HIGHLIGHTS AND INSIGHTS FROM

MEDS Metabolic & Endocrine Disease Summit

A CME/CE CERTIFIED SUPPLEMENT TO
Clinical Endocrinology News

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SUPPORTED BY AN EDUCATIONAL GRANT FROM MERCK

A CME/CE CERTIFIED SUPPLEMENT TO
Clinical Endocrinology News.

This continuing medical education (CME/CE) supplement was developed from faculty presentations at the ***Metabolic & Endocrine Disease Summit*** October 5–8, 2016.

The faculty acknowledge the editorial assistance of Global Academy for Medical Education, LLC, and Eileen McCaffrey, medical writer, in the development of this supplement.

It has been reviewed and approved by the faculty as well as the editors of *Clinical Endocrinology News*.

Neither the editors of *Clinical Endocrinology News* nor the Editorial Advisory Board nor the reporting staff contributed to its content. The opinions expressed are those of the faculty and do not necessarily reflect the views of the supporter or of the Publisher.

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Release Date: May 31, 2017 ***Expiration Date:*** May 31, 2018

Estimated time to complete this activity: 2.0 hours

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Target Audience

This supplement is intended for physicians, nurses, nurse practitioners, physician assistants, CDEs, and other clinicians involved in the diagnosis and management of metabolic and endocrine disorders.

Educational Needs

Primary care providers are often the first point of care for diabetes and kidney disease. *The Metabolic & Endocrine Disease Summit* 2016, a CME/CE conference, explored the latest advances in the management of these conditions.

Obesity raises the risk of many other conditions. Providers would benefit from a discussion of how to address this frequently encountered problem in clinical practice.

Lipoprotein (Lp) (a) is an inherited, independent risk factor for atherosclerotic cardiovascular disease. New therapies show some promise for addressing this form of dyslipidemia.

Diabetes raises the risk of major depressive disorder, and depression increases the risk of diabetic complications. Psychosocial intervention can improve glycemic control and symptoms of diabetes-related distress.

Nephropathy is a common complication of diabetes but glycemic control, careful choice of medications, and regular monitoring can promote renoprotection.

Diabetes presents issues throughout a patient's life; three touchpoints are the transition of a young adult from pediatrics to adult care, the detection and management of diabetes during pregnancy, and diabetes in the older adult. Anticipation of the relevant issues and implementation of a transition program can contribute to retaining young adults in care. Preconception counseling and early detection of diabetes can reduce the risk of adverse outcomes.

Clinicians must be knowledgeable about how to balance the many complex issues to consider when establishing glycemic targets and selecting a treatment plan for an older adult with diabetes.

At this writing, four new insulin-only preparations have been approved by the US Food and Drug Administration (FDA) since February 2015. The ability to differentiate these options is important for clinicians.

Learning Objectives

After reading and studying this journal supplement, participants should be better able to:

- Differentiate the many insulin options available to treat people with diabetes, and their applications in clinical practice
- Display an understanding of the contributors to and consequences of obesity, and interventions to address unhealthy weight
- Evaluate the contribution of elevated Lp (a) to vascular risk and its influence on treatment
- Apply the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) glycemic goals and pharmacologic recommendations in the context of individual patient concerns and practical limitations
- Incorporate consideration of renal function in monitoring, medication choice, and general management of diabetes
- Understand common errors in medication choice and dosing that are associated with kidney injury, and plan how to avoid them
- Demonstrate an understanding of the effect of depression—and its treatment—on diabetes
- List tools to assess and manage depression in patients with diabetes
- Identify risks of transitioning of young adults with diabetes from pediatric to adult services, and list elements of successful transition
- Demonstrate familiarity with assessment and treatment recommendations for older adults with diabetes
- Detect and manage pregestational and gestational diabetes mellitus to reduce risk of complications for the mother and child during and after pregnancy

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HIGHLIGHTS AND INSIGHTS FROM

MEDS | Metabolic & Endocrine Disease Summit

INTRODUCTION

Nurse practitioners (NPs) and physician assistants (PAs) serve as primary caregivers for many patients with diabetes and other endocrine disorders. ***The Metabolic & Endocrine Disease Summit***, an intensive two-day conference, offers updates about these conditions for front-line clinicians. This educational supplement summarizes the highlights of clinical sessions presented during this CME/CE conference, which took place October 5-8, 2016.

The prevalence and seeming intractability of obesity confounds practitioners. The common experience of regaining weight may leave patients demoralized. Obesity is a chronic disease, not a character flaw, and growing knowledge of its pathophysiology and risk factors is improving our ability to address this serious condition. Unhealthy weight raises the risk of diabetes, cardiovascular disease, many cancers, and other conditions. The faculty urges providers to address it even when patients do not ask us to do so—just as most clinicians would not ignore an incidental finding of dangerously high blood pressure. Another serious cardiovascular risk factor, lipoprotein (Lp) (a), is inherited and is associated with premature cardiovascular disease. The president of the National Lipid Association offers an update about the risk of elevated levels of Lp (a) and how to address this when managing dyslipidemia.

Depressive symptoms are common among patients with diabetes. They may stem from major depressive disorder (MDD) or diabetes-related distress, a recognized and separate condition. MDD and diabetes-related distress each affect the management of diabetes. Our faculty discusses screening and intervention to identify and ease the distress of patients with these disorders.

Renoprotection is an important aspect of care for patients with diabetes. It includes prevention, detection, and management of deteriorating kidney function as well as avoidance of iatrogenic kidney injury. A case-based discussion of prescribing errors will make it difficult to forget mistakes that can cause acute kidney damage in our vulnerable patients.

Young adults with diabetes transitioning out of pediatric care, pregnant women with diabetes and those who develop gestational diabetes, and older adults with diabetes pose specific challenges to practitioners. Faculty focused on these life stages present those issues and how to address them.

Four new insulin preparations have entered the US market within the last 2 to 3 years. This supplement includes a primer on the differences between these agents and how those factors affect clinical use.

Customizing treatment guidelines to each patient's needs and concerns challenges the already complex care of diabetes. Two cases illustrate how to apply professional society recommendations to patients such as those whom PAs and NPs see on a regular basis. We hope that these highlights offer the readers practical information to incorporate into their busy practices.

THE CHANGING OPTIONS FOR INSULIN THERAPY

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The types of insulin available for treating diabetes have proliferated in recent years, with four new insulin-only products approved by the US Food and Drug Administration (FDA) since February 2015.[1] One, basaglar, represents the first biosimilar or follow-on insulin available in the United States.[2] This article will discuss the differences among those options and recommendations for their use.

Davida F. Kruger, MSN, APRN-BC, BC-ADM

Types of Insulins

The Table lists the insulins available in the United States.[3] Those most recently approved by the FDA are: basaglar (a biosimilar to Lantus [insulin glargine, U-100]), Ryzodeg (70% insulin degludec, 30% insulin aspart; U-100), Tresiba (insulin degludec, U-100 or U-200), and Toujeo (insulin glargine, U-300).[1] These products are available only in pens.[3]

Basal Insulins

Basal insulins available in the United States include long-acting analog insulins (detemir U-100, glargine U-100 and U-300, and degludec U-100 and U-200), the majority of which were approved within the last two years, and the intermediate-acting human insulin NPH. The long-acting insulin analogs are characterized by relatively even patterns of activity and durations of action lasting 24 hours or more—up to 42 hours or more for degludec.[4-7] Glycemic variability is minimal, with a flat, consistent glucose-lowering effect across the dosing interval.[8,9] NPH has a shorter duration of action (12.7 hours, in one study; up to 18 hours in another).[10,11] Evidence points to a lower risk of hypoglycemia with newer analog basal insulins compared with NPH. However, in the author's practice, many patients cannot afford the copays for the newer products. Individuals without a history of hypoglycemia can use NPH safely.[3]

Basal insulins generally are given at the same time each day.[5,6] Insulin degludec's pharmacologic profile allows for flexible dosing at any time of day.[4] Degludec injection at intervals of 8 to 40 hours led to glycemic control noninferior to that achieved by administering insulin glargine once daily at the same time each day. Rates of overall and nocturnal hypoglycemia with these regimens showed no statistical difference.[12] Flexible dosing is more forgiving of missed doses and convenient for patients.

