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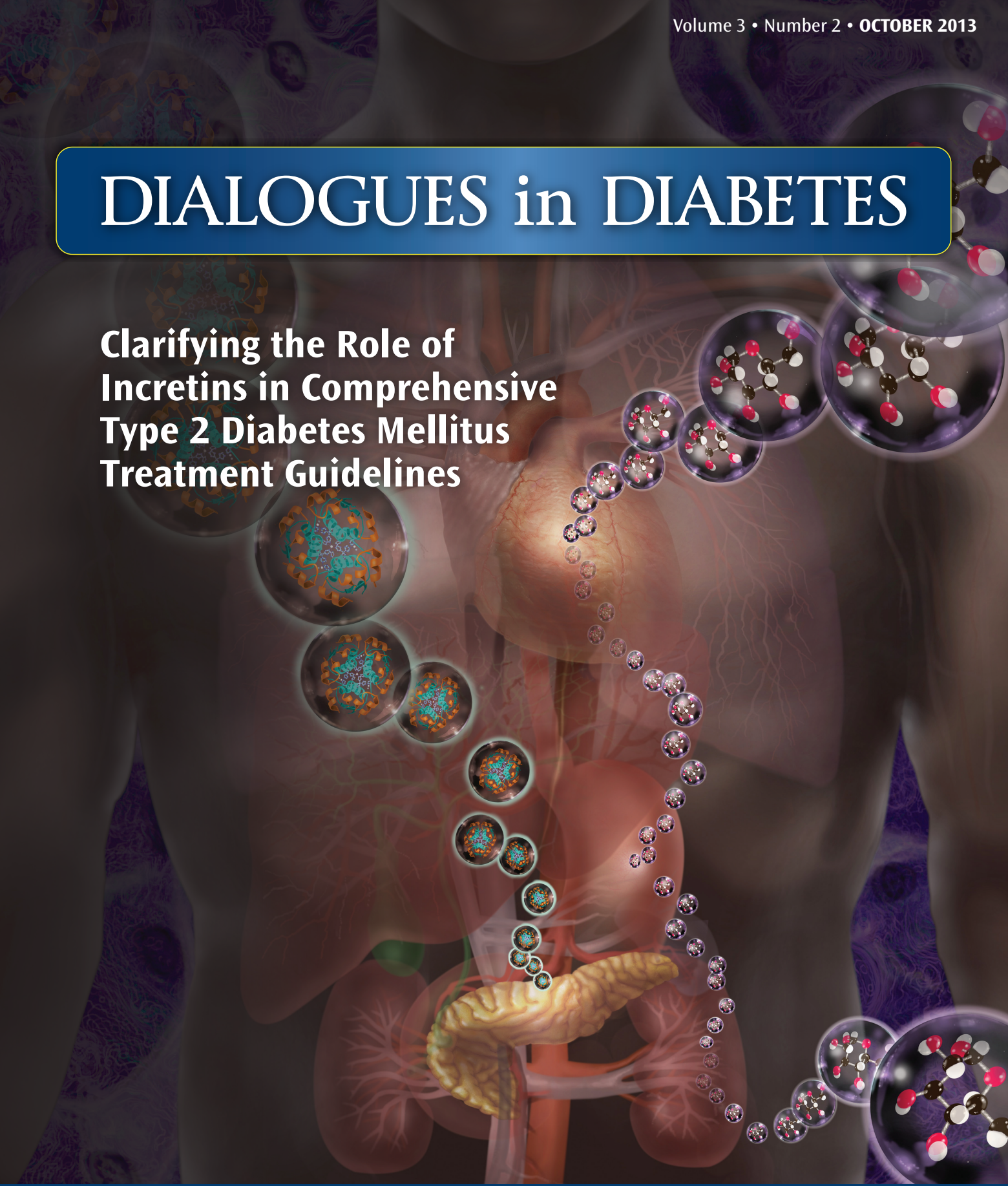
DIALOGUES in DIABETES

Clarifying the Role of Incretins in Comprehensive Type 2 Diabetes Mellitus Treatment Guidelines



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DIALOGUES in DIABETES

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Introduction

This issue will focus on the incretins and their role in the treatment guidelines for patients with type 2 diabetes. The 2 major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released with an oral glucose load. Both enhance endogenous insulin secretion but only GLP-1 receptor agonists inhibit glucagon release. The enzyme dipeptidyl peptidase-4 (DPP-4) degrades GLP-1 rapidly. Incretin impairment, which is associated with relative incretin resistance or deficiency, is characteristic of type 2 diabetes. The incretin impairment can be treated with DPP-4 inhibitors or GLP-1 receptor agonists. DPP-4 inhibitors increase endogenous GLP-1 receptor agonist levels from 2-fold to 4-fold. GLP-1 receptor agonists activate GLP-1 receptors but are resistant to degradation by the DPP-4 enzyme and enhance GLP-1 receptor activation to an even greater degree than DPP-4 inhibitors. Both treatments improve hyperglycemia with a low risk for hypoglycemia unless given in combination with insulin or an insulin secretagogue. DPP-4 inhibitors are weight neutral while GLP-1 receptor agonists are associated with modest weight loss.

Endocrinology experts are featured in this issue addressing the important role of GLP-1 receptor agonists and DPP-4 inhibitors in the antihyperglycemic management of patients with type 2 diabetes, including those who are overweight or obese. An illustrative case is reviewed and will reinforce the current guidelines for achieving a patient centered approach to disease management. A special focus of this edition is the AACE Complications Centric Model for Care of the Overweight and Obese Patient.

I thank Vindico Medical Education for enlisting these specialists to share with us their invaluable expertise in managing complex patients with T2DM and for their cooperation in the preparation of this issue of Dialogues in Diabetes.

Lawrence Blonde, MD, FACP, FACE

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Learning Objectives

At the conclusion of this series, participants should be able to:

- Assess the pathophysiology of hyperglycemia, its role in macrovascular and microvascular diseases, and the role of incretin pathways in type 2 diabetes mellitus.
- Examine the differences in mechanism of action, efficacy, and safety of treatment options that target the incretin pathway.
- Incorporate evidence-based guidelines and recommendations into practice when considering the use of incretin-based therapies for type 2 diabetes.
- Examine approaches to managing the obese patient with type 2 diabetes.
- Utilize GLP-1 agonists and DPP-IV inhibitors in combination with insulin and oral agents to achieve optimal glycemic control.
- Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.

DIALOGUES in DIABETES

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Comprehensive Guideline Review: Focus on Glycemic Control

Samuel Dagogo-Jack, MD, FRCP

Diabetes mellitus is a heterogeneous group of metabolic disorders that lead to hyperglycemia. Of the 2 broad types, one type results from absolute insulin deficiency, whereas a combination of insulin resistance and progressive beta-cell dysfunction underlies type 2 diabetes. Other recognized elements in the pathophysiology of diabetes include hyperphagia and impaired satiety, amylin deficiency, impaired postprandial glucagon suppression, incretin deficiency, incretin resistance, dysregulated gastric emptying, dyskinetic gastrointestinal motility, upregulated renal glucose transport, altered central dopaminergic tone, among others.[1-8] Based on data from the 2011 National Diabetes Fact Sheet, 25.8 million adults in the United States have diabetes. Approximately 2 million new cases of diabetes were diagnosed in people 20 years of age and older in 2010. Diabetes is the leading cause of blindness, lower extremity amputation, chronic kidney disease and end-stage kidney failure, and cardiovascular disease.[9] The health care costs associated with diabetes have increased each year and amounted to $245 billion in 2012.[10-13]

