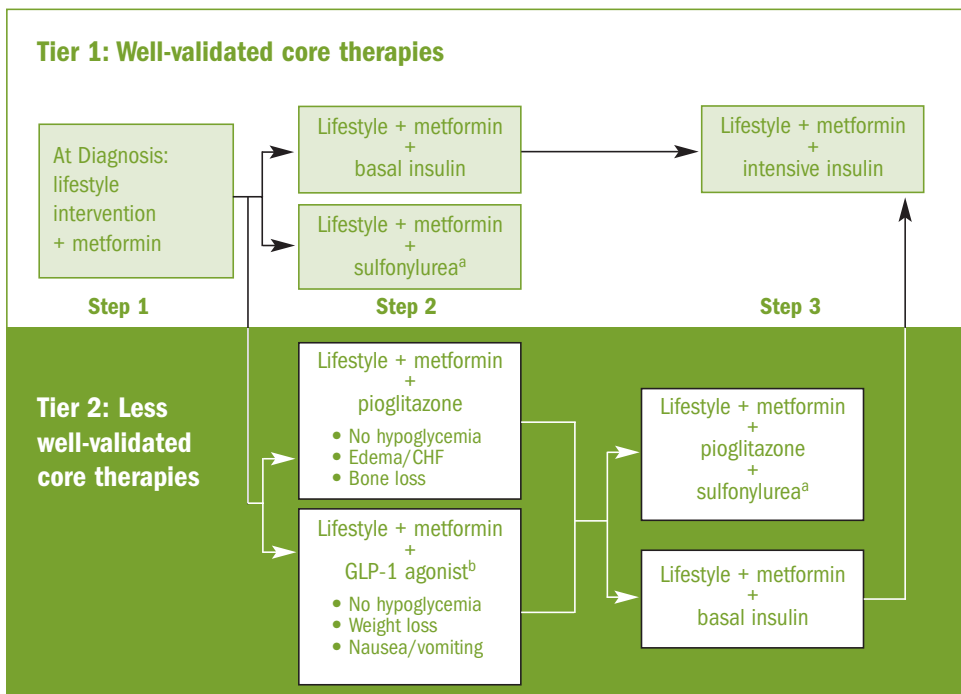


Figure 3. ADA/EASD 2009 consensus treatment algorithm for the management of hyperglycemia in T2DM. ^aExcludes glyburide or chlorpropamide; ^binsufficient clinical use to be confident regarding safety. CHF = congestive heart failure. Amylin agonists, alpha-glucosidase inhibitors, glinides, and DPP-4 inhibitors are not included in the 2 tiers of preferred agents in this algorithm owing to their lower or equivalent overall glucose-lowering effect and/or to their limited clinical data or relative expense compared with current tier 1 and tier 2 agents. Used with permission of *Diabetes Care*, from Nathan DM, et al⁷; permission conveyed through Copyright Clearance Center, Inc.

exenatide, which primarily reduces post-meal glucose levels only, the investigational long-acting formulation significantly reduces levels of both PPG and FPG.¹⁸ In patients with A1C levels <9%, both formulations lowered A1C levels significantly and similarly. For A1C levels ≥9%, the longer-acting formulation was significantly more effective. Weight loss appears to be similar for the 2 formulations.¹⁸ Twice-daily exenatide resulted in progressive reductions from baseline in body weight: -2.4 kg at 30 weeks and -5.3 kg at 3 years.¹⁹ These effects are more pronounced in those with greater body mass index at baseline.²⁰ Once therapy is discontinued, it appears that weight returns toward the baseline value.²¹

Liraglutide has undergone extensive clinical study as monotherapy and with all major classes of oral agents. Monotherapy has produced A1C placebo-subtracted reductions of -1.7%, with demonstrated reductions in both FPG and PPG.²² A randomized placebo-controlled trial compared liraglutide as an add-on to metformin therapy (ie, ADA/EASD “step-2” therapy) with another step-2 agent, a sulfonyleurea (glimepiride). Once-daily liraglutide combined with metformin resulted in similar glycemic control, reduced body weight, and a lower occurrence of hypoglycemia compared with glimepiride combined with metformin.²³ With respect to