U-200 degludec and U-300 glargine are two and three times as concentrated as U-100 degludec and glargine formulations and deliver higher doses per volume of insulin used.[3] The lower volume of insulin may be attractive to patients who require high insulin doses. U-300 glargine exhibits a flatter, more stable pharmacokinetic profile compared with U-100, with more prolonged and tighter glycemic control.[13,14] Both are available only in pens, which may minimize the risk of dosing errors. A U-500 human regular insulin formulation is five times as concentrated as U-100 regular insulin, with a delayed onset and longer duration of action compared to its less concentrated counterpart. It became available last year in pen form and with a dedicated syringe for use with the vial.[3] It can be used in basal or bolus dosing.[15]

Table: Insulins Available in the United States

Type	Form	Dosage and Delivery
Basal		
Glargine	Analog	U-100 vial; U-100 pen; U-300
Detemir	Analog	U-100 vial; U-100 pen
Degludec	Analog	U-100 pen; U-200 pen
NPH	Human	U-100 vial; U-100 pen
Prandial		
Regular	Human	U-100 vial
Lispro	Rapid-acting Analog	U-100 vial, U-100 3 mL cartridges, U-100 pen, U-200 pens
Aspart	Rapid-acting Analog	U-100 vial, U-100 3 mL cartridges, U-100 pen
Glulusine	Rapid-acting Analog	U-100 vial, U-100 pen
Inhaled insulin	Rapid-acting Analog	Inhalation cartridges
Basal and Prandial		
Regular	Human	U-500 vial, U-500 pen
Premixed		
NPH/Regular 70/30	Human	U-100 vial, U-100 pen
Lispro 50/50	Analog	U-100 vial, U-100 pen
Lispro 75/25	Analog	U-100 vial, U-100 pen
Aspart 70/30	Analog	U-100 vial, U-100 pen

Adapted from Table 8.3, 8. Pharmacologic approaches to glycemic treatment, *Diabetes Care.* 2017;40(Suppl1):S64-S74.[3]

Bolus and Premixed Insulins

Prandial, or bolus, insulin products include short-acting regular human and rapid-acting analog formulations. Of these two types, analog products offer pharmacologic profiles more similar to that of endogenous insulin.[16] The standard recommendation is to administer prandial insulins before meals. Yet the rapid-acting analog insulin glulusine has been associated with similar glycemic control when given before or after meals, allowing for patient convenience. No additional risk of severe hypoglycemia was observed; the effect of postmeal administration on weight gain was noninferior to that of premeal dosing. Postmeal administration allows dosing to be based on actual food consumption.[16] Inhaled insulin offers another mode of delivery for prandial insulin. The requirement for bronchial studies[3] has limited its clinical use, in the author's experience.

Premixed insulins enable administration of a basal and bolus dose with one injection.[3] Patients who in practice will give only two injections daily may benefit from these formulations. The newest premixed insulin approved by the FDA combines 70% insulin degludec and 30% insulin aspart in set doses.[17]

Conclusions

Compared with NPH, the newer basal analog insulins offer flatter pharmacokinetic profiles, longer durations of action, and—in the case of degludec—flexible dosing. Degludec U-200 is

the only insulin that delivers a maximum dose of 160 units per injection.[4] Concentrated insulins deliver higher doses per volume, a potential benefit for patients who require high insulin doses. A biosimilar or follow-on to insulin glargine U-100 has been approved.

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LIPOPROTEIN(A) AND VASCULAR RISK

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Lipoprotein(a) (Lp[a]) is a highly heritable, independent, causal risk factor for atherosclerotic cardiovascular disease (CVD)—especially premature CVD.[1,2] Median Lp(a) levels are lowest in Caucasians and Asians, somewhat higher in people of Hispanic descent, and higher yet in blacks.[2]

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How Does Lp(a) Raise CV Risk?

The Lp(a) particle contains an apolipoprotein (apo) B covalently linked to apo(a). A region of apo(a) is structurally homologous to plasminogen while apparently lacking the fibrinolytic activity of this enzyme. It has been postulated that Lp(a) exerts some of its effect on CVD risk by interfering with thrombolysis.[3] Evidence also suggests that Lp(a) binds proinflammatory oxidized phospholipids and that it may bind to the arterial intima more readily than low-density lipoprotein cholesterol (LDL-C).[1]

When to Measure Lp(a)

Lp(a) is not included in a standard lipid panel. The Table lists recommendations for when to measure Lp(a).[1]

Treatment

Reducing Lp(a) levels has not decreased CV risk in randomized clinical trials.[1] Aggressive LDL-C lowering in patients with elevated levels of Lp(a) may reduce some of the CV risk associated with Lp(a). In one epidemiologic analysis, Lp(a) >30 mg/dL was associated with elevated risk of angiographic stenosis, three-vessel disease, and major adverse cardiovascular events, but the association was eliminated when LDL-C was <70 mg/dL.[4] Therefore, at least one authority recommends treating LDL-C to <70 mg/dL (or 50% reduction from baseline) in patients with Lp(a) >30 mg/dL who meet the aforementioned criteria for Lp(a) screening.[1]

Therapeutic lifestyle modification has little effect on Lp(a) levels.[5] Among the medications used to treat dyslipidemia, only niacin has been shown to lower Lp(a).[2,3] However, a recent trial reported that adding niacin to statin therapy did not reduce CV risk in patients with low HDL-C and CVD.[6] Adding extended-release niacin to statin-based LDL-C–lowering therapy has raised the risk of myopathy.[7]

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab reduce Lp(a) levels according to pooled analyses of phase II trials.[8,9] In vitro studies have revealed a possible mechanism of this benefit. PCSK9 enhances secretion of Lp(a) from human hepatocytes; alirocumab inhibited this effect.[10] More data are needed to determine the therapeutic implications of these findings.[3]

Conclusions

Lp(a) is an inherited, independent, causal risk factor for atherosclerotic CVD. Aggressive LDL-C–lowering therapy, to <70 mg/dL, is advised in patients with elevated Lp(a) levels (>30 mg/dL). No Lp(a)-lowering therapy has been demonstrated to reduce the CV risk associated with this lipoprotein. Preliminary data about the effect of the PCSK9 inhibitors on Lp(a) are encouraging.[1]

Table: When to Measure Lipoprotein(a)

- Measure lipoprotein(a) in patients with elevated LDL-C and any of the following:
  - Personal or family history of premature cardiovascular disease
  - Familial hypercholesterolemia
  - Recurrent cardiovascular events despite maximum statin treatment
  - Insufficient LDL-C response to statins
- Testing also may be considered in individuals with a 10-year Framingham risk score of 5% to 19% or a coronary heart disease risk equivalent

LDL-C=low-density lipoprotein cholesterol.

Source: Jacobson TA. *Mayo Clin Proc.* 2013;88:1294-1311.[1]

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ADIPOSITY AND WEIGHT MANAGEMENT

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More than a decade of evidence has established that obesity is a disease rather than a failure of will.[1-3] Its prevalence among US adults has climbed from 30.5% to 37.7% within 15 years (1999-2014).[4] Obesity has been associated with type 2 diabetes mellitus (T2DM), hypertension, stroke, coronary artery disease, congestive heart failure, chronic kidney disease, asthma, gallbladder disease, chronic back pain leading to early retirement, and osteoarthritis leading to joint replacement, as well as a variety of cancers, including breast, endometrial, ovarian, colorectal, pancreatic, and kidney cancer.[5-8] Abdominal obesity (waist circumference >35 inches for women, >40 inches for men) is a component of the metabolic syndrome (Table 1), which raises cardiovascular risk.[9,10] Among individuals with metabolic abnormalities (having at least two of the following: dyslipidemia, hypertension, and elevated blood glucose), obesity has been associated with more rapid cognitive decline.[11]

Contributors to the Obesity Epidemic

A greater understanding of the pathogenesis and etiology of obesity can help to counter both medical bias and treatment inertia when dealing with this devastating, chronic disease. Simply eating too much and moving too little is an outdated etiologic view of a condition that has multifactorial causes, chiefly genetics, an altered gut microbiome and disruption of the gut-brain axis.[1,3]

Genetics. At least 50 chromosomal loci have been associated with body mass index (BMI), waist-to-hip ratio, body fat percentage, and extreme obesity. Yet the combined predictive value of these loci is low.[3] Some data indicate that physical activity mitigates the effect of a gene associated with fat mass and obesity; findings are inconsistent, however.[3]

Less sleep. Sleeping fewer hours per night has been associated with higher BMI as well as hormonal changes favoring food consumption.[12-14] Sleep apnea, a complication of obesity, contributes to interrupted sleep and thereby creates further risk of weight gain and metabolic disruptions.[15]

Endocrine disruptor chemicals. A growing body of evidence suggests that chemicals such as bisphenol A (BPA) can affect metabolic pathways, the gut microbiome, and energy homeostasis.[16,17]

Appetite: The Brain and Gut Hormones

The body's regulation of appetite, energy, adiposity, and weight involves regulatory feedback loops between the gut and the hypothalamus with the coordinated interplay of numerous hormones, peptides and neurotransmitters.[18] The hypothalamus regulates eating behavior and energy expenditure, and is influenced by an array of gastrointestinal hormones. Cholecystokinin, glucagon-like peptide (GLP)-1, peptide YY, insulin, and oxyntomodulin suppress appetite.[18] Leptin increases energy expenditure as well as suppressing food intake.[12,19] Most individuals with obesity are resistant to the effects of leptin and have high circulating levels of the hormone.[1,18]