Treatment Targets

The therapeutic goals in diabetes treatment include sustained glycemic control, and prevention of acute and long-term complications. There is compelling evidence that maintenance of an HbA1c target of 7% or lower reduces the risk for diabetes complications.[14-16] A study employing a lower (<6%) HbA1c target caused harm.[17] Thus, the current position of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) is that the glycemic target be individualized.[18] A tighter HbA1c target (6.0% to 6.5%) may be appropriate for otherwise healthy, younger persons, whereas a target of 7% to 8% HbA1c seems prudent for persons with limited life expectancy or serious comorbidities (Table 1).[18]

In the United Kingdom Prospective Diabetes Study (UKPDS), blood pressure (BP) control to 144/82 mmHg (vs. 154/87 mmHg in the comparison group) in persons with hypertension and diabetes reduced the risks of development of any diabetes-related end point by 24%, diabetes-related death (32%), stroke (44%), microvascular complications (37%), and heart failure (56%).[19] However, lower blood pressure targets (<120/<80 mmHg) did not yield further risk reduction in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial.[20] Similarly, the addition of fenofibrate to increase high-density lipoprotein (HDL) cholesterol levels and decrease triglycerides was without added benefit in patients whose low-density lipoprotein (LDL) cholesterol has been optimally lowered with a statin drug.[21] Based on these data, the ADA[14] has reiterated the existing glycemic and lipid targets, and revised the systolic BP goal to <140 mmHg (Table 2).[14] The American Association of Clinical Endocrinologists has recommended a glycemic

Table 1. Glycemic Goals for Diabetes Management

HbA1c <7.0%
Mean PG ~150 to 160 mg/dL
Pre-prandial PG <130 mg/dL
Post-prandial PG <180 mg/dL
Individualization
Tighter targets (6.0% to 6.5%)
Younger, healthier, highly motivated patients
Looser targets (7.5% to 8.0%)
Older patients with multiple comorbidities, preexisting cardiovascular disease (CVD), hypoglycemia prone, etc.

The current position of the ADA and EASD is that the glycemic target be individualized.

Source: Inzucchi SE, et al. *Diabetes Care.* 2012;35(6):1364-1379.

Table 2. Comprehensive Treatment Goals

HbA1c	<7.0%
Systolic blood pressure	<140 mmHg
Lipids	LDL-C: <100 mg/dL <70 mg/dL (with overt CVD) HDL-C: >40 mg/dL (male) >50 mg/dL (female) TG: <150 mg/dL
Other	Healthy BMI and waist circumference, based on race/ethnicity

The existing glycemic and lipid targets and revised systolic BP goal is <140 mmHg.

Source: American Diabetes Association. *Diabetes Care.* 2013;36(Suppl 1):S1-S110.

target of HbA1c <6.5%, but is otherwise in philosophical alignment with the ADA and EASD regarding the emphasis on lifestyle intervention as a foundation of management and individualization of glycemic targets and approaches.[22]

Approach to Glycemic Control

Overall strategy

Goals are the therapeutic road maps that direct and focus all clinical efforts. Achievable goals should be set, and strategies and tactics marshalled toward their attainment. A typical goal in a patient with initial HbA1c of 9% could be to reduce that number by 1% by the next follow-up visit in 2 to 3 months.[23]

Specific Tactics

The management of type 2 diabetes hinges on nonpharmacological measures (diabetes education, diet, exercise, weight loss) and drug therapy. The mnemonic *MEDEM* (monitoring, education, diet, exercise, medications)[24,25] can be used to recall the key modalities and organizing framework for diabetes management.

Non-pharmacological measures

Self-monitoring of blood glucose (SMBG) is associated with superior glycemic control.[26] The standard recommendation for patients with type 1 diabetes is to perform self-testing of blood glucose 3 to 4 times daily. The optimal frequency of self-testing for patients with type 2 diabetes has not been determined and can be negotiated with patients. Physicians should review the home record with interest during office visits, so patients realize that the numbers are actually used to make treatment decisions. Physicians should monitor HbA1c levels at a frequency of 2 to 4 times/year, depending on the state of glycemic control,[14] and explain the value of the test to patients. Referral for diabetes education is an integral part of diabetes management.[27]

Diet and exercise interventions

Restriction of total and saturated fat intake, limitation of simple carbohydrates, augmentation of fruits and vegetables, whole grain, and dietary fiber has been demonstrated to enhance and improve cardiometabolic health.[28] Regular exercise, caloric restriction, and weight reduction are effective in preventing type 2 diabetes and improving glycemic and lipid control in persons with diabetes.[29,30] The same lifestyle measures were effective in reversing early type 2 diabetes in some patients.[31] The dietary goals can be pursued through referral to dietitians and medical nutrition therapists. However, until clinical exercise physiologists become routinely available, physicians should become the major protagonists of exercise. This might involve issuing written exercise prescriptions to help trigger the behavioral change.[23,32]

Medications for Treatment of Type 2 Diabetes

Owing to the progressive nature of type 2 diabetes, the use of medications often becomes necessary for optimal glycemic control. The agents that are currently approved for the treatment of type 2 diabetes belong to 10 distinct chemical classes (Table 3, page 6). These agents (in chronological order) include sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), glinides, glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogs, dipeptidyl-peptidase-4 (DPP-4) inhibitors, bile acid sequestrant, bromocriptine-QR, and sodium glucose cotransporter (SGLT)-2 inhibitors. All of these agents have tissue-specific actions to improve blood glucose control. Thus, the initial choice of medication for control of hyperglycemia in patients with type 2 diabetes is largely a matter of clinical judgment.

Although many guidelines recommend prescribing metformin as the initial agent, monotherapy with maximal doses of metformin, sulfonylureas, GLP-1 receptor agonists, or TZDs yield comparable glucose-lowering effects.[1,2,14,18,22,23] The DPP-4 inhibitors, SGLT2 inhibitors, and bromocriptine-QR (a quick-release formulation that works centrally to reset dopaminergic tone) have an intermediate glycemic efficacy, compared with sulfonylureas, metformin, or TZDs.[33-35] The alpha-glucosidase inhibitors are less potent in monotherapy but may be useful options for combination therapy. Colesevelam, a bile acid sequestrants, lowers HbA1c by ~0.5% when added to other antidiabetes agents.[36] Since residual pancreatic islet-cell function is required for the glucose-lowering effects of

Table 3. Oral Hypoglycemic Agents Used in the Treatment of Type 2 Diabetes*

Medication	Mechanism of Action	Typical A1C Change	Adverse Effects
Sulfonylureas	Insulin secretion	1.0% to1.5%	Hypoglycemia, weight gain
Biguanides	Decrease HGP	1.0% to1.5%	GI intolerance, lactic acidosis
Alpha glucosidase inhibitors	Slow carbohydrate absorption	~0.5%	GI intolerance
Thiazolidinediones	Increase insulin sensitivity through PPARγ agonism	1.0% to1.5%	Edema, weight gain, CHF
Glinides	Insulin secretion	0.5% to1%	Hypoglycemia, weight gain
GLP-1 receptor agonists	Insulin secretion, glucagon suppression, delayed gastric emptying, satiety	1% to 2%	Nausea, rare pancreatitis
Amylin analogs	Inhibits glucagon secretion and gastric emptying	~0.6%	GI intolerance
DPP-4 inhibitors	Preventing degradation of GLP-1 and GIP	~0.7%	Rare pancreatitis
Bile acid sequestrants	Bile acid effects via farnesoid X receptor, FGF-19, HGP, and GI glucose absorption	~0.5% when added to oral agents or insulin	GI intolerance
Bromocriptine-QR	Resets central dopaminergic tone	0.6%	Nausea
SGLT2 inhibitors	Promote glycosuria	~0.7%	Genital mycotic infections

Decreases in HbA1c vary according to baseline levels, chronicity of diabetes, lifestyle, and other factors.
*Medication classes are listed roughly in chronological order of their approval in the United States.
GI, gastrointestinal; HGP, hepatic glucose production; CHF, congestive heart failure

Source: Courtesy of Dr. Dagogo-Jack.

most of the available agents, many patients with advanced type 2 diabetes are unlikely to reach glycemic goal on monotherapy with any of these agents. Insulin therapy thus becomes the choice for these patients. Moreover, the toxicity profile of a given oral agent may preclude its use in patients with comorbid conditions, such as renal dysfunction, liver disease, congestive heart failure, and other states that contraindicate the use of some antidiabetes drugs.

