Who Wants to be a Diabetologist?
Individualizing Type 2 Diabetes Therapy with GLP-1R Agonists
November 2013
(Part 1 of 2)

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Authors

Edward Shahady, MD, FAAFP, ABCL
Medical Director
Diabetes Master Clinician Program
FAFP/F
Fernandina Beach, Florida
Clinical Professor of Family Medicine
University of Miami
Miami, Florida
Clinical Professor of Family Medicine
University of Florida
Gainesville, Florida

Eden M. Miller, DO
Executive Director and Co-Founder
Diabetes Nation
High Lakes Health Care
St. Charles Hospital
Bend, Oregon

Jeffrey R. Unger, MD
Director, Metabolic Studies
Catalina Research Institute
Associate Clinical Professor of Family Medicine
Loma Linda University School of Medicine
Loma Linda, California

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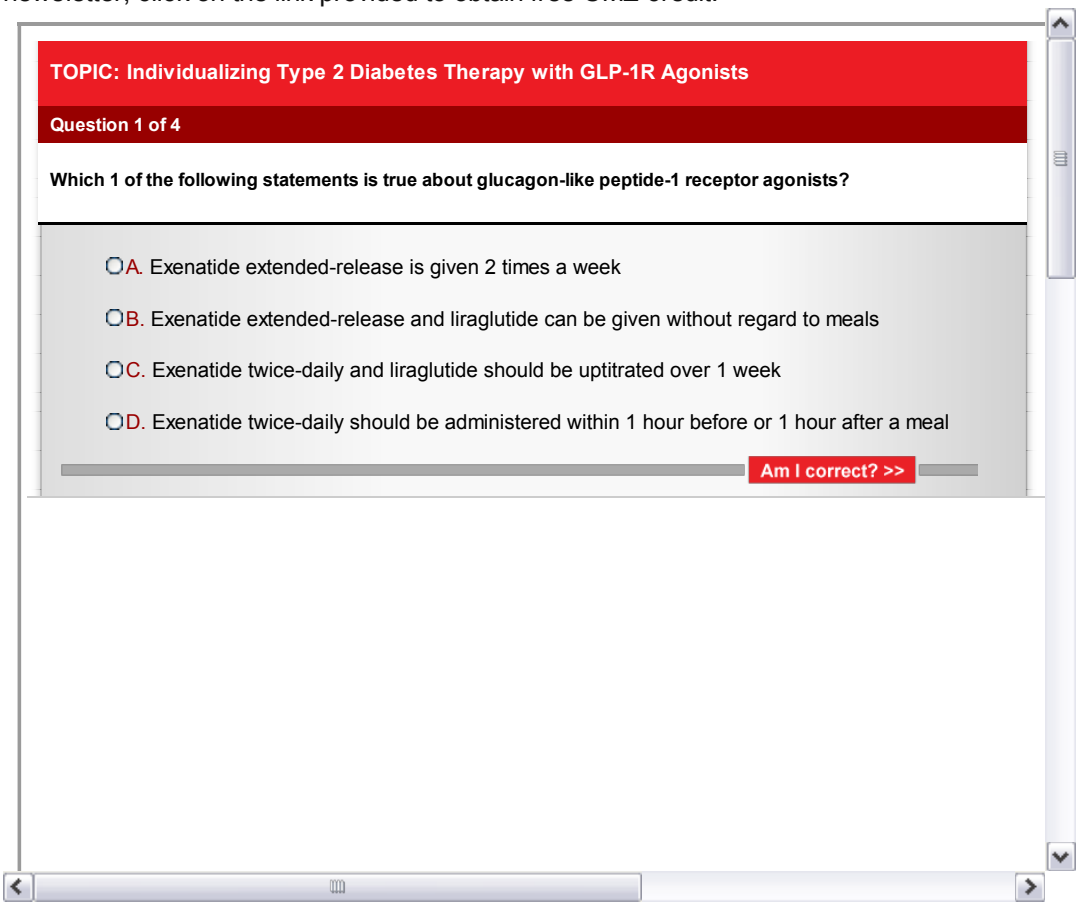

Glucagon-like peptide-1 receptor agonists in chronic kidney disease and when hypoglycemia is a special concern

Since approval of the first glucagon-like peptide-1 receptor (GLP-1R) agonist in the United States in 2005, this group of medications has taken an increasingly prominent role in the recommended management of individuals with type 2 diabetes mellitus (T2DM).[4,5] In this e-newsletter, the use of GLP-1R agonists in patients with kidney dysfunction, as well as their use when hypoglycemia is a special concern, will be explored. In an e-newsletter next month, the combined use of a GLP-1R agonist and basal insulin will be discussed.