One type of adipose tissue, brown fat, is metabolically active, promoting nonshivering thermogenesis and expending energy.[13] Irisin, a hormone released from muscle during exercise, has been shown to upregulate expression of genes associated with brown fat. It also may lead white adipose tissue to become more metabolically active and expend greater energy.[20] Circulating irisin levels are decreased in individuals with T2DM and obesity.[21] Irisin and the promotion of brown fat energy expenditure have been discussed as therapeutic targets in obesity.[13,20]

The Challenge of Keeping Weight Off

The experience of regaining weight is familiar to clinicians and patients. Reducing calorie intake leads to physiological changes promoting weight regain. Weight loss is followed by a reduction in overall energy metabolism[22] and a reversal of appetite regulatory hormones. Increases in the appetite stimulator ghrelin and decreases in the appetite suppressors leptin, GLP-1, cholecystokinin, and peptide YY ensue as the body attempts to return to its body weight set point. These changes may persist for 1 year after losing weight through a very-low-calorie diet.[19]

What Clinicians Can Do

Weight management must be an integral part of primary care in order to impact the increasing mortality, morbidity, and financial burdens of obesity. However, effective weight management must start with the elimination of obesity bias and a "shame and blame" viewpoint by healthcare providers.

BMI and waist circumference should be measured at least annually in every patient. Waist circumference should be measured more often in adults who are overweight (BMI, 25.0-29.9 kg/m^2) or obese (>30.0 kg/m^2). The author assesses BMI at every visit, and suggests intervening at a BMI of 25 kg/m^2 in patients with a family history of weight challenges or whose weight has been rising over time.

Broaching the topic of body weight can be difficult. The author often starts with asking, "How satisfied are you with your health?" Overweight or obese patients who say they are satisfied, or do not mention body weight, can be asked how satisfied they are with their weight. Characterizing weight as unhealthy or using the word adiposity may avoid some of the stigma attached to

Table 1 Metabolic Syndrome Components

Waist circumference	>40 inches for men, >35 inches for women
Triglycerides	≥150 mg/dL
HDL-C	<40 mg/dL for men; <50 mg/dL for women
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

HDL-C=high-density lipoprotein cholesterol.

Source: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.[10]

Table 2
CMS Reimbursement for Intensive Behavioral Therapy for Obesity

- **Must be delivered by a primary care physician or practitioner, in a primary care setting, to a Medicare beneficiary with obesity (BMI ≥30 kg/m²) who is competent and alert**
- **For 14 visits in first 6 months:**
  - **One face-to-face visit every week for the first month**
  - **One face-to-face visit every other week for months 2–6**
- **If 3 kg (6.6 lb) loss is achieved in 6 months (and documented in physician office records):**
  - **One face-to-face visit every month for months 7–12**
- **Intensive behavioral intervention for obesity should be consistent with the USPSTF 5-A Framework highlighted by**
  - **Assess** – **Advise** – **Agree** – **Assist** – **Arrange**

CMS=Centers for Medicare and Medicaid Services; USPSTF=US Preventive Services Task Force.

Source: Centers for Medicare and Medicaid Services. Decision memo for intensive behavioral therapy for obesity (CAG-00423N). https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NcaName=Intensive%20Behavioral%20Therapy%20for%20Obesity&bc=ACAAAAAAIAAA&NCAId=253. Accessed April 10, 2017.[26]

the terms overweight and obese. Many patients with unhealthy weight present to clinicians for other reasons, often including obesity-related complications, which pose opportunities to discuss weight management. When hesitating to mention the issue, the author suggests considering whether a clinician would ignore an incidental finding of 190/110 mm Hg blood pressure in a patient who presents with a sore knee.

Guidelines recommend an initial goal of 5% to 10% weight loss within 3 to 6 months,[23] which is sufficient to positively impact obesity-related complications.[24] Inform patients that losing even 3% to 5% of body weight can improve their health, and provide them what that weight loss target equates to in pounds.[23] For overweight or obese adults with cardiovascular risk factors (elevated blood pressure, hyperlipidemia, and hyperglycemia), sustained loss of 3% to 5% of body weight may lead to clinically meaningful reductions in triglycerides, blood glucose, A1C, and risk of developing T2DM, according to the recent guidelines for managing obesity. Losing more weight further improves blood pressure, blood glucose, and lipids, and reduces the need for medications to control these risk factors.[23]

Weight management programs should include behavioral modification, meal planning, and physical activity.[25]

Behavioral modification. Medicare reimburses primary care providers for intensive behavioral therapy for beneficiaries with obesity, if certain criteria are met (Table 2).[26]

Meal planning. Pre-diet assessment includes the patient's history of weight loss attempts, what has worked or not worked, weight gain triggers (eg, stress, carbohydrates, binging on certain foods), food preferences, and cultural influences.

All weight loss diets can achieve similar results. Pivotal to any effective weight loss diet—whether it is a low-fat, low-carbohydrate, Mediterranean, or vegan diet—is calorie reduction and long-term adherence. An average daily caloric reduction of 500 kcal is recommended.[23] Professional programs such as Weight Watchers, Jenny Craig, and Nutrisystem, as well as packaged meals, may be initially helpful for some patients. The author suggests reducing or eliminating consumption of sweetened beverages as a first step in calorie restriction.

Activity. Patients may accept the word activity more readily than exercise. Pain levels, mobility concerns, cardiovascular and respiratory capacity, and motivation should be evaluated prior to recommending an exercise program. Education about the health benefits of exercise beyond weight loss may motivate patients. In one randomized, controlled trial, older adults with obesity who were assigned to a diet without exercise lost more lean body mass and hip bone density than those engaged in diet plus activity. Strength, balance, and gait improved more in the diet and activity group.[27] Therapeutic exercise should include endurance, isometrics, and flexibility activities. Advising patients to start small may encourage them to integrate activity into their daily lives.

Pharmacotherapy may be added to diet, physical activity, and behavioral modification for patients with BMI >30 kg/m², or BMI ≥27 kg/m² and at least one complication.[23,25] The FDA has approved five drugs for long-term use in the chronic disease of obesity: orlistat, lorcaserin, pherntermine/topiramate ER, naltrexone/bupropion ER, and liraglutide. An Endocrine Society clinical practice guideline details pharmacologic options.[25]

Bariatric surgery. Patients with a BMI >35 kg/m² and obesity-related complications, or those with a BMI >40 kg/m² who have not responded to lifestyle modification with or without pharmacotherapy, should be considered for bariatric surgery.[23] There are many health benefits from bariatric surgery, although these benefits tend to decrease in those with excessive morbid obesity. A significant impact of bariatric surgery is its effect on appetite-regulating incretins and the microbiome.[28,29]

Conclusions

Obesity is a chronic disease that increases the risk of numerous complications. Although obesity is a treatable disease, it requires lifelong management and persistence on the part of both patient and clinician.

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DIABETES AND DEPRESSION

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Patients with diabetes face roughly double the risk of major depressive disorder (MDD), compared with people who do not have diabetes, according to a meta-analysis. The rate of depression in individuals with diabetes varied with the assessment tool but was 11% based on Diagnostic and Statistical Manual of Mental Disorders criteria current at the time of the study (1987, 1994).[1]

Comorbid depression in patients with diabetes has been associated with a nearly 1.5-fold higher risk of all-cause and cardiovascular death (hazard ratios [HR], 1.46 and 1.39, respectively), according to a systematic review and meta-analysis.[2] Comorbid major depression in diabetes has been linked to a 36% increased rate of microvascular complications and a 24% increased rate of macrovascular events, compared with diabetes and no depression.[3]

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A systematic review sheds light on the possible pathologic underpinnings of the links between depression and diabetes and the risk of complications. Depression was positively, significantly associated with three inflammatory markers (C-reactive protein, interleukin [IL]-6, and IL-1). Evidence is inconclusive as to whether depression or inflammation come first, or whether there is a bidirectional relationship.[4]

In addition, depression and diabetes are each independently associated with an elevated risk for dementia. People with both depression and diabetes face a higher risk of dementia than the sum of the risk associated with each condition separately, based on a national population-based cohort study of nearly 2.5 million people.[5]

Which comes first—diabetes or depression? An analysis of 6 years of claims data on 1 million beneficiaries from Taiwan National Health Insurance evaluated whether the risk of developing diabetes was higher in people with depression, and the converse. Findings supported a bidirectional relationship, with a stronger association between baseline depression and subsequent diabetes (HR, 2.02; 95% confidence interval [CI], 1.80-2.27; compared with individuals without baseline depression) than between baseline diabetes and subsequent depression (HR 1.43; 95% CI, 1.16-1.77, compared with individuals without baseline diabetes).[6]