Additional criteria for selecting oral agents relate to their adverse effects, tolerability, and nonglycemic activity profile, especially those that impact on cardiovascular risk factors. Preliminary data from a randomized trial demonstrated a potential for cardiovascular disease (CVD) risk reduction in patients treated with bromocriptine-QR.[35] However, most other agents (including sulfonylureas, biguanides, TZDs, insulin, alpha-glucosidase inhibitors, SGLT2 inhibitors) have not been demonstrated to significantly decrease CVD events as a primary outcome measure. Several multicenter trials are ongoing to determine the cardiovascular effects of DPP-4 inhibitors and GLP-1 receptor agonists. DPP-4 inhibition with saxagliptin decreased the rate of progression of microalbuminuria and did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased.[37] As a matter of good clinical practice, comprehensive control of hypertension, dyslipidemia, and obesity should be integrated into the routine management of patients with diabetes.

Combination Therapy

The UKPDS showed the futility of monotherapy as a strategy for long-term glycemic control in type 2 diabetes.[38] After 3 years, only ~50% of patients enrolled in the UKPDS were able to maintain the HbA1c goal of 7% or lower; by 9 years, the number had declined to ~25%. Thus, early use of drug combinations is the requirement for sustained glycemic

control in patients with type 2 diabetes. If the HbA1c level at presentation is markedly elevated (eg, >8.5%), consideration should be given to combination therapy as an initial step.[22] Most of the individual drugs approved for monotherapy can also be used in combination with drugs from other classes. The introduction of fixed-dose combination agents facilitates the practice of combination therapy. Theoretically, use of these fixed-dose agents may fair well for long-term medication adherence in patients with diabetes, who often also take several medications for comorbid conditions. Combination therapy will be most effective if initiated as part of a comprehensive diabetes care plan and after careful consideration of possible barriers to metabolic control. The decision to continue a combination regimen should be based on evidence of continuing efficacy, safety, and tolerability, and such evidence should be re-evaluated at frequent intervals. The efficacy of most combination regimens can be reliably evaluated over a 3 to 6 month period. Thus, patients who have been on an oral drug combination regimen for 3 to 6 months, whose HbA1c is >7%, are on a failing regimen. These patients may require supplemental insulin therapy. However, a trial of GLP-1 receptor agonist injection in combination with oral agents may be effective in select patients.[39, 40]

Insulin

An unrelenting decline in beta-cell function over the course of type 2 diabetes mellitus (T2DM) means that exogenous insulin will prove necessary in most patients. When insulin therapy is contemplated, members of the health care team must take care to explain to patients the rationale for, and benefits of, optimizing glycemic control and the demonstrated efficacy of insulin in accomplishing that objective. While patient concerns regarding weight gain and hypoglycemia are reasonable, caregivers need to address exaggerated and often inaccurate fears that some patients may harbor regarding the safety of insulin. Preemptive discussion of the phenomenon of "pseudohypoglycemia"[23,24] may also help increase patients' confidence in the period immediately following initiation of insulin therapy. There is no evidence that insulin therapy increases cardiovascular risk. Indeed, long-term follow-up data from the UKPDS and DCCT/EDIC studies show a reduction in the risk of CVD with intensive insulin treatment.[41,42] Similarly, in the recently concluded ORIGIN trial, no increased risk of cancer was observed with prolonged use of insulin.[43]

The most widely used approaches include (1) basal insulin at bedtime, with continuation of oral agents; (2) split-mixed regimens that deliver a mixture of regular insulin or analogue and an intermediate-acting insulin (NPH) delivered in 2 injections; or (3) basal-bolus regimens consisting of basal insulin and premeal boluses of short-acting insulin. More recently, the basal-plus regimen that offers more flexibility by allowing the patient to select one meal for prandial coverage, has also been shown to be effective in glycemic control.[44,45] Basal insulin can be started as a bedtime dose of NPH, glargine, or detemir at a low initial dose (~10 units) and increased by 2 to 4 units every 2 to 3 days (while continuing oral agents) until a fasting blood glucose level of 80 to 120 mg/dL is achieved. Obviously, patient cooperation in monitoring and relaying home blood glucose levels to the clinic is critical to the success of this titration approach. In the Treat-to-Target trial,[46] the average bedtime dose of basal insulin (NPH or glargine) needed to achieve a fasting plasma glucose level of ~100 mg/dL was approximately 50 units. Patients who do not achieve a fasting glucose target of 80 to 120 mg/dL, despite injecting >50 units of basal insulin at bedtime, may require multiple injections of mixed short-acting and longer-acting insulin preparations for optimal control. The addition of GLP-1 receptor agonists to basal insulin is also an emerging option.[47]

Surveillance for Complications

The comprehensive management of diabetes includes control of comorbid risk factors and surveillance for the long-term macrovascular and microvascular complications.[9] Meticulous modification of macrovascular risk factors is recommended, because most patients with diabetes die from heart disease or stroke. Therapeutic interventions include smoking cessation, control of dyslipidemia (LDL-cholesterol goal in diabetes is <100 mg/dL; 70 mg/dL in higher risk groups), blood pressure control, and judicious use of antiplatelet prophylaxis.[14,22]

The microvascular complications (retinopathy, nephropathy, neuropathy) develop after several years of uncontrolled diabetes. The best prophylaxis against microvascular complications is glycemic control.[15,16] There is also tremendous value in early detection through surveillance and prompt action. Thus,

While patient concerns regarding weight gain and hypoglycemia are reasonable, caregivers need to address exaggerated and often inaccurate fears that some patients may harbor regarding the safety of insulin.

periodic referral for dilated funduscopy and regular foot examinations and assessment of sensation (using a 5.07/10 gm monofilament) can help detect early retinopathy and neuropathy and increase the chances of sight and limb preservation.[23]

Both microalbuminuria, the earliest (and reversible) stage of kidney disease, and gross proteinuria precede end-stage renal failure by variable but lengthy intervals. This knowledge creates a window of opportunity for timely interventions to prevent further decline in renal function.

Interventions that have been proven to delay the decline in renal function include tight control of blood glucose (HbA1c <7%), blood pressure (<120/80 mmHg), dyslipidemia, smoking cessation, and other risk factors.[9] Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are most effective in preserving renal function in patients with diabetes with microalbuminuria as well as those with more advanced forms of proteinuria and nephropathy. The concurrent use of an ACE inhibitor and an ARB in combination is not recommended due to increased risks of hypotension, syncope, and renal dysfunction.[48]

Summary

Diabetes and its complications contribute a great economic and personal burden to society. A multi-modality intervention approach for optimization of glycemic control and prevention of metabolic, renal, retinal, neuropathic, and cardiovascular complications is recommended. The key elements of a comprehensive diabetes management strategy include monitoring, education, dietary modification, exercise, and medications. Non-pharmacological measures form the foundation of management; medications (often in combination) can be added, as needed, to reach targets. Aggressive surveillance for diabetes complications and prompt intervention for prevention or containment is an integral part of the comprehensive strategy.