Table 2. LEAD Studies: Liraglutide Combination Intervention—Effect on Weight

LEAD Study #	N	Weeks	Intervention	Weight Effect (kg @ Lirag 1.8 mg)
1 (Marre et al ²⁴)	1041	26	Glimep + lirag Glimep + rosi	-0.2 +2.1
2 (Nauck et al ²)	1091	26	Met + lirag Met + glimep	-2.8 +0.9
3 (Garber et al ²⁵)	746	52	Lirag 1.8 Glimep	-2.45 +1.12
4 (Zinman et al ²⁶)	533	26	Met + rosi + lirag Met + rosi	-2.02 +0.6
5 (Russell-Jones et al ²⁷)	581	26	Met + glimep + lirag Met + glimep + glargine Met + glimep	-1.8 +1.62 -0.42
6 (Blonde et al ²⁸)	464	26	Met and/or SU + lirag Met and/or SU + twice-daily exenatide	-3.84 -2.87

Glimep = glimepiride; lirag = liraglutide; rosi = rosiglitazone; met = metformin; SU = sulfonyleurea.

glucose-lowering ability, adding liraglutide to a sulfonylurea was more effective than adding a TZD to a sulfonylurea. Weight loss was observed in liraglutide-treated patients, and weight gain in TZD-treated patients.²⁴ Liraglutide induces weight loss regardless of the drug used in combination (Table 2). Preliminary data comparing liraglutide with other injectable agents also are available.²³⁻²⁸ Liraglutide resulted in significantly better glycemic control and weight reduction compared with insulin glargine when each of these agents was added to metformin and a sulfonylurea.²⁷ In a head-to-head study of liraglutide and the available short-acting exenatide used with metformin and/or a sulfonylurea, liraglutide was associated with greater A1C reductions, possibly owing to greater FPG reductions, and greater weight loss in 26 weeks.²⁸ Liraglutide also was associated with less hypoglycemia and less-persistent nausea.²⁸

Safety

DPP-4 inhibitors generally are well tolerated. They lack the gastrointestinal effects seen with metformin and alpha-glucosidase inhibitors taken alone. They also have a low risk of hypoglycemic events common to agents that directly lower blood glucose levels. However, hypoglycemia may occur when sitagliptin is used with sulfonylureas.²⁹ Dose reduction of sitagliptin is suggested for patients with kidney disease (from 100 to 50 mg/d) or with creatinine clearance of 30 to 50 mL/min; reduction to 25 mg daily is suggested for those with creatinine clearance <30 mL/min (product labeling). Sitagliptin has been safe and effective at doses of 25 mg, even in patients with end-stage renal disease on dialysis.³⁰ Patients with moderate or severe kidney impairment should receive no more than 2.5 mg/day of saxagliptin.

Hypoglycemia is uncommon with GLP-1 agonists, but it can occur. Patients should be educated about the signs and symptoms of hypoglycemia and methods of prevention and treatment. As with DPP-4 inhibitors, hypoglycemia is more common when GLP-1 agonists are combined with sulfonylureas. For reasons not well understood, hypoglycemia was more common at the initiation of exenatide therapy, then decreased over time. The primary adverse effects of GLP-1 agonists are gastrointestinal in nature. These present primarily as “feelings of fullness,” nausea and/or vomiting, and diarrhea. These effects appear to be dose-related and abate with continued treatment. Gastrointestinal side effects appear to be less common with liraglutide than exenatide.³¹ Pancreatitis has occurred in exenatide-treated patients; however, patients with T2DM may have an increased background risk of acute pancreatitis and biliary disease.³² Data from a large safety-surveillance database suggest that the likelihood of pancreatitis occurring in initiators of exenatide or sitagliptin is no greater than in initiators of metformin or glyburide.³³ Nonetheless, patients with T2DM should be advised to consult a clinician if they experience unexplained persistent severe abdominal pain, which may be accompanied by vomiting.

Benefits Beyond Glucose Control: What Else Do GLP-1 Agonists Offer?