Diabetes-Related Distress Distinct From Depression

Clinicians are beginning to appreciate the impact of the stress that many patients experience with managing diabetes, given its relentless impact on what and when to eat, the need for blood glucose monitoring and medication taking, and the worry about disease progression, complications, employment, and other issues. These symptoms are distinct from those of clinical depression. Approaching half (44.6%) of the participants in the multinational Diabetes Attitudes, Wishes and Needs second study (DAWN2™; n=8596) met the criteria for diabetes-related distress, whereas 13.8% exhibited likely depression, based on standardized instruments.[7]

Both depression and diabetes-related distress affect behaviors involved in managing diabetes. Diabetes-related distress has predicted poorer glycemic control and medication adherence. Depression symptoms have been linked to lower frequencies of diet adherence, physical activity, and glucose testing.[8]

Just raising the issue with patients can uncover symptoms, as well as demonstrate concern, which in itself may be therapeutic. Only 23.7% of patients in the DAWN2™ study reported being asked by their health care team how diabetes affects their life "most of the time" or "always."[7]

Patients with diabetes should be monitored for both depression and diabetes distress. Screening for the latter is especially important at stress points such as when treatment targets are not being met or when diabetes complications develop.[9] The Table lists screening instruments for each condition.[10-14] The 2-question initial screening tools—the PHQ-2 one each for depression and the DDS2 for diabetes distress—may be especially useful for clinical practice.

Psychosocial Intervention and Glycemic Control

A systematic review and meta-analysis evaluating the impact of psychosocial interventions on glycemic control found that intervention was associated with improved levels of glycosylated hemoglobin (A1C) (standardized mean difference, −0.29; 95% CI, −0.37 to −0.21, over a mean 6.8 months' follow-up) as well as mental health.[15] The interventions included education, cognitive-

Table: Screening and Evaluating for Depression or Diabetes Distress

Instrument	Description	Source
PHQ-2[10]	**2-question initial screening for depression; those who screen positive should be evaluated further (eg, PHQ-9)**	http://www.cqaimh.org/pdf/tool_phq2.pdf
PHQ-9[11]	**9-question screener**	http://www.phqscreeners.com/
GDS12[12]	**5-question initial screening for depression in older adults**	http://sagelink.ca/sites/default/files/clinical-resources/geriatric_depression_scale_5_item.pdf
DDS2[13]	**2-question initial screening for diabetes distress; those who screen positive should be evaluated further (eg, DDS17)**	http://www.diabetesed.net/page/_files/diabetes-distress.pdf
DDS17[14]	**17-question screening for diabetes distress**	http://www.diabetesed.net/page/_files/diabetes-distress.pdf

DDS=Diabetes Distress Scale; **GDS**=Geriatric Depression Scale; **PHQ**=Patient Health Questionnaire

Sources: Kroenke K et al. *Med Care.* 2003;41:1284-1292.[10] Kroenke K et al. *J Gen Intern Med.* 2001;16:606-613.[11] Hoyl MT et al. *J Am Geriatr Soc.* 1999;47:873-878.[12] Fisher L et al. *Ann Fam Med.* 2008;6:246-252.[13] Polonsky WH et al. *Diabetes Care.* 2005;28:626-631.[14]

behavioral therapy, social support, and relaxation; more than half (53%) focused on lifestyle only.[15] The review and meta-analysis characterized the A1C change as "modest," but in the author's clinical experience, medications do not always deliver the larger A1C improvements of 0.4 to >1.0% associated with them.[16] Often this is due to adherence issues.

Interventions to foster self-management have eased symptoms for patients with diabetes distress. Computer-assisted diabetes self-management improvement, alone or combined with problem-solving treatment, has been shown to significantly reduce levels of diabetes distress in patients who were not clinically depressed.[17] The American Association of Diabetes Educators offers downloadable material for patients about 7 self-care behaviors (https://www.diabeteseducator.org/patient-resources/aade7-self-care-behaviors). Small-group cognitive-behavioral therapy specific to patients with diabetes has been shown to lower scores on instruments measuring both depression and diabetes distress, compared with the impact of standard diabetes education. Participants in this study had symptoms of depression but did not meet the criteria for major depressive disorder.[18] Providers should consider referring patients with symptoms of depression or diabetes distress for additional assistance.

Conclusions

Depression is more common in patients with diabetes than in the general population[1] and is associated with a higher rate of death as well as of microvascular and macrovascular complications.[2,3] Comorbid diabetes and depression raises the risk of dementia more than the sum of risk observed with either condition alone.[5]

Distress related to the challenges of managing diabetes is common.[7] Both depression and diabetes-related distress can negatively impact patient self-management of diabetes.[8] Routinely evaluating patients for these conditions, even with 2-question screening tools, can identify patients in need of further evaluation. Diabetes self-management education, as well as problem-solving therapy and cognitive-behavioral therapy, can improve symptoms of depression and diabetes-related distress. Psychosocial intervention has been shown to improve A1C levels as well as mental health.

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TRANSITION TO ADULT CARE: EMERGING ADULTS WITH TYPE 1 DIABETES

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For patients with type 1 diabetes mellitus (T1DM) who are in their late teens or early twenties, the transition to adult health care services is a high-risk period. Given the currently longer periods of education, older age at marriage and establishing a separate home, the period from age 18 to 30 years has been called "emerging adulthood."[1] Medical practices may move an 18-year-old to adult care, but the psychological transition to full management of diabetes is a gradual process for most individuals.

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The issues of this life stage—eg, separating oneself from the family yet still requiring support, wanting to blend in with peers, engaging in high-risk behaviors (such as smoking, alcohol and substance abuse, and sex without protection and contraception), as well as, in some cases, incipient mental illness—affect diabetes management. The shift from the "warm and fuzzy," supportive atmosphere in pediatrics to the brisk, businesslike appointments in adult health care services, along with an aversion to assuming responsibility for self-injection, also conspire to raise the risk of worsening glycemic control and withdrawal from medical care.[2]

Glycemic Control

Among youth with diabetes (type 1 or type 2), teens have the highest rate of poor control (23.3%, ages 13-18; 28.5%, ≥19 years). Nearly one-third (32.4%) of adolescents ages 13 to 18 years old have good control; this drops to 17.8% for those ≥19 years of age.[3]

Psychosocial Issues

Self-reported depressive symptoms, which affected 15.2% of youth with type 1 diabetes in one series, have been associated with less frequent blood glucose monitoring and higher glycated hemoglobin (A1C) values.[4] Anxiety disorders also can complicate diabetes management.[2]

Eating disorders often surface in adolescence and pose a particular danger for individuals with diabetes. Type 1 diabetes has been associated with a 2.4-fold higher risk of developing an eating disorder.[5] Disordered eating was identified in 26% of young females with type 1 diabetes in one study.[6] More than one-third of the full cohort (35.6%) and 61% of the subset with a history of disordered eating reported reducing or skipping insulin doses to control weight,[6] a practice known as diabulimia.[7] Disordered eating and insulin misuse were each associated with an increased risk of having two or more serious diabetes complications.[6]

Tobacco, alcohol, and substance abuse. Evidence suggests that teens with diabetes engage in these risky behaviors at rates similar to those of their peers without diabetes.[2] Discussing these difficult topics with young patients—especially their effect on diabetes management—is an important element of health care. Marijuana use has been associated with lower fasting blood glucose levels.[8] Alcohol and substance abuse in adolescents have been associated with poorer glycemic control.[2,9] Cigarette smoking has been linked to elevated triglycerides and physical inactivity[10] and, in patients with poor glycemic control, microalbuminuria.[11]

Sex and Contraception

Half of sexually active teens reported engaging in sex without birth control while trying to avoid pregnancy. Many (43%) incorrectly said that all birth control methods are less effective for women with diabetes, and one-third said that women with diabetes have limited choice of birth control methods.[12]

Diabetic complications surface during adolescence and young adulthood (Table 1),[13] underlining the importance of regular follow-up care.

Lack of Follow-Up Care

Young adults transitioning from pediatrics to adult medical care are at high risk of being lost to follow-up.[2] A review identified five studies evaluating the frequency of follow-up appointments after the transition from pediatrics to adult care; all showed a decrease.[14] The rate of clinic attendance fell from 94% to 57% within 2 years after transfer to adult health care services, in a UK-based study.[15] Compared with continuous follow-up, missing a full year of planned medical appointments has been associated with poor glycemic control, as well as episodes of diabetic ketoacidosis (DKA) and retinopathy.[16]

Table 1. Complication Rates in Adolescents With Type 1 Diabetes (N=1433)

Complication	Percentage of Patients
Autonomic neuropathy	61%
Peripheral neuropathy	27%
Retinopathy	20%
Hypertension	16%
Microalbuminuria	6%

All patients <18 years old (median age, 15.7 years).