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Comprehensive Guideline Review: Focus on Obesity

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Obesity is a condition that threatens the future health of millions, with more than two-thirds of American adults being overweight or obese. The prevalence of obesity in the United States continues to be elevated and is increasing, affecting more than 30% of adults, in addition to being associated with an increased risk of death as well as type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), sleep apnea, hypertension, various types of cancer, gallstones, and disability.[1]

According to recent Centers for Disease Control and Prevention (CDC) estimates, nearly 26 million Americans are living with T2DM. In the past 3 decades, 1990 through 2010, the annual number of new cases of diabetes has tripled.[1] Based on the CDC estimates, the incidence of diabetes mellitus will increase dramatically over the next 40 years. It is anticipated that by the year 2050, 1 in 3 adults could have T2DM.[1]

While tight glycemic control remains a focus of therapy for T2DM patients, only 53.5% of adults aged 18 years and older with T2DM had achieved adequate glycemic control (an A1C value of less than 7%) from 2005 to 2008.[2] Improved glycemic control is associated with reduced risk of microvascular complications such as retinopathy, neuropathy, and foot ulcers and may reduce the incidence of preventable macrovascular complications related to the disease, such as heart attack, stroke, high blood pressure, kidney failure, and related disabilities.[2]

Managing the Obese Patient with Type 2 Diabetes Mellitus

Treating the obese diabetic can be quite a daunting challenge. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD),[2] and the American Association of Clinical Endocrinologists (AACE)[3] treatment guidelines recommend starting metformin or another oral antidiabetic agent for patients who fail in their lifestyle (diet and exercise) modifications. The ADA/EASD and AACE differ in their recommendations as to the "trigger" level of hemoglobin A1c (HbA1c) for treatment intensification (HbA1c $\geq$7% and $>$6.5%, respectively) and which agents are preferred as second-line therapies. The ADA and the European counterpart, the EASD, recommends a tiered approach to treatment. Both societies recommend starting with well-validated second-line agents, such as sulfonylureas and basal insulin for patients unable to achieve target glucose levels with metformin.

Two other very prominent societies take a different philosophy toward initial treatments. The AACE/American College of Endocrinology (ACE) recommendations are based on the patient's HbA1c level and include a broader range of first-line and second-line therapies and combinations. In addition to metformin, the AACE/ACE treatment algorithm includes incretin medications (dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists), thiazolidinediones, α-glucosidase inhibitors, sulfonylureas, and glinides. The basic difference between these two sets of recommendations is trying to avoid agents known to promote hypoglycemia, as well as agents known to cause central adiposity. This is a significant difference and can make both the physician and the patient's life much easier.

Both organizations advocate individualizing therapy to meet patient needs and recommend starting insulin immediately for patients with very high blood glucose and out of control HgA1c levels.

Although metformin has been associated with initial gastrointestinal adverse effects, it is still the first line treatment for T2DM.[4] As the patient advances in the disease, its effect on glycemia will be reached and other drugs will need to be added.[2,3]

Sulfonylurea insulin secretagogues, the oldest class of oral agents, are effective in controlling glucose levels but their use is associated with weight gain and a significant risk of hypoglycemia.[2,3] Thiazolidinediones (TZDs), which are good insulin sensitizers, are associated with peripheral fat gain and fluid retention, both of which can increase risk of cardiovascular disease.[2,3]

Incretins are hormones produced and secreted by endocrine cells in the mucosa of the intestine. When food enters the small intestines the "incretins" are released into the blood stream to signal the pancreas to produce insulin and decrease glucagon. Incretins also signal the brain that food has been consumed and to decrease eating. They have been

shown to provide positive effects on fasting and postprandial glucose, islet function, and body weight in patients with T2DM.[4]

GLP-1 receptor agonists are medications that are copies of the incretin hormone but have a much longer half-life and are able to improve glucose control in the patient with diabetes. GLP-1 receptor agonists have been shown to cause significant weight loss in patients with diabetes due to its effects on satiety, food intake, and gastric emptying. Several GLP-1 receptor agonists are available for the treatment of T2DM.[5] Liraglutide and exenatide have been the focus of several clinical research studies in the treatment of obesity in patients who are obese without diabetes, with prediabetes, and with T2DM.[5-8]

Weight-loss interventions (ie, behavior-based metformin and orlistat) have been shown to reduce the incidence of diabetes, particularly in patients with elevated risk. A study looking at patients who are prediabetic and diabetic and also overweight and obese found that one-third of patients reported not receiving advice about lifestyle changes they should be making, including reducing calories and increasing physical activity.[9]

Weight-loss interventions have been shown to reduce the incidence of diabetes, particularly in patients with elevated risk.

Patients with T2DM are usually obese and have a comorbid disease (impaired glucose). It is well known that if this group loses weight, their glucose control will improve. Thus one might want to consider a weight loss medication for this group since blood sugar control would benefit them. Until 2012, the available drugs for weight loss were very limited and not surprisingly less than 3% of adults who are obese take prescription medications for weight control.[10]

Clinicians may not be selecting the optimal therapeutic regimen for individuals with obesity-related comorbidities, including patients with prediabetes and T2DM.[11] In patients who are obese with diabetes, selection of diabetes medication that causes weight loss could benefit overall health in multiple ways. Some older antidiabetic medications have been associated with weight gain.[2,12] Newer incretin-based therapies lack this undesirable adverse effect; specifically, DPP-4 inhibitors, including sitagliptin, linagliptin, and saxagliptin, which tend to be weight-neutral, whereas GLP-1 receptor agonists, such as exenatide and liraglutide, as well as the amylin analog, pramlintide, may produce weight loss.[12] Interestingly enough, GLP-1 hormones are deficient in patients with T2DM. Endogenous GLP-1 is broken down within minutes by the action of enzyme DPP-4 and is eliminated from the circulation. Stimulation of the GLP-1 receptor is felt by many researchers to increase pancreatic beta-cell mass by stimulating beta-cell proliferation.[4] By increasing insulin secretion, inhibiting glucagon release, and delaying emptying of the stomach to slow glucose absorption, research has shown that patients on GLP-1 receptor agonists lose more weight compared to patients on a placebo; which is particularly important for patients who are overweight or obese.[13]

A number of phase 3 head-to-head trials have been conducted investigating the efficacy and tolerability of long-acting vs. short-acting GLP-1 receptor agonists. Results from a trial comparing twice-daily exenatide with once-daily liraglutide revealed liraglutide provided a significantly greater reduction in mean A1C and fasting plasma glucose as compared to exenatide. Patients in both groups lost weight and both drugs were well tolerated.[14]

Comparing the safety and efficacy of once-weekly (long-acting) exenatide with twice-daily exenatide in patients naïve to drug therapy or on one or more antidiabetic oral medication revealed the long-acting formulation significantly reduced A1C and fasting plasma glucose.[15] Both groups achieved similar reductions in weight. A 22-week extension study where patients either switched from twice-daily exenatide to once-weekly exenatide or remained on long-acting exenatide maintained reductions in A1C and fasting plasma glucose.[15] GLP-1 receptor agonists were associated with nausea, diarrhea, and vomiting, although transient, but not with hypoglycemia. Comparing the safety and efficacy of once-weekly (long-acting) exenatide with liraglutide was done in a 26-week, open-label study. Both once-daily liraglutide and once-weekly exenatide led to improvements in glycemic control, with greater reductions noted with liraglutide (-1.48% vs. -1.28%, not meeting noninferiority criteria). Both therapies were associated with decreases in body weight, however, patients taking liraglutide lost more weight than those taking exenatide, irrespective of body-mass index.[16]

Several studies have compared GLP-1 receptor agonists in combination with oral antidiabetics and insulins. In the LEAD-1 trial, liraglutide lowered the mean A1C in a dose-dependent manner, in combination with other oral antidiabetic therapies.[17] The LEAD-2 study, compared liraglutide 0.6 mg, 1.2 mg, or 1.8 mg daily, glimepiride 4 mg daily, and placebo all in combination with metformin. A1C reductions were significant

in all treatment groups as compared to placebo. Weight loss was dose-dependent with increases in doses of liraglutide.[18] In another study, dose-dependent liraglutide (1.2 mg and 1.8 mg) reduced A1C significantly as compared to sitagliptin 100 mg, all in combination with metformin. Weight circumference was also significantly decreased in subjects given liraglutide.