The actions of the GLP-1R agonist on the incretin system produce several effects that are important in the treatment of patients with T2DM. First, the GLP-1R agonists stimulate insulin secretion and inhibit glucagon secretion, both in a glucose-dependent manner.[9-11] In addition, the GLP-1R agonists slow the gastric emptying rate.[12-14] The results of randomized clinical

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Learning Objectives

- Provide an overview of the rationale and role of incretin-based therapy as described in updated practice guidelines for the management of persons with T2DM
- Compare the efficacy, safety, and tolerability of the incretin-based therapies currently available
- Describe strategies to individualize treatment with a GLP-1R agonist

Target Audience

Family physicians and clinicians with an interest in diabetes treatment and management

Sponsor Disclosure Statement

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trials with GLP-1R agonists as monotherapy or in combination with 1 or more glucose-lowering agents show a reduction in glycated hemoglobin (HbA_{1c}) of 0.5% to 1.1% with exenatide twice daily (BID), 1.5% to 2.0% with exenatide once weekly (QW), and 0.5% to 1.5% with liraglutide.[6,15-21] The GLP-1R agonists typically lower systolic blood pressure (BP) 1 to 7 mm Hg, but have little effect on diastolic BP.[6,16,19,22-24] Of their effects on the lipid profile, the largest is on triglycerides, with a reduction of 12 to 40 mg/dL with the GLP-1R agonists.[6,19,22,25,26] The GLP-1R agonists have been compared in head-to-head clinical trials and the differences are summarized in the **Table**.[6,18,27,28]

Table. Head-to-head comparison of glucagon-like peptide-1 receptor agonists[6,18,27,28]

- HbA_{1c} reduction
  - Liraglutide 1.8 mg QD > exenatide 10 mcg BID
  - Exenatide 2 mg QW > exenatide 10 mcg BID
- FPG reduction
  - Liraglutide 1.8 mg QD > exenatide 10 mcg BID
  - Exenatide 2 mg QW > exenatide 10 mcg BID
- PPG reduction
  - Exenatide 10 mcg BID ≈ exenatide 2 mg QW
  - Exenatide 10 mcg BID ≥ liraglutide 1.8 mg QD
- Nausea
  - Exenatide 10 mcg BID > liraglutide 1.8 mg QD
  - Exenatide 10 mcg BID > exenatide 2 mg QW
- Proportion of patients who achieved HbA_{1c} <7%
  - Liraglutide 1.8 mg QD > exenatide 10 mcg BID
  - Exenatide 2 mg QW > exenatide 10 mcg BID
  - Liraglutide 1.8 mg QD > exenatide 2 mg QW

Abbreviations: BID, twice daily; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, postprandial glucose; QD, once daily; QW, once weekly.

CASE STUDY

A 67-year-old white male was diagnosed with T2DM 8 years ago. In the past 3 months, he has experienced 4 episodes of confirmed hypoglycemia (blood glucose <70 mg/dL).

- Past medical history: essential hypertension for 15 years; nonproliferative retinopathy; sleep apnea
- Social history: lives alone; smoker; 1 glass of wine before dinner
- Physical examination: BP, 142/90 mm Hg; weight, 194 lb; body mass index (BMI), 30 kg/m^2; 1+ distal sensory neuropathy; diabetic retinopathy
- Current treatment
  - Metformin 850 mg BID, glyburide 10 mg once daily, enalapril 20 mg once daily
  - Simvastatin 40 mg once daily
  - Stopped taking aspirin and lovastatin a year ago
  - Exercise: previously walked for 30 minutes daily; now exercises less due to fatigue and balance issues
- Laboratory
  - Total cholesterol, 245 mg/dL; low-density lipoprotein cholesterol (LDL-C), 135 mg/dL; high-density lipoprotein cholesterol (HDL-C), 38 mg/dL; triglycerides, 350 mg/dL; non–HDL-C, 207 mg/dL
  - Serum creatinine, 1.9 mg/dL; estimated glomerular filtration rate (eGFR), 36 mL/min/1.73 m^2; spot urine microalbumin ratio, 75 mcg/mg
  - HbA_{1c} levels since diagnosis: see table below

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Lifestyle | Metformin 850 mg BID

	Diagnosis	2 years	3 years	5 years	6.5 years	8 years
HbA_{1c} (%)	9.1	8.2	7.9	8.0	8.3	8.5
BMI (kg/m^2)	31	29	28	29	30	30
eGFR ($mL/min/1.73\ m^2$)	55	51	45	41	39	36

Appropriateness of current glucose-lowering therapy

Lifestyle management (nutrition and exercise), alone or in combination with metformin, is appropriate as initial therapy for patients with T2DM and should be continued throughout management. However, lifestyle management is generally associated with a 1% to 2% decrease in HbA_{1c} from baseline, which alone was unlikely to provide the glycemic improvement needed for this patient at the time of diagnosis.[29] Metformin was not initiated within a few months of diagnosis and he did not achieve acceptable glycemic control over the first 5 years since diagnosis. It is not clear why the addition of metformin 5 years after diagnosis had little effect on the patient's HbA_{1c}. The reason for this should be investigated, particularly adherence, given his history of discontinuing aspirin and lovastatin. His continuing hyperglycemia has contributed to the development of the observed microvascular complications of retinopathy, sensory neuropathy, and chronic kidney disease. Because of his uncontrolled hyperglycemia and microvascular complications, intensification of his glucose-lowering therapy is of paramount importance. However, before changes are made, the patient needs to be educated regarding the emerging consequences of his hyperglycemia, hypertension, and hyperlipidemia. Given his history of discontinuing medications, it is especially important to determine his willingness to make the needed changes to his treatment plan. Smoking cessation should also be discussed.