Source: Eppens MC, Craig ME, Cusumano J, et al. *Diabetes Care.* 2006;29:1300-1306.[13]

What Keeps Young Adults Engaged?

Table 2 lists the American Diabetes Association recommendations for moving patients from pediatric to adult diabetes care systems.[2] A structured transition program has been associated with retaining patients in care and, in some reports, improved glycemic control or reduced DKA-related admissions after entering adult services.[17-19] Elements of beneficial programs include an introduction to the adult provider prior to transition (eg, a joint visit between the pediatric and adult provider), a coordinator or patient navigator to assist with appointment scheduling, and after-hours phone support.[18,19] Availability of a navigator—in a program also featuring a patient website, newsletter, and a casual evening drop-in group—has been associated with a lower dropout rate from adult care after transition (11% vs 40%).[20]

Table 2. American Diabetes Association Recommendations for Care Transition

- Work with the patient's family so that the adolescent begins to assume self-care and appointment scheduling responsibilities, with parental support, at least 1 year ahead of transition
- Explain the difference in approach between pediatric and adult medical services
- Identify and discuss any issues with retaining health insurance
- Refer to adult provider(s); consider offering assistance with scheduling the first appointment
- Discuss birth control, preconception planning, as well as alcohol, drugs, and smoking, with a special focus on diabetes-related issues
- Evaluate young adults for disordered eating and affective disorders

Source: Peters A, Laffel L; American Diabetes Association Transitions Working Group. *Diabetes Care.* 2011;34:2477-2485.[2]

The author sponsors a young adult support group featuring activities such as rock climbing, bowling, and mini-golf. These settings offer opportunities for informal conversations about diabetes. Older young adults mentoring younger ones can be beneficial as well. The author was prompted to start the group after one young patient had 17 admissions for DKA within 9 months; this individual has had no admissions since joining the group 3 years ago. Conveying a nonjudgmental attitude and encouraging blood glucose monitoring and taking medication rather than emphasizing only A1C reduction may provide the emerging adult with the support to mature into diabetes self-management.

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HELPING PATIENTS ACHIEVE THEIR A1C GOALS: CASE STUDIES IN TYPE 2 DIABETES

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Clinicians apply glycemic goals and pharmacologic recommendations in the context of patient concerns and practical limitations. The best treatment option in theory may be one that is incompatible with patient goals, lifestyle, finances, or other issues. The following cases illustrate challenges in the application of American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) guidelines to patient care.

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Case 1. A Young Woman Newly Diagnosed With Type 2 Diabetes

Sonja, a 38-year-old female, presented for routine follow-up of prediabetes diagnosed 2 years ago. No medication was initiated at that time. Her past medical history includes gestational diabetes mellitus (GDM) 4 years ago. Her father and two sisters, as well as several aunts and uncles, have type 2 diabetes mellitus (T2DM). Comorbid conditions include irritable bowel syndrome (diarrhea-dominant), for which she receives no treatment. Sonja is Hispanic. She is a nonsmoker who works full time as a dentist.

Sonja was diagnosed with T2DM at this visit based on the following changes in her laboratory values compared with those of 2 years ago: fasting glucose increased from 113 to 133 mg/dL; glycated hemoglobin (A1C), from 5.8% to 7.1%; weight, from 179 to 185 lb; and body mass index (BMI), from 29 to 30 kg/m^2. Over the last 2 years, she lost 9 lb (about 5% body weight), then regained 15 lb. She walks or jogs four to five times per week unless it is "too cold outside."

GDM, Prediabetes, and Preventing Progression to T2DM

As a Hispanic woman with a history of GDM and a family history of T2DM, Sonja has multiple strong risk factors for developing T2DM.[1-3] Therapeutic lifestyle changes can prevent or delay T2DM to a greater degree than metformin. A lifestyle intervention program with goals of 7% weight loss and at least 150 minutes per week of physical activity reduced the incidence of diabetes by 58% compared with placebo over 2.8 years of follow-up; metformin reduced diabetes incidence by 31%.[4]

The AACE consensus statement recommends consideration of metformin or acarbose therapy to reduce the risk of progression to T2DM. Given Sonja's risk for T2DM, it would have been reasonable to start medication along with therapeutic lifestyle changes 2 years ago. Cardiovascular (CV) risk factors such as dyslipidemia and hypertension also should be addressed at this stage.[5]

T2DM: Choosing Treatment

Sonja's A1C of 7.1% suggests that postprandial glucose (PPG) excursions account for a preponderance of her diurnal hyperglycemia.[6] Results of Sonja's testing before and 1 or 2 hours after different meals yielded fasting glucose values of 111 to 130 mg/dL and post-meal levels of 152 to 185 mg/dL, confirming the prominence of PPG elevations. Other considerations in selecting therapy include avoiding weight gain and minimizing the risk of hypoglycemia, as well as minimizing cost and the risk of other side effects. The Figure displays a metric for integrating the multiple considerations involved in choosing therapy.[7]

The clinician initiated treatment with metformin immediate release, 500 mg twice daily. Sonja experienced stomach cramping and diarrhea—a common side effect—several times daily within 3 weeks of starting the medication.[8] Switching to the extended-release formulation eased the symptoms somewhat, but gastrointestinal (GI) intolerance remained. Metformin was discontinued. Sonja expressed strong reluctance to try another medication associated with GI side effects.

What's Next for Sonja?

Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) may be a good choice for managing Sonja's hyperglycemia but can be associated with GI side effects. Sulfonylureas are cost-effective but are associated with hypoglycemia and potential weight gain. Thiazolidinediones are not associated with GI side effects and are cost-effective but have the potential to cause weight gain. Using a lower dose may reduce this risk, in the authors' clinical experience. The increased insulin sensitivity associated with thiazolidinedione therapy may be beneficial for Sonja.[9]

Dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT-2) inhibitors allow for once-daily dosing[10-16] and are not associated with GI side effects. DPP-4 inhibitors are weight neutral; SGLT-2 inhibitors may lead to modest weight loss. DPP-4 inhibitors reduce PPG, which is an issue for this patient. The increased urinary volume associated with SGLT-2 inhibitors may be incompatible with Sonja's work schedule and limited time between patients.[9]

The clinician and Sonja decided to initiate treatment with a DPP-4 inhibitor. An SGLT-2 inhibitor or low-dose thiazolidinedione would have been a reasonable choice as well. Sonja tolerated the medication well. Her postprandial and fasting blood glucose values reached goal after 1 month. Her A1C at 3-month follow-up was 6.4%.

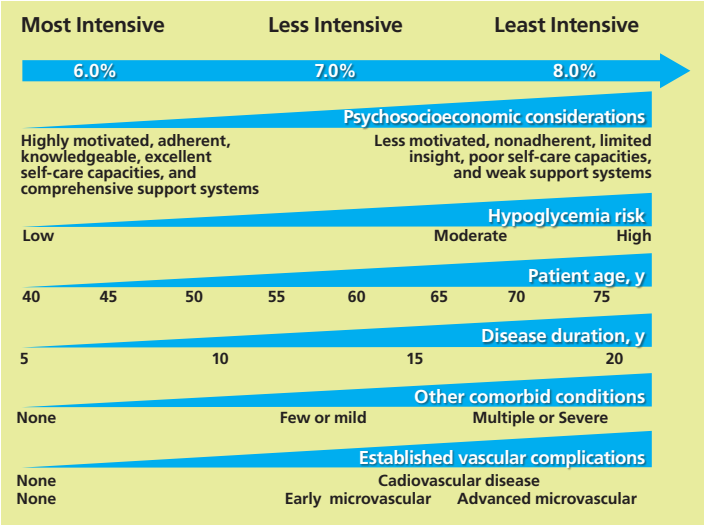
Case 2. New-Onset Heart Failure in an Older Man With T2DM

James, a 69-year-old African American male with a 15-year history of T2DM, presents to his primary care clinician following diagnosis with congestive heart failure at an emergency department (ED) visit. His comorbidities include diabetic retinopathy, diabetic peripheral neuropathy, chronic kidney disease (eGFR of 67 mL/min/1.73m2), coronary artery disease, and a myocardial infarction 11 years ago. Historically, his T2DM is well controlled, ranging from 6.8% to 7.4% over the past several years. He exercises year-round but is more active in the spring, summer, and fall. His A1C varies with this pattern: <7.0% for 3 seasons per year and higher during the colder weather months. James takes metformin 1,000 mg twice daily, pioglitazone 30 mg once daily, and glimepiride 4 mg once daily.