Two 26-week trials, LEAD-5 and LEAD-6, studied the effects of liraglutide when used in combination with metformin and a sulfonylurea. When weight loss is a goal in the patient's treatment plan and there is a risk of hypoglycemia, GLP-1 receptor agonists are viable treatment options.[19] Of interest, a study of the pharmacokinetics and pharmacodynamics of exenatide revealed weekly dosing with either 0.8 mg or 2 mg of exenatide improved fasting plasma glucose. Surprisingly, only the 2-mg dose was associated with enhanced postprandial glucose control and weight loss. As one would surmise, 2 mg is the only dose of exenatide available.

Given their safety and tolerability profiles, an emerging therapeutic trend toward initial or early combination therapy with metformin-based and incretin-based therapy is anticipated for patients with type 2 diabetes. In short, the available GLP-1 receptor agonists cause sustained weight loss and improved glycemic control. The long-acting GLP-1 receptor agonists may improve the effects of GLP-1 even further. There is the potential to optimized pharmacokinetic profiles resulting in fewer adverse effects and increased adherence relative to shorter-acting agents. This would be particularly useful in patients who are obese and cannot maintain adequate glycemic control on metformin.

A recent systematic meta-analysis of 25 clinical trials sought to determine whether treatment with GLP-1 receptor agonists result in weight loss in patients who are overweight or obese with or without type 2 diabetes mellitus.[20] Patients were adults with a body mass index (BMI) of 25 kg/m^2 or higher, with or without type 2 diabetes mellitus, who received twice-daily exenatide, once-weekly exenatide, or once-daily liraglutide at clinically relevant doses for at least 20 weeks. Control interventions assessed were placebo, oral antidiabetic drugs, or insulin. Simply, the meta-analysis showed that GLP-1 receptor agonist groups achieved a greater weight loss than control groups. This applied to the patients with diabetes as well as the patients who are obese without diabetes.[20]

Most of what is known concerning the effect of GLP-1 receptor agonists on body weight is from the clinical trials in patients with T2DM. Currently, liraglutide and exenatide have also been the focus of several clinical research studies in the treatment of obesity in patients with prediabetes and patients who are obese with T2DM.[7,8,11] The SCALE trial about the use of liraglutide for obesity and prediabetes had an estimated primary completion date of March 2013.[7] The SCALE-Diabetes trials looking at obesity and weight loss in the patients with diabetes was completed in January 2013 and results are forthcoming.[8]

Researchers are increasingly recognizing other contributing factors to the pathophysiologic defects in type 2 diabetes, such as enhanced glucose reabsorption in the kidneys.[21] Placing the kidney in the center of a therapeutic approach for glucose regulation is unfamiliar to physicians.[21] Newer therapies, such as the sodium glucose co-transporter 2 (SGLT2) inhibitors are attempting to address the issue by a truly novel approach. SGLT2 inhibitors are first-in-class oral agents that control hyperglycemia by the inhibition of glucose absorption in the proximal kidney tubule independent of insulin.[22]

Recent studies show that the kidneys play a central role in glucose homeostasis through the processes of gluconeogenesis, glucose filtration, glucose reabsorption, and glucose consumption.[5,23] Under normal circumstances, up to 180 g/day of glucose is filtered by the renal glomerulus and virtually all of it is subsequently reabsorbed in the proximal convoluted tubule, rendering the urine virtually glucose free.[24] This reabsorption is effected by two sodium-dependent glucose co-transporter (SGLT) proteins; SGLT2, situated in the S1 segment of the proximal tubule, is a low-affinity high-capacity transporter reabsorbing up to 90% of filtered glucose. SGLT1, situated in the S3 segment, is a high-affinity low-capacity transporter reabsorbing the remaining 10%. Once glucose has been reabsorbed into the tubular epithelial cells, it diffuses into the interstitium across specific facilitative glucose transporters (GLUTs). GLUT1 and GLUT2 are associated with SGLT1 and SGLT2, respectively.[5] The proximal tubule absorptive mechanism becomes altered in patients with T2DM such that hyperglycemia augments the expression and activity of the SGLT2 in the proximal tubule.[25,26] As a result, glucose reabsorption may be increased by as much as 20% in individuals with poorly controlled diabetes. In these circumstances the kidneys play

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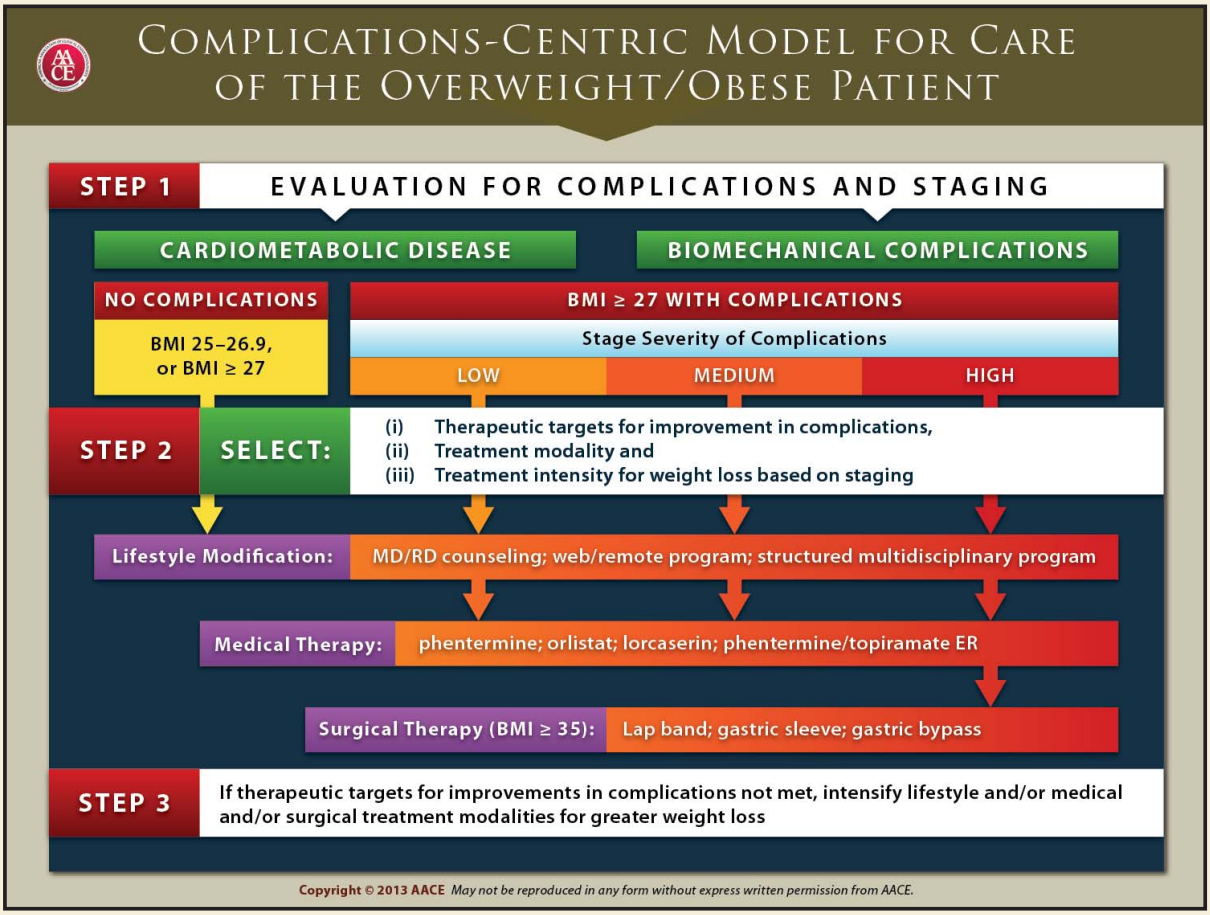
Figure. AACE Complications-Centric Model for Care of the Overweight/Obese Patient



This algorithm targets the patient who is obese with type 2 diabetes. IFG=Impaired fasting glucose. Data are mean ± SE.