In considering changes to his glucose-lowering therapy, it is important to review the appropriateness of metformin. Although most patients achieve a reduction in HbA_{1c} of 1% to 2% from baseline with metformin, this patient achieved little benefit. Perhaps more importantly, his kidney function continues to decline and his eGFR is approaching 30 $mL/min/1.73\ m^2$, the level below which the use of metformin is not recommended.[30] For these reasons, discontinuing metformin in the near future should be considered.

His declining kidney function becomes an important consideration in selecting therapy. The glucose-lowering agents that can be used when the eGFR is <30 $mL/min/1.73\ m^2$ are pioglitazone, nateglinide, liraglutide, alogliptin, linagliptin, saxagliptin, sitagliptin, and pramlintide. Other factors to consider are his recent episodes of hypoglycemia, despite his HbA_{1c} being 8.5%. The reason for this, such as erratic eating patterns, should be investigated. Education regarding hypoglycemia recognition and management should also be undertaken and it may be helpful to provide a written action plan. When avoidance of hypoglycemia is an important treatment objective, the American Diabetes Association/European Association for the Study of Diabetes recommend the addition of a dipeptidyl peptidase-4 inhibitor, GLP-1R agonist, or thiazolidinedione.[4] According to the American Association of Clinical Endocrinologists, all glucose-lowering agents have a low risk of hypoglycemia except insulin, meglitinides, and sulfonylureas.[5] A third consideration is the magnitude of glycemic lowering needed. While a target HbA_{1c} <7.0% would be appropriate for most patients with T2DM, the presence of microvascular disease and several recent hypoglycemic episodes (although not severe) suggest that a less aggressive HbA_{1c} goal, perhaps 7.0% to 7.5%, might be reasonable.[31] Thus, treatment should lower his HbA_{1c} 1% to 1.5%. The glucose-lowering agents that include these 3 attributes (ie, can be used when the eGFR is <30 $mL/min/1.73\ m^2$, are recommended when hypoglycemia is a concern, and would be expected to reduce the HbA_{1c} by 1%-1.5%) are pioglitazone and liraglutide. Other issues to consider include cost and willingness to adhere to the agreed treatment plan.

Method of Physician Participation

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Appropriateness of other therapy

Patients with diabetes require comprehensive care to reduce their risk of cardiovascular and other complications of diabetes. One important change to his treatment plan is to reinitiate low-dose aspirin unless the patient had a compelling reason to discontinue it previously. To achieve the BP goal of <130/80 mm Hg, intensification of his antihypertensive therapy is needed. One option is to increase the dose of enalapril as tolerated. Alternatively, an angiotensin receptor blocker, such as losartan 50 mg once daily, could be initiated and enalapril discontinued. In addition, consideration could be given to starting a low-dose diuretic such as hydrochlorothiazide 12.5 mg once daily.

Since his eGFR has declined and is approaching 30 mL/min/1.73 m^2, the level below which simvastatin and most statins should be used cautiously, consideration should be given to discontinuing simvastatin and starting atorvastatin. Atorvastatin can be used safely in individuals with severe renal dysfunction. Although the patient's triglyceride level is elevated, it is <500 mg/dL. Therefore, the immediate focus should be on achieving the LDL-C goal of <70 mg/dL, as this poses a greater cardiovascular risk than his mild hypertriglyceridemia. Once the LDL-C is <70 mg/dL, the hypertriglyceridemia can be addressed if the triglyceride level remains above 200 mg/dL and his non–HDL-C level is above 100 mg/dL.

In summary, the following is the treatment plan for this patient:

- Discontinue glyburide, simvastatin
- Continue metformin
- Increase enalapril to 25 mg once daily
- Begin
  - Liraglutide 0.6 mg once daily; increase to 1.2 mg once daily after 1 week or as tolerated
    - Educate about adverse events such as nausea, vomiting, dehydration
  - Hydrochlorothiazide 12.5 mg once daily
  - Atorvastatin 20 mg once daily at bedtime
  - Aspirin 81 mg once daily
- Avoid use of nonsteroidal anti-inflammatory drugs
- Monitor fasting blood glucose daily until target achieved, then first 7 days of each month
- Repeat tests for HbA_{1c} and eGFR in 2 to 3 months
- Monitor for chronic kidney disease-induced anemia and mineral abnormalities
- Refer to 1-800-QUIT-NOW for help with smoking cessation
- Consider consultation with a nephrologist

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Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054. Tel: 973-206-3434