His ED visit was prompted by shortness of breath. He previously had been experiencing some fatigue, swelling, and weight gain. The ED clinician discontinued pioglitazone, given its association with heart failure (HF) risk and exacerbation.[9,17]

His current A1C is 7.9%. Blood glucose logs demonstrate acceptable fasting glucose levels with PPG elevations (103-130 mg/dL for prebreakfast [fasting] levels and 158-196 mg/dL for PPG levels).

Figure. Individualizing Glycemic Control



Source: Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. *Ann Intern Med*. 2011; 154:554-559[7]

Choosing Therapy

Given James's age, duration of T2DM, microvascular and macrovascular comorbidities, and resulting hypoglycemic risk, less intensive glycemic control (A1C goal >7.0%) is appropriate (Figure).[9,18] James would like to reduce his pill burden and is willing to accept an injectable medication. SGLT-2 inhibitors may increase diuresis and risk of volume depletion, especially if James receives a loop diuretic. They are not associated with hypoglycemia.[9] An SGLT-2 inhibitor has reduced relative risk of all-cause death, CV death, and HF hospitalization compared with placebo in patients with T2DM and high CV risk.[18] GLP-1 RAs are not associated with hypoglycemia and may offer greater antihyperglycemic efficacy than DPP-4 inhibitors.[9] A GLP-1 RA has been associated with lower risk of CV disease events and hospitalization compared with other antihyperglycemic therapies.[20]

The clinician, in consultation with James, decides to initiate GLP-1 RA therapy. A DPP-4 inhibitor or an SGLT-2 inhibitor also would have been a reasonable choice. The sulfonylurea agent is stopped to reduce the risk of hypoglycemia. The decision about which GLP-1 RA to prescribe would depend on factors such as insurance coverage, cost, and patient preference regarding injection frequency.

Conclusions

Metformin is recommended as first-line therapy in T2DM but is not always the best choice for every patient. Evaluating the relative contribution of fasting and post-meal glucose excursions to hyperglycemia, as well as assessing tolerability, safety, adherence, cost, and patient preference, are important considerations in choosing therapy. Patient adherence to self-monitoring blood glucose, healthy diet, physical activity, and treatment are central to the management of T2DM. Treating the patient as a partner in decision-making—including listening to the patient's opinions and fears—is imperative to successful care.

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PREVENTING AND MANAGING DIABETES IN OLDER ADULTS

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Diabetes among older adults is common (22%-33% of US adults >65 years old) and remains undiagnosed in an estimated one-third of patients. The incidence of diabetes rises with age until about 65 years old, when it levels off. Many diabetes complications are more common in older than younger adults (eg, myocardial infarction [MI], major lower extremity amputations, visual impairment, and end-stage renal disease).[1,2] Adults aged 75 years and older have the highest rate of emergency department visits for hypoglycemia of all adults with diabetes—roughly double the rate of visits for adults 45 to 74 years old.[3]

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Treatment goals. Guidelines for glycemic control, blood pressure (BP), and statin therapy depend on the patient's health status and life expectancy, eg, presence, number, and severity of chronic conditions, as well as level of cognitive and functional status (Table).[1] Glycated hemoglobin (A1C), glucose, and BP targets rise as health status falls. Those with more complicated health issues may face a higher risk of hypoglycemia and falls. The advisability of intensive glycemic control is questionable for frail adults in long-term care or with end-stage chronic illness. These individuals may not live long enough to derive benefit from such therapy and may be more vulnerable to adverse events.[1] Intensive glycemic control in middle-aged and older patients has been associated with a higher rate of death,[4] hypoglycemia, and serious adverse events.[5]

Screening for early detection and prevention. Prediabetes affects 51% of US adults who are at least 65 years old.[6] Type 2 diabetes mellitus often can be prevented or postponed by lifestyle changes or medication therapy.[1] Increasing physical activity within the patient's functional capacity as well as nutrition counseling, both for those of normal and excessive weight, are important. Poor nutrition may stem from factors such as lack of knowledge about nutrition or food preparation, dependence on someone else buying food, or visual, dental, or sensory impairments that affect cooking and eating. Discussing these matters with patients and their families may uncover issues in these domains. The American Diabetes Association (ADA) recommends screening all adults older than 45 years of age at least every 3 years.[7]

Functional assessment. Older adults with diabetes should be screened—and periodically reevaluated—for history and risk of falls, cognitive impairment, neuropathy, visual and hearing impairment, depression, and gait and balance issues. Impairments may affect the mental and physical ability to learn and execute tasks needed in diabetes self-management (eg, blood glucose testing, adherence to a complex diet, self-injection if applicable), and suggest the need for caregiver support or a change in regimen. Functional limitations may affect social interaction and lead to withdrawal, which may exacerbate cognitive and mental health status. Medication review and reconciliation is important to identify potential drug-drug interactions. This review should include an inquiry about over-the-counter products, vitamins, and herbal supplements that patients may not mention when asked about medications. All impairments and potential drug interactions identified should be addressed.[1]

Nutrition. Older adults are at risk for nutritional insufficiencies. Energy needs decline with age, potentially making it difficult to meet micronutrient requirements on a lower-calorie diet. Dulled or altered perceptions of taste and smell, difficulty swallowing, ill-fitting dentures, and a restrictive diet followed in part to control diabetes may lead to deficiencies.[1]

Pharmacotherapy. Avoid polypharmacy in older adults and minimize the use of medications associated with hypoglycemia (eg, sulfonylureas, especially glyburide). Metformin is the preferred choice, depending on the patient's glomerular filtration rate.[1,8] Medication cost burden must be considered when choosing therapy. As with any patient with diabetes, cardiovascular risk must be evaluated.[2]

Blood pressure control. Controlling blood pressure in adults with diabetes lowers the risk of many long-term diabetes complications and should be a focus in the care of older patients. Controlling BP to a mean of 144/82 mm Hg (with a goal of <150/85 mm Hg) significantly reduced the risk of diabetes-related death, stroke, microalbuminuria, and visual acuity deterioration and nonsignificantly lowered the risk of MI and death from all causes in one study (Figure).[9]

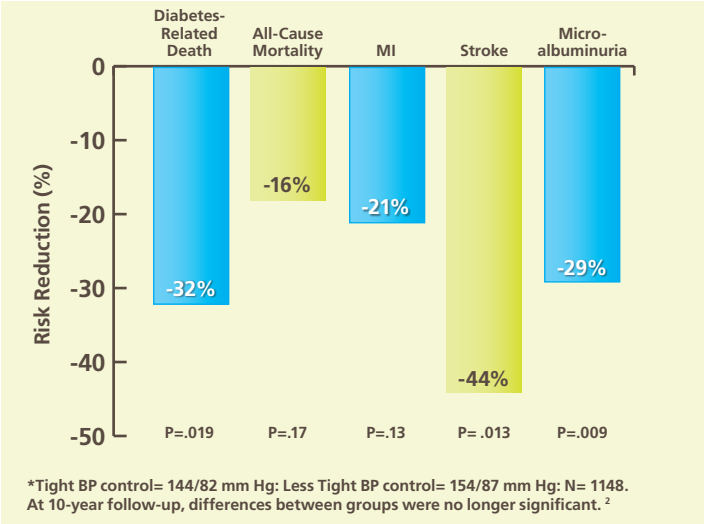
Table: Recommended Treatment Goals for Older Adults With Diabetes[1]

Health Status/Life Expectancy	A1C	Fasting Glucose (mg/dL)	Bedtime Glucose (mg/dL)	BP (mmHg)	Statins?
Healthy	<7.5%	90-130	90-150	<140/80	Yes, unless contraindicated or not tolerated
Intermediate/Complex[a]	<8.0%	90-150	100-180	<140/80	Yes, unless contraindicated or not tolerated
Very complex/Poor health[b]	<8.5%	100-180	110-200	<150/90	Consider likelihood of benefit

A1C=glycated hemoglobin; **ADL**=activities of daily living; **BP**=blood pressure.
[a]Multiple comorbid conditions requiring medication or 2+ ADL impairments or mild to moderate cognitive impairment.
[b]Long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies.

Source: Kirkman MS, Briscoe VJ, Clark N, et al. *J Am Geriatr Soc.* 2012;60:2342-2356.[1]

Figure. Patients With Diabetes Derive Significant Benefits on Numerous End Points With Tight* BP Control[1]



*Tight BP control= 144/82 mm Hg: Less Tight BP control= 154/87 mm Hg: N= 1148. At 10-year follow-up, differences between groups were no longer significant. [2]

1. UKPDS 38. BMJ. 1998;317:703-713
2. Holman RR, et al. *N Engl J Med.* 2008; 359; 1565-1576

Source: UK Prospective Diabetes Study Group. *BMJ.* 1998;317:703-713.[9]

Diabetes self-management education and care plan. When providing education and developing a care plan, consider any cognitive, physical, or functional impairments previously identified. Involving family members or other caregivers may increase the likelihood of creating a care plan to which the patient and his or her support network can adhere.