Source: Reprinted with permission from American Association of Clinical Endocrinologists. Garber AJ, et al. Endocr Pract. 2013;19(2):327-336.

an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.[24]

In animal studies, SGLT2 inhibition reduces plasma glucose levels, resulting in improved beta-cell function and enhanced insulin sensitivity in liver and muscle. SGLT2 inhibition offers a novel approach to the treatment of hyperglycemia in T2DM. Human studies have confirmed the efficacy of SGLT2 inhibition in improving glucose control and reducing the A1C.[25] Selective SGLT2 inhibitors have been demonstrated to reduce glucose reabsorption, causing reduction in plasma glucose by eliminating excess glucose in the urine. SGLT2 inhibitors in clinical development inhibit only 30% to 50% of the filtered glucose load (ie, induce a maximum of 50 g to 80 g of urinary glucose excretion per day) in healthy volunteers.[27] The mechanism of SGLT2 inhibition of glucose reabsorption is independent of circulating insulin levels or insulin sensitivity, therefore SGLT2 inhibitors can be combined with other oral agents. In T2DM, the glucosuria produced by SGLT2 inhibitors is associated with weight loss and the mild osmotic diuresis may assist in a reduction of blood pressure. Since the mechanism is independent of insulin, it carries a low risk of hypoglycemia.[25,28]

Recently the U.S. Food and Drug Administration (FDA) approved the SGLT2 drug, canagliflozin, which has been evaluated with 3 large studies in special populations including older patients with T2DM, patients with T2DM with moderate renal impairment, and patients with T2DM at high risk for developing CVD. These studies showed greater improvement in glycemic control, weight reduction, and systolic blood pressure compared with patients treated with sitagliptin 100 mg, and was well tolerated in subjects with T2DM inadequately controlled with metformin plus sulfonylurea or with diet and

exercise.[29,30] Similarly, compared to glimepiride, canagliflozin showed consistent HbA1c lowering capacity and reduced body weight, and was well tolerated in subjects with T2DM inadequately controlled with metformin.[17] As an add-on to stable insulin therapy, canagliflozin improved glycemic control and produced significant improvements in a number of efficacy parameters important in the management of T2DM. In this setting, canagliflozin was generally well tolerated but was associated with a greater frequency of genital fungal infections and a slightly higher risk of hypoglycemia.[29,30] Several other SGLT2 inhibitors are in the late stages of development.

AACE Complications-Centric Model for Care of the Patient Who is Overweight/Obese

Within the last year, AACE came out with recommendations and an algorithm targeting the patient who is obese with type 2 diabetes.[3] What was unique and well thought out about this algorithm is considering the use of weight loss medications in a patient with a known comorbid disease of obesity, such as diabetes. In the algorithm, weight loss medications are named and put in as part of medical weight loss for the patient with diabetes (Figure).[31]

It is quite clear that there are patients that are obese yet are "well" and live just as long as someone who is normal weight. What has recently been shown is that the patient who is obese with diabetes is at much higher risk of early mortality than the obese person without diabetes. Getting the diabetics weight down now becomes an important priority. The way this applies to weight loss medications is an issue of risks and benefits. All medications, including weight loss medications, have some risk. In looking at the risk vs. benefit in the patient who is obese with diabetes, the risks of using weight loss medications is far outweighed by benefits of not losing weight in these patients.

Until recently, only two anti-obesity medications have received approval by the FDA for long-term use in treatment of obesity. In June and July of 2012, lorcaserin and the combination of phentermine/topiramate extended release (ER) were approved by the FDA for use in the treatment of obesity.[32,33] Two other medications are well into Phase III clinical trials, bupropion/naltrexone and liraglutide.[8,34]

Recently approved anti-obesity medications have shown encouraging results in patients with T2DM and prediabetes. The 1-year, 604-patient Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) trial examined the use of 2 different dosages of lorcaserin in patients with type 2 diabetes.[35] In this study, HbA1c levels were significantly decreased by lorcaserin. Mean HbA1c was reduced by approximately 1%. Patients were also able to decrease their use of diabetes medications. More patients lost 5% or more body weight with twice-daily lorcaserin (37.5%; $P<.001$) or once-daily lorcaserin (44.7%; $P<.001$) than with placebo (16%).[35] Weight was reduced by 4.5% and 5% with lorcaserin twice-daily and once-daily, respectively, and by 1.5% with placebo ($P<.001$ in each case). Symptomatic hypoglycemia occurred in 7.4% of patients on twice-daily lorcaserin, 10.5% with once-daily dosing, and 6.3% on placebo. It should be noted that in the other weight loss studies twice-daily lorcaserin in obese subjects had better weight loss and it is unclear why the patient who is obese with diabetes had comparable weight loss with both once-daily and twice-daily dosing.

Phentermine/topiramate ER is the other newly approved weight loss medication. In the two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate ER in obese and overweight adults (SEQUEL) study, sustained weight loss and metabolic benefits were seen.[36] This phase 3 extension study also yielded interesting results in a subset of dysglycemic patients.

Within the last year, AACE came out with recommendations and an algorithm targeting the obese type 2 diabetic.

Significant dose-related improvements were seen in glucose and insulin levels in fasting-glucose and 2-hour oral glucose-tolerance testing.[36] Progression to type 2 diabetes was significantly reduced at the 15 mg/92 mg dose level, with annualized incidence of type 2 diabetes of 0.9%, a 76% reduction from the 3.7% seen in the placebo group ($P=.0078$).[36] Phentermine/topiramate ER also outperformed placebo in HbA1c reduction, with fewer increases in use of diabetes drugs among patients on medication than those on placebo.

The future is now. The emergence of these newer medications has the potential to dramatically help the patient who is obese with T2DM. All these drugs have two things in common. They all cause weight loss and help glycemic control. The newer diabetic medications lower glucose by a direct mechanism on glucose metabolism yet have the positive side effect of weight loss. The weight loss medications lower body weight, which then improves glucose control.

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Case Presentation: Patient-Centric Approach to Diabetes Care

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The patient is a 52-year-old African American male with a 12-month history of type 2 diabetes, hypertension, and dyslipidemia taking metformin 1 g twice-daily, rosuvastatin 10 mg once-daily, and lisinopril/hydrochlorothiazide 20/12.5 once-daily. His weight: 256 lbs; height: 6'2"; BMI: 32.9 kg/m^2; and A1C: 8.2%.