In addition to the effects on weight noted previously, GLP-1 agonists may have other

pharmacologic effects of potential benefit to patients with T2DM. These include effects on the cardiovascular system. Cardiovascular disease is the primary cause of death for patients with T2DM. GLP-1 infusion in patients with New York Heart Association Class III/IV heart failure led to improved left ventricular (LV) ejection fraction, VO_2 max, 6-minute walk distance, and quality of life.³⁴ A pilot study of GLP-1 infusion after acute myocardial infarction and angioplasty resulted in reduced hospital stay and substantial improvement in LV wall motion.³⁵ Adjunctive exenatide treatment for ≥ 3 years in patients with T2DM produced not only sustained improvement in glycemic control and progressive weight reduction, but improvement in cardiovascular risk factors such as lipids and blood pressure. Triglycerides decreased 12%, total cholesterol decreased 5%, LDL-C decreased 6%, and HDL-C increased 24%.¹⁹ In studies of liraglutide in patients with T2DM, reductions in systolic blood pressure consistently have been observed.³⁶ The effect of liraglutide on biomarkers for cardiovascular risk in patients with T2DM was an exploratory end point in a recent clinical study by Courrèges and colleagues.³⁷ Significant decreases in plasminogen activator inhibitor-1, B-type natriuretic peptide (BNP), and triglyceride levels occurred after treatment with liraglutide. There was a nonsignificant (but dose-dependent) reduction in levels of high-sensitivity C-reactive protein. Although intriguing, these data require further exploration to determine their clinical relevance.

GLP-1 Agonists and Effects on T2DM Pathophysiology

Pancreatic beta-cell dysfunction and apoptosis are the hallmarks of T2DM, and therapeutic approaches to improve beta-cell survival and function remain a “holy grail” in efforts to improve T2DM treatment (“preserve the pancreas”). Short-term use of insulin in severely hyperglycemic patients at the time of diagnosis may result temporarily in remission, possibly due to a second-wind effect on beta cells.³⁸ Likewise, TZDs may have some positive effects on beta-cell function.³⁹

What is known about the effects of GLP-1 agonists on beta-cell function? Studies demonstrate that GLP-1 plays an important role in maintaining beta cells. Animal data show that GLP-1 receptor agonists induce beta-cell regeneration, proliferation, and mass; and reduce apoptosis. In humans, GLP-1 agonists have improved beta-cell responsiveness and restored first- and second-phase insulin secretion in a glucose-dependent manner.^{40,41} These restorations are crucial.

Choosing Between Incretin-Based Therapies: Patient Considerations

- If patients are close to, but not at, goal on combination therapy, then DPP-4 inhibitors may be useful. However, if additional A1C lowering of more than 1% is needed, the more potent GLP-1 agonists would be preferred
- Both classes of incretins are excellent choices for patients who have hypoglycemic unawareness, a job that does not permit use of insulin therapy (eg, long-distance truck driver), or for whom hypoglycemia is an especially worrisome potential side effect (eg, in the elderly at risk for falls)

- DPP-4 inhibitors are oral agents with a simple once-daily administration schedule. Patients must be willing to self-inject medication using a pen delivery device to benefit from GLP-1 agonist therapy
- Neither class of incretins is associated with weight gain, which is often a concern for patients with diabetes. Only GLP-1 agonists consistently have been associated with weight loss
- Incretin-based therapies represent a new mechanism of action with which to target the adverse effects of T2DM. They may be used in a complementary fashion with more traditional agents as part of combination treatment strategies

Read Q&A from the live symposia at www.practicingclinicians.com/H2_2009/incrqa.pdf

PCEFORUM

It's your turn. Post your comments
to this clinical question.



How do you manage a patient with diabetes who has an A1C $\geq 7.6\%$ and a history of repeated hypoglycemia reported by the patient?

Post your answer to this question and more on the PCE Forum www.practicingclinicians.com/forumhomestudy

CASE STUDY

A 55-Year-Old Woman With a 5-Year History of T2DM

Presentation

A 55-year-old woman who is a computer programmer has a 5-year history of T2DM. She has been on metformin (sensitizer) 1000 mg twice daily for 5 years and glimepiride (secretagogue) 4 mg/d for the past 2 years. She has been treated for dyslipidemia for 2 years with a statin. She does not smoke and uses alcohol modestly. She walks her dog twice a day (~30 minutes each time). When she comes in for her 6-month diabetes checkup, she has no complaints except gradual weight gain over the past year. Her A1C at the last checkup was 6.9%.