Conclusions

Individualizing the treatment of older adults with diabetes based on a thorough assessment of health status and life expectancy is central to care.[1] Well-controlled blood pressure reduces the risk of many long-term complications, including diabetes-related death.[9] Preventing hypoglycemia is paramount.[1]

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DIABETES AND PREGNANCY: THE IMPORTANCE OF PRECONCEPTION COUNSELING

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Women with both type 1 and type 2 diabetes mellitus require special attention before becoming pregnant. Pregestational (pre-existing) diabetes is associated with significant and potentially life-threatening complications for both the pregnant woman and her unborn child. These complications include spontaneous abortion, fetal demise, fetal anomalies, macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia, and maternal preeclampsia.[1] When pregestational diabetes is not optimally controlled, especially prior to conception, the risk for these complications is much higher.[2]

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Gestational diabetes mellitus (GDM) occurs during the latter part of pregnancy in women with no prior history of type 2 diabetes mellitus (T2DM) and can lead to complications that may affect the safe delivery of a healthy baby. While this condition usually resolves after delivery, as many as >70% of these women will develop T2DM later in life.[3] In fact, GDM is one of the major risk factors for the development of T2DM.

The great news is that good medical care-- (prioritizing patient education and counseling about the importance of pre-pregnancy planning, self-care, strict glycemic control, and risk reduction before pregnancy-- makes it possible for women with either pregestational diabetes or GDM to have successful, safe pregnancies and healthy babies. This article reviews the importance of preconception counseling.

Pregestational Diabetes

Optimize glycemic control. Hyperglycemia is a known teratogen. Complications resulting from uncontrolled diabetes during pregnancy include intrauterine fetal demise and infant death (4.56-fold and 1.86-fold higher risk, respectively, for offspring of mothers with pregestational diabetes).[1,4] The risk of fetal malformations increases in proportion to A1C elevations during the first 10 weeks of pregnancy, when many women do not realize that they are pregnant. The seriousness of this risk is underscored by a consensus panel's recommendation that patients use effective contraception until blood glucose levels are stable.[5] The risk of fetal and infant death has been associated with glycated hemoglobin (A1C) >6.6% during pregnancy.[4]

Macrosomia, which occurs in the third trimester, affects 27% to 62% of infants born to mothers with diabetes, compared with roughly 10% of children of nondiabetic women. This complication raises the risk of cesarean delivery, birth trauma, fetal death, and neonatal complications.[5]

Diabetes places the pregnant woman at risk for complications, too. Of particular concern is the development of preeclampsia, especially if the woman has underlying hypertension. Women with type 1 diabetes have a 2- to 4-fold higher risk of preeclampsia when compared to women without diabetes.[6,7] Elevated prepregnancy A1C values have been associated with a higher risk of preeclampsia.[6] In addition, microvascular complications, in particular the development and progression of diabetic retinopathy and nephropathy, are also associated with pregnancy.[1,5] Urinary albumin excretion rises during pregnancy.[1] Preeclampsia raises the risk of diabetic nephropathy in women with type 1 diabetes.[8]

Despite these data, women with diabetes often do not receive preconception counseling (≤62% of those with type 1 and <36% of those with type 2).[9] Preconception counseling about these risks and the importance of effective contraception should be included in well visits and routine diabetes visits for all females of childbearing age, starting at puberty and including women who have recently given birth.[5] Preconception counseling also should address the importance of achieving A1C <6.5% or as close as possible without severe hypoglycemia in order to reduce the risk of congenital anomalies.[1]

Address comorbidities. Women planning pregnancy may have had diabetes for a decade or more and may have underlying diabetes-related microvascular complications. These include retinopathy, nephropathy, and neuropathy. Those with type 2 diabetes are particularly at risk for having cardiovascular disease as well. Assessment for and aggressive treatment of the comorbid conditions associated with cardiovascular disease (hypertension, dyslipidemia, and peripheral vascular disease) must occur at all preconception appointments as well as at the initial prenatal visit. Specialist care is often required. Women with diabetes will benefit from a multidisciplinary approach to care during preconception planning, pregnancy, and the postpartum period.[5]

Stop potentially harmful medications. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and statins are potentially teratogenic and are contraindicated during pregnancy. These agents should be stopped in women actively attempting to become pregnant. The American Diabetes Association advises against prescribing these medications to sexually active women of childbearing potential who do not use reliable contraception.[1] Most antihyperglycemic agents other than insulin also are contraindicated in pregnancy.[5] Safety data in pregnancy are not available for most oral agents. While metformin and glyburide are sometimes used during pregnancy, both agents cross the placenta, and concern for adverse effects to the fetus exists. There are reports that metformin may increase the risk of prematurity.[1] Compared with insulin, glyburide has been associated with an elevated risk of complications for the newborn (eg, respiratory distress, birth injury, being large for gestational age, and neonatal intensive care unit admission).[10] Insulin is the antihyperglycemic treatment of choice during pregnancy as it does not cross the placenta in measurable amounts.[1]

Monitor weight. A higher maternal body mass index (BMI) is associated with higher risk of various complications, including a large neonate (>90th percentile birthweight), cesarean delivery, cord blood C-peptide in the >90th percentile, and preeclampsia. These risks are independent of maternal glycemic control.[11]

Appropriate weight gain is recommended for all pregnant women, regardless of prepregnancy body weight.[5] Therefore, weight loss should take place prior to pregnancy. Maternal weight gain of less than 11 lb during pregnancy in women who are overweight or obese raises the risk of negative outcomes for the baby, including decreased neonatal fat and lean mass, smaller head circumference, and the newborn being small for gestational age.[12]

Gestational Diabetes

GDM affects 4.6% to 9.2% of US pregnancies and by definition is first identified in the second or third trimester of pregnancy.[13] Diabetes diagnosed in the first trimester should be classified as

pregestational diabetes. Women should be screened for diabetes at their first prenatal visit in order to detect previously undiagnosed diabetes as early as possible.[14]

Risk factors for GDM include body weight (overweight or obesity), advanced maternal age, and family history of type 2 diabetes mellitus (T2DM).[15,16] Overweight or obesity affects 45% of women at the beginning of pregnancy, up from 24% in 1983.[17] GDM prevalence is higher among women of Asian and Pacific Islander (17.1%) or Hispanic (11.4%) descent, compared with African American, non-Hispanic white, and other women (7.4%, 6.9%, and 7.7%, respectively).[18]

GDM also is associated with elevated risk of fetal complications such as macrosomia, perinatal asphyxia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, and neonatal hypoglycemia.[19] Women should be tested for GDM at 24 to 48 weeks' gestation.[14] Most cases of GDM (70%-85%) can be managed with diet and lifestyle therapy. Insulin is the first choice if medication is required.[1]

Diabetes persists in some women after delivery. As many as 5% to 10% of women with GDM are diagnosed with T2DM shortly after pregnancy.[20] GDM sharply raises a woman's risk for developing T2DM later in life—by 7-fold within 5 to 10 years after giving birth.[13] GDM conveys a life-long risk for the development of type 2 diabetes. Women with GDM must be screened for diabetes at 4 to 12 weeks postpartum, and at least every 3 years thereafter.[14]

Conclusions

Uncontrolled diabetes during pregnancy is associated with a high risk of fetal and infant death, fetal malformations and anomalies, and maternal preeclampsia. Many of these outcomes are linked to A1C level; aggressive glycemic control reduces these risks.[1,4-7] Preconception counseling is a must for women with pregestational diabetes, as is optimal glycemic control prior to pregnancy.[1] Medications should be adjusted, and comorbidities, including overweight or obesity, should be addressed prior to pregnancy where possible.

All women should be screened for diabetes at the initial prenatal visit, then again at 24 to 48 weeks gestation. If a woman develops GDM, she must be screened at 4 to 12 weeks postpartum. Reported lifetime risk of T2DM after GDM is as high as >70%, mandating lifetime surveillance for T2DM. If medication is necessary in GDM, insulin is the recommended first-line treatment.[14]

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PREVENTING AND MANAGING DIABETIC KIDNEY DISEASE

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Diabetes is the most common cause of end-stage renal disease (ESRD) in the United States.[1] Protecting the diabetic kidney involves monitoring kidney function—including urinary albumin—while avoiding iatrogenic kidney damage when choosing and dosing drug therapy.