A position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasized a "patient-centric approach" to type 2 diabetes mellitus (T2DM) management.[1] That statement and an algorithm recently published by the American Association of Clinical Endocrinologists (AACE) both emphasized that hemoglobin A1C (HgA1c) targets should be individualized based on numerous factors.[2] The AACE goal for most patients is an A1C <6.5%, while the ADA goal is <7%. More stringent (lower) goals may be appropriate for highly motivated patients with readily available resources, who have newly diagnosed diabetes, a long life expectancy, a low risk for hypoglycemia, and who do not have important comorbidities or established vascular complications. In contrast, higher A1C goals are usually needed for those who have a short life expectancy, a history of frequent or severe hypoglycemia or hypoglycemic unawareness, increased risk for adverse consequences from hypoglycemia, significant comorbidities especially vascular complications, a long history of diabetes, or limited resources.

The antihyperglycemic therapies in both organizations' algorithms begin with lifestyle interventions. The AACE algorithm points out that "lifestyle optimization is essential for all patients with diabetes, but lifestyle optimization is multifaceted, ongoing, and should engage the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response."

What would you do for this patient besides reemphasizing lifestyle?

The ADA/EASD algorithm states that considerations for selecting therapies include patients' present A1C and magnitude of reduction needed to reach goal; the potential effects of various treatments on body weight and BMI, the potential for hypoglycemia, effects on cardiovascular disease risk factors, existent comorbidities, such as coronary artery disease, heart failure, chronic kidney disease, and liver dysfunction. Patient factors include a preference for oral or injectable therapy, and economic considerations.

For those patients who do not need insulin at the time of diagnosis, metformin is the first line recommended agent, unless there is a contraindication. If that does not get the patient to goal, then one could add either a sulfonylurea, a thiazolidinedione, a DPP-4 inhibitor, a GLP-1 receptor agonist, or insulin (usually basal).

The AACE algorithm includes virtually every U.S. Food and Drug Administration (FDA) approved class of medications and stratifies the choice of therapies based on the initial A1C, with initial combination therapy recommended for those with an A1C of ⩾7.5%. The algorithm provides guidance as to what therapies to initiate and add, but respects individual circumstances that could lead to different choices. For optimal glycemic control, one should combine agents with complementary mechanisms of action.

The ADA/EASD recommends a DPP-4 inhibitor or a GLP-1 receptor agonist when the goal is to avoid weight gain as well as to improve glycemic efficacy. The AACE algorithm also favors these agents for this goal but also includes SGLT2 inhibitors, colesevelam, quick release bromocriptine mesylate, and alpha glucosidase inhibitors.

What about the efficacy of GLP-1 receptor agonists added to the regimen of a patient like our patient?

With exenatide BID as an add-on to metformin, there was a 0.9 percentage point placebo-subtracted improvement in A1C.[3] With liraglutide as an add-on to metformin in one study,[4] there was a 1.1 percentage point placebo-subtracted improvement in A1C that was equal to that observed with the sulfonylurea glimepiride. In another study,[5] liraglutide added

to metformin reduced A1C by 1.5 percentage points from baseline compared to a 0.9 percentage point reduction with sitagliptin. In the DURATION-2 trial, exenatide once-weekly as an add on to lifestyle plus metformin reduced A1C by 1.5 percentage points compared to a reduction of 0.9 percentage points with sitagliptin and 1.2 percentage points with pioglitazone.[6]

Although not approved for weight loss, change in weight was a prespecified endpoint in clinical trials of GLP-1 receptor agonists. In a meta-analysis by Vilsboll, et al.,[7] GLP-1 receptor agonist groups achieved a greater weight loss than control groups (weighted mean difference -2.9 kg, 95% confidence interval -3.6 to -2.2; 21 trials, 6411 participants). Overall in clinical trials, the weight loss with different GLP-1 receptor agonists has been fairly similar.

As with all medications, health care professionals should review the prescribing information before using incretin medications in their patients.

Weight loss with GLP-1 receptor agonists is not primarily driven by gastrointestinal adverse events. In a meta-analysis of 6 of the 26-week trials with liraglutide,[8] even those individuals who had no nausea, vomiting, or diarrhea had significant weight loss. Similarly, in the DURATION ONE trial,[9] among patients taking exenatide once-weekly or exenatide BID, even those who had no nausea lost significant amounts of weight.

What about DPP-4 inhibitor therapy for patients with type 2 diabetes inadequately controlled with metformin alone?

Studies with sitagliptin, saxagliptin, linagliptin, and alogliptin have shown a reduction in A1C from 0.5 to 1 percentage point.[10-15] So, a consistent glycemic improvement has been demonstrated when adding DPP-4 inhibitors to patients with type 2 diabetes inadequately controlled with metformin alone. With both GLP-1 receptor agonists and DPP-4 inhibitors, there is a low risk for hypoglycemia (unless given with an insulin secretagogue or insulin). DPP-4 inhibitors are weight-neutral.

Therefore, DPP-4 inhibitors and GLP-1 receptor agonists are agents that one can add to the regimen of metformin in patients like the one that we have presented, and one would anticipate improved glycemic efficacy with a low risk for hypoglycemia, and for either weight neutrality or weight loss.

How do these two classes of agents compare?

In a 26-week trial that compared the DPP-4 inhibitor sitagliptin to liraglutide,[5] there was a greater A1C reduction of 1.5% with the 1.8 mg dose of liraglutide compared to 0.9% reduction with sitagliptin 100 mg, with a decrease in weight with liraglutide 1.8 mg of 3.4 kg compared to a decrease in weight of 1 kg with sitagliptin. In a study that compared exenatide once-weekly to sitagliptin,[6] the reduction in A1C was 1.5% with exenatide once-weekly compared to 0.9% with sitagliptin and a 2.3 kg weight loss with exenatide once-weekly compared to a 0.8 kg weight loss with sitagliptin.

One of the therapeutic options that could be considered for our patient would be to add basal insulin, and there have been a number of studies that have compared the addition of basal insulin or a GLP-1 receptor agonist to patients not at goal on multiple oral agents.[16-20] In these studies, usually from a baseline A1C between 8% and 8.5%, basal insulin was not superior to the GLP-1 receptor agonist; and in three of the trials, the GLP-1 receptor agonist was modestly more efficacious than the basal insulin. In these trials, hypoglycemia was usually about the same or sometimes less with the GLP-1 receptor agonist, and there was a fairly consistent weight benefit with either no weight gain or weight loss with the GLP-1 receptor agonists, and a tendency to weight gain with basal insulin. However, it should be pointed out that the baseline A1C in these trials was approximately from 8% to 8.5%. It is likely that at some higher A1C level, basal insulin would be superior to GLP-1 receptor agonists but we do not yet know with certainty what that A1C level would be.

What can we say about the safety of incretin based therapies?

As with all medications, health care professionals should review the prescribing information before using incretin medications in their patients. When administered to rodents, exenatide once-weekly and liraglutide were found to cause an increase in C-cell tumors, including medullary thyroid cancer. Whether there is any increased risk in humans is not known, although the FDA concluded that increases in the incidence of carcinomas among rodents translated into a low risk for humans.[21] However, these agents are not recommended for 1st line therapy and should not be used if there is a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2.

Prescribing information for incretin agents (both GLP-1 receptor agonists and DPP-4 inhibitors) carry a warning about postmarketing reports of pancreatitis. However, no causal relationship has been established. Patients who take these agents should know the signs and symptoms of pancreatitis (including severe abdominal pain often associated with nausea and vomiting) and should stop taking the agents if they occur. If pancreatitis is confirmed, the incretin agents should not be restarted. In patients with a history of pancreatitis, one should consider other agents because it is not known if such a history would increase the risk for pancreatitis.

GLP-1 receptor agonists are not nephrotoxic, but should be used with caution in

patients with renal impairment. Exenatide BID and once-weekly, but not liraglutide, are actually excreted by the kidney, so neither exenatide preparation should be used in patients with severe renal insufficiency or end staged renal disease.