Physical Examination

- Well-developed, well-nourished female
- Blood pressure: 140/80 mm Hg
- Height: 5 ft 2 in
- Weight: 165 lb
- BMI: 30.2 kg/m² (obesity = BMI ≥30 kg/m²)
- Foot examination: normal
- Funduscopic examination: normal

Laboratory Results

- A1C: 8.0%
- FPG: 145 mg/dL
- Lipids
 - LDL-C: 78 mg/dL
 - Triglycerides: 130 mg/dL
 - HDL: 48 mg/dL
 - non-HDL: 108 mg/dL
- Electrolytes: normal
- Complete blood count (CBC): normal
- Thyroid-stimulating hormone: normal
- Test for urine microalbuminuria: negative

this patient's hyperglycemia?

- Add rosiglitazone (another sensitizer)
- Start intensive insulin therapy (insulin replacement)
- Add a DPP-4 inhibitor (incretin enhancer)
- Add a GLP-1 agonist (incretin mimetic)

The following treatment options are not sequential choices—potential advantages and drawbacks of each option for this patient are presented. In all 4 scenarios, therapeutic lifestyle changes should be reinforced. Referral to a diabetes educator and/or dietitian also may enhance this patient's outcome.

Option 1: Add a Thiazolidinedione Comment

If a TZD is started, pioglitazone is preferred. However, TZDs are associated with weight gain and peripheral edema, effects that may not be tolerated by this patient. In patients who require a decrease in A1C of >1%, use of 3 oral agents is unlikely to bring the patient to goal. TZDs also have been associated

Clinical Decision Point

What would be your next step in managing

with an increased risk of osteoporotic fracture in postmenopausal women. For these reasons, it is standard practice in many clinics to obtain BNP, CBC, and vitamin D levels (and DXA if appropriate) when initiating TZD therapy.

Option 2: Start Intensive Insulin Therapy

Comment

Using intensive insulin therapy after failure of metformin and a sulfonylurea is recommended in the ADA consensus statement on the management of hyperglycemia in T2DM, as a “step-3” therapy, that is, after combination therapy of metformin (+ lifestyle change) with a sulfonylurea, TZD, or basal insulin has been tried. Insulin remains the most powerful agent to lower blood glucose and certainly would lower the patient’s A1C level to <7%, the current ADA-recommended treatment goal. If insulin is started, the sulfonylurea could be reduced/ discontinued to lower the risk of hypoglycemia. Switching this patient to an intensive insulin regimen from her present 2-oral-agent regimen might be met with some resistance. The most common starting insulin strategy begins with a single injection of a basal insulin (24-hour) or a single injection of a premixed insulin. Insulin analogs provide more convenient and more physiologic insulin replacement with less hypoglycemia than human insulin (regular or isophane insulin [NPH]). Insulin therapy often is associated with weight gain, which may not be welcomed by this patient. The long-acting insulin analog detemir is associated with less weight gain than other basal insulins and might be an option for this patient.

Option 3: Add a DPP-4 Inhibitor

Comment

Adding an oral DPP-4 inhibitor would be an attractive choice for this patient. DPP-4 inhibitors are well tolerated and, compared with sulfonylureas (for example), do not result in weight gain or hypoglycemia. If a DPP-4 inhibitor is added, the dose of sulfonylurea might need to be reduced because concomitant use increases the risk for hypoglycemia. A DPP-4 inhibitor may not be the best choice for this patient because a decrease of at least 1.1% in A1C is required to achieve goal (A1C <7%). When sitagliptin was added to metformin therapy, it resulted in a 0.67% decrease in A1C, which was comparable to that achieved with glipizide in a recent randomized controlled trial.⁹

Option 4: Add a GLP-1 Agonist

Comment

Adding a GLP-1 agonist to this patient’s therapy has potential advantages. When used with metformin and a sulfonylurea, an A1C reduction of 1%⁴² to 1.3%²⁷ has been observed. This would be enough to achieve the goal level. In addition, GLP-1 agonists have been associated with sustained weight loss, which would appeal to this patient. If a GLP-1 agonist is started, the patient should be counseled about the likelihood of transient nausea and other gastrointestinal side effects. GLP-1 agonists are not associated with a high risk of hypoglycemia, but use with a sulfonylurea may increase this possibility and the sulfonylurea dose should be reduced. Currently available GLP-1 agonists are administered subcutaneously twice a day, 45 to 60 minutes before meals. In the future, longer acting agents will reduce the number of injections needed.

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