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Monitor urinary albumin

The most recent guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group define chronic kidney disease (CKD) prognosis by albuminuria level as well as estimated glomerular filtration rate (eGFR) (Figure).[2] Urinary albumin predicts progression to ESRD, adding predictive value to the older model using only eGFR.[3-5] A urine albumin-to-creatinine ratio (UACR) is the preferred method for measuring albuminuria,[2] which can be performed by the lab or by use of a urine.[4,5] Testing for urinary total protein, of which albumin is one component, is not recommended due to the superior sensitivity and specificity of urinary albumin for CKD diagnosis and staging.[2] Yet in 2014, urinary albumin was tested in less than half (48%) of Medicare patients with the risk factors for ESRD: diabetes and hypertension.[6]

Glycemic control

Guidelines from kidney and diabetes organizations recommend less stringent targets (ie, not treating to ≤7.0%) for those at risk of hypoglycemia and/or with comorbidities.[2,7] This is especially true for those patients with underlying cardiac disease or the "fragile" elderly patient.

ACEI or ARB not ACEI + ARB

Use of an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is recommended in ALL adults with CKD. For those patients with diabetes and a positive UACR, an ACE or ARB is recommended even if the patient is not hypertensive.[2] An acute rise in serum creatinine (SCr) of up to 25% may be associated with initiation of ACEI or ARB therapy. Treatment can be continued as long as SCr stabilizes within a couple of months.[8,9] Concomitant ACEI and ARB therapy should not be used; compared with either agent alone, combination therapy has been associated with a higher rate of adverse events (eg, hyperkalemia, hypotension, and kidney failure) without improving survival.[10]

Whether to stop ACEI or ARB therapy in CKD stages 4 or 5 is under investigation.[11] Current KDIGO guidelines recommend continuing ACEIs and ARBs although they do note that "sick day" rules may be introduced. That is, stopping any medication (blood pressure pills, oral hypoglycemic, statins or other potentially nephrotoxic agents) when a patient is not eating and/or drinking to protects a patient with CKD from acute kidney injury (AKI).[2]

Antihyperglycemic Therapy in CKD

- New metformin labeling: The US Food and Drug Administration recently revised the threshold at which metformin should be discontinued due to the risk of lactic acidosis from an eGFR of 50 mL/min to an eGFR of 30 mL/min. Starting metformin in patients at an eGFR of 30 to 45 mL/min is not recommended.[12]
- Sodium-glucose cotransporter 2 (SGLT-2) inhibitors: Early studies are identifying a renoprotective side to these medications, though the supporting outcomes data are obtained from a sub-analysis of a cardiac trial. Kidney-specific endpoint trials are pending but it appears that both the glucose- and blood-pressure-lowering properties of this medication class make it an excellent choice in CKD.[13]
- Insulin: Exogenous insulin is mainly excreted by the kidney,[14] and thus, less insulin is needed as loss of kidney function progresses.
- Sulfonylureas and meglitinides: Glipizide and repaglinide are the safest of these classes of medications for the kidney.[14]
- Thiazolidinediones: While these medications are safe in CKD, they are rarely used due to their tendency toward fluid retention.[14]
- Dipeptidyl peptidase (DPP)-4 inhibitors: These are generally safe in CKD but only linagliptin does not require renal dosing adjustments.[14] Trials are pending as to the renoprotective efficacy of this class (eg, clinicaltrials.gov identifier NCT02106104). Stay tuned!
- Glucagon-Like Peptide (GLP)-1 Receptor Agonists (RA): Although there have been reports of AKI with GLP-1 RAs, most cases resulted from gastrointestinal symptoms leading to dehydration and thus kidney injury.[15-17] The LEADER trial showed liraglutide was renoprotective.[18]

Hypertension

Even if hypertension did not cause CKD, most patients will develop hypertension as kidney function deteriorates. Whether primary or secondary in nature, management of hypertension is vital. In terms of mortality risk, blood pressure for patients with CKD should be maintained at 130–149/70–89 mmHg. Lowering diastolic BP below <70 mmHg may be harmful[19], ACEI, ARBs, diuretics, calcium channel blockers, and beta-blockers all play a role in management of hypertension in diabetic kidney disease (DKD). Often the patient with DKD will need three or four blood pressure medications.

First Do No Harm: Healthy Lifestyle and Kidney Function

A small study (n=6) reported that weight loss of 12% over 12 weeks was associated with significantly reduced SCr and UACR levels in patients with diabetes and CKD.[20] Smoking is associated with kidney disease progression, especially in adolescents[21] and African Americans.[22] Regular physical activity in people with mild to moderate CKD has been shown to reduce the risk of death.[23]

Conclusions

Management of the patient with DKD is multi-factorial and requires frequent monitoring of kidney function to decrease incidence of iatrogenic AKI. Diabetic medications that are acceptable in one stage of CKD are may not be acceptable in a different stage.[14] The goal A1C for the patient with DKD is 7 to 7.5%[2] The blood pressure goal is 130-159/70-89 mmHg.[19] Lifestyle management is vital for this population and stopping smoking, adding exercise, and/or losing weight can prolong the lifespan of the diabetic kidney.[23] Studies of the newer diabetic medications (DPP-4 inhibitors, SGLT-[2] inhibitors, and GLP-1 RAs) show promise for the patient with DKD.[13,18] Final results from specific renoprotective trials are 1–2 years away.

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IATROGENIC KIDNEY INJURY: CASES AND LEARNINGS

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Inappropriate prescribing of medications occurs often in patients with chronic kidney disease (CKD). In a 2015 analysis of data from more than 83,000 Veterans Affairs outpatients nationwide, nearly one-sixth (13%) of veterans with stage 3 CKD (creatinine clearance [CrCl] of 30 to 49 mL/min) and nearly one-third (29%) of those with stage 4 CKD (CrCl of 15 to 29 mL/min) received one or more drugs that were contraindicated or prescribed at an excessive dose given the patient's kidney function.[1]

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Medications are a common cause of iatrogenic adverse drug reactions in patients with CKD. More than two-thirds (69.3%) of patients with CKD (n=267) in the Safe Kidney Care study developed either an adverse safety incident that the patient attributed to medication or a hazardous clinical disturbance that move the potential correction with treatment or medication modification.[2]

Antibiotics are a frequent culprit; two-thirds of 1,464 antibiotic prescriptions written for ambulatory older patients (≥66 years old) with CKD stage 4 or 5 reflected treatment in excess of kidney dose adjustment guidelines, according to a database analysis.[3]

The physician assistants (PAs) and nurse practitioners of the National Kidney Foundation have shared the following true stories of the consequences of inappropriate medication dosing in patients with CKD. For medication dosing purposes, a CrCl and a GFR are interchangeable.

Sam, a 45-year-old, wheelchair-bound man with hypertension, diabetes, CKD (stage 4), peripheral vascular disease (PVD), hyperkalemia, edema, right leg amputation below the knee, and left foot ulcer, was diagnosed with pneumonia by a pharmacy clinic. Not knowing the patient's stage of CKD, the clinic used a standard dose of levofloxacin, which caused prolongation of the QT interval and Sam's death. All fluoroquinolones, including levofloxacin, can prolong the QT interval. Renal dosing for levofloxacin can either be managed at a lower dose or with a loading dose for the first day, followed by a less frequent and/or lower doses.[4] The author often uses levofloxacin 250 mg every other day in patients with CKD stage 4/5.

Yvette is a 48-year-old female with a past medical history of hypertension, coronary artery disease, CKD stage 4, and obesity. She notes that the left side of her face looks frozen and presents to the emergency department (ED) to rule out a stroke. After being diagnosed with Bell's palsy (inflammation of cranial nerve VII), she is placed on prednisone (20 mg/day) and acyclovir 400 mg three times daily. Three days later, she again presents to the ED with mental status changes. A quick look at the US Food and Drug Administration (FDA) package insert highlights the fact that due to Yvette's CKD, her mental status changes are due to the acyclovir dosing.[5] As there is no antidote, Yvette's body eventually clears the dose but it takes 3 more days for her mental status to return to normal.

Ted, a 64-year-old PA with a past medical history of coronary artery disease, benign prostatic hypertrophy and CKD (stage 3), was seen by cardiology with a slightly elevated blood pressure. His cardiologist doubled Ted's lisinopril dose. After the dose increase, Ted became dizzy and collapsed. An EKG revealed peaked T waves, later determined a SCr of 6.8 mEq/L. Ted was treated with intravenous fluids and a Foley catheter, lowering his potassium to 4.5 mEq/L. Yet his kidney function remained low (GFR12 mL/min), only rebounding to 15 mL at 30 days post-collapse. The acute kidney injury (AKI) caused permanent damage, and even a transurethral resection of the prostate only increased his kidney function to 24 mL/min. The acute iatrogenic damage will stay with Ted for his kidney's lifespan.

Conclusions

AKI can result from inappropriate medication dosing in a patient with CKD. Kidney impairment raises the risk for AKI and AKI can promote CKD progression.[6] Following kidney dosing guidelines found in FDA package inserts and, if possible, a pharmacist consult can save lives and prevent adverse drug reactions.

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