The most common adverse reactions with DPP-4 inhibitors include nasopharyngitis, headache, nausea, hypersensitivity, and skin reactions.[22] As noted there have been postmarketing reports of pancreatitis with DPP-4 inhibitors. DPP-4 inhibitors can be used in patients with renal impairment but with all except linagliptin, dose reductions are required based on the degree of impairment.

Summary

Recently published algorithms from both ADA/EASD and AACE emphasize a patient-centered, individualized approach to glycemic control for patients with type 2 diabetes. Lifestyle interventions remain the cornerstone of therapy. In addition to lifestyle changes, most patients will require combination pharmacotherapy with agents that have complementary mechanisms of action. Incretin-related agents have good glycemic-lowering efficacy, a low risk for hypoglycemia, and weight neutrality or weight loss.

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Full references are available at www.healio.com/endocrinology/education-lab.

CME Posttest

CME Instructions

1. Review the activity learning objectives stated on the front cover.
2. Read the articles, including the tables and illustrative materials.
3. Proceed to the CME Registration Form. Type or print your name, address, and date of birth in the spaces provided.
4. Answer each test question by circling the letter corresponding to the correct answer or by entering it in the space provided on the Registration Form. Be sure to retain a copy of your answers for your records.
5. Complete the evaluation portion of the CME Registration Form. CME Registration Forms will be returned to you if the evaluation is not completed.
6. CME Registration Forms will not be accepted after the expiration date. Return the CME Registration Form before the test expires to:

   Vindico Medical Education
   PO Box 36
   Thorofare, NJ 08086-0036
   Or Fax to: 856-384-6680

7. The CME test will also be available online (within 1 month of mailing date) at:

   www.healio.com/endocrinology/education-lab

1. According to the current ADA and EASD recommendations, what is an appropriate A1C goal for persons with limited life expectancy or serious comorbidities?
- A. 6.0% to 7.0%
- B. 5.5% to 6.0%
- C. 7.0% to 8.0%
- D. 9.0% to 9.5%

2. Self monitoring of blood glucose
- A. is associated with superior glycemic control.
- B. is not effective in achieving glycemic control.
- C. should only be done if symptoms of hypoglycemia occur.
- D. yields unreliable results.

3. Physicians should monitor A1C levels:
- A. Once yearly
- B. Twice yearly
- C. Once monthly
- D. Every 3 to 6 months

4. According to most guidelines, which drug should be used as initial monotherapy in patients with T2DM, unless otherwise contra-indicated?
- A. Sulfonylureas
- B. Thiazolidinediones
- C. DPP-4 inhibitors
- D. Metformin

5. Bromocryptine CR
- A. resets adrenergic tone.
- B. resets dopaminergic tone.
- C. acts peripherally with no central effects.
- D. has very low glycemic efficacy.

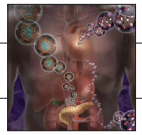
6. The major adverse effects of biguanides are:
- A. Hypoglycemia
- B. Renal toxicity
- C. GI intolerance
- D. Cardiac toxicity

7. DDP-4 inhibitors:
- A. degrade GLP-1 and GIP.
- B. prevent degradation of GLP-1 and GIP.
- C. have a high incidence of hypoglycemia when used as monotherapy.
- D. decrease A1C by 2.0% when used as monotherapy.

8. You are managing a 59-year-old female patient with T2DM who continues to gain weight on sulfonylureas and metformin, while her A1C has increased from 7.5% to 8.3% in one year. What drug would you choose next to improve glycemic control and help her lose weight?
- A. GLP-1 receptor agonist
- B. Insulin glargine
- C. DPP-4 inhibitor
- D. Thiazolidinedione

9. GLP-1 receptor agonist therapy
- A. may cause weight gain.
- B. increases systolic blood pressure.
- C. may result in significant weight loss by delaying gastric emptying and promoting satiety.
- D. is effective in achieving glycemic control only in the obese patient with T2DM.

10. The LEAD series of trials evaluated the efficacy of:
- A. Exenatide once-weekly
- B. Exenatide twice-daily
- C. DPP-4 inhibitor therapy
- D. Liraglutide



CME Registration Form

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DIALOGUES in DIABETES

Volume 3 • Number 2

POSTTEST

1	2	3	4	5	6	7	8	9	10

***Time spent on this activity: Hours ☐ Minutes ☐**
(reading articles and completing the learning assessment and evaluation)
This information MUST be completed in order for the quiz to be scored.

Release date: October 1, 2013
Expiration date: October 1, 2014

PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking credits ONLY)

Phone Number FAX Number E-mail

Degree: *Please select one*

❑ MD ❑ PA
❑ PhD ❑ NP
❑ DO ❑ Other_____

Specialty: *Please select one*

❑ Primary Care ❑ Diabetes
❑ Endocrinology ❑ Obesity
❑ Other_____

EVALUATION (must be completed for your CME Quiz to be scored)

Please circle answers neatly and write legibly.

1. The content covered was useful and relevant to my practice. Yes No

2. The activity was presented objectively and was free of commercial bias. Yes No
[Please use the additional comments field below to provide further information.]

Additional comments regarding bias: _____

3. Based on the information I learned during this activity, I feel more confident in treating patients within my practice. Yes No

4. Knowledge acquired from this activity will be utilized to improve outcomes in my patients. Yes No

5. Future activities concerning this subject matter are necessary. Yes No

6. I plan to make the following changes to my practice:

Y = Yes N = No 2 = I Already Do This in My Practice 1 = Not Applicable

Examine more closely the differences, efficacy, and safety of treatment options that target incretin pathway.	Y	N	2	1
Assess the pathophysiology of incretin pathways in type 2 diabetes mellitus.	Y	N	2	1
Examine approaches to managing the obese patient with type 2 diabetes.	Y	N	2	1
Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.	Y	N	2	1

Other - *Please explain:*

_____

_____

7. These are the barriers I face in my current practice setting that may impact patient outcomes:

Lack of evidence-based guidelines	Yes	No
Lack of applicable guidelines for my current practice/patients	Yes	No
Lack of time	Yes	No
Organizational/institutional	Yes	No
Insurance/financial	Yes	No
Patient adherence/compliance	Yes	No
Treatment-related adverse events	Yes	No

Other - *Please explain:*

_____

_____

8. This activity supported achievement of each of the learning objectives. Yes No

Please explain:

_____

_____

9. I see the following number of patients per week with type 2 diabetes mellitus:

A. <10
B. 10 to 25
C. 26 to 50
D. >50

10. Please list CE/CME topics that would be of value to you.

_____

_____

_____

CME ACTIVITY REQUEST

❑ Yes, I would like the opportunity to earn CME credits through activities sponsored by Vindico Medical Education.

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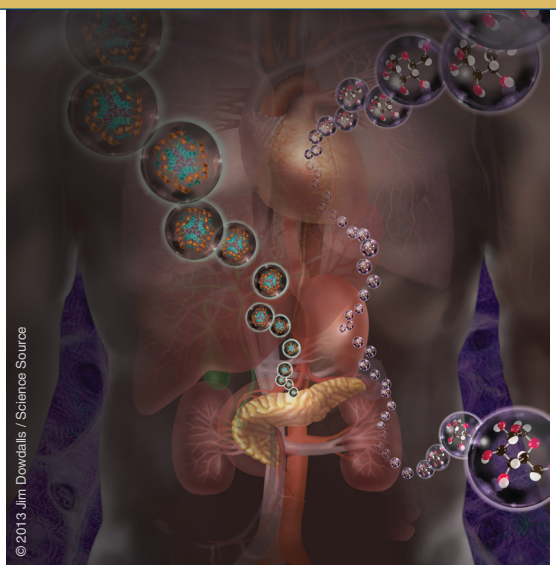
DIALOGUES in DIABETES



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