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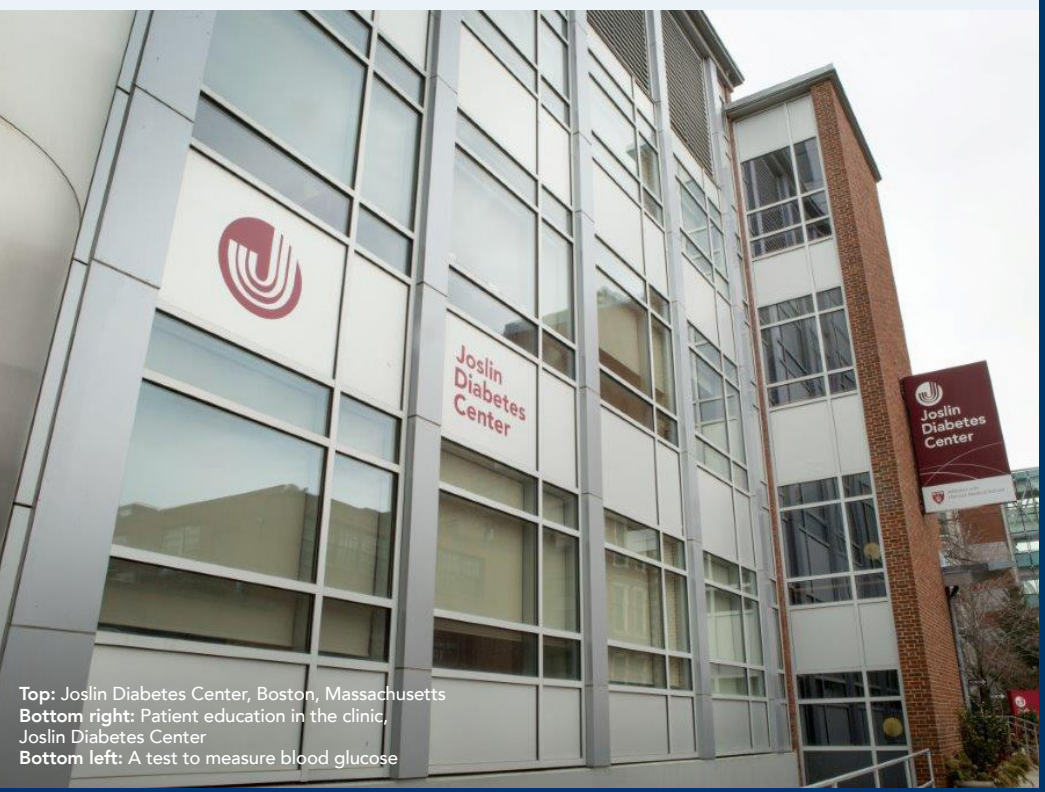
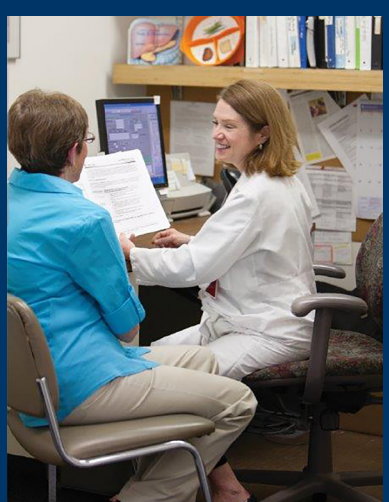
Joslin Diabetes Center CLINICAL GUIDELINES



Top: Joslin Diabetes Center, Boston, Massachusetts
Bottom right: Patient education in the clinic, Joslin Diabetes Center
Bottom left: A test to measure blood glucose



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FROM THE CHAIRMAN

Collaborating With Joslin Diabetes Center to Save Lives

AT *THE AMERICAN JOURNAL OF MANAGED CARE*®, we say it often: Collaboration saves lives. Bringing the most recent developments in research, clinical practice, and quality measurement to a wider audience gives clinicians the ability to learn from one another no matter where they practice.

With this issue of *Evidence-Based Diabetes Management*™ (*EBDM*™), we are taking our long-term partnership with Joslin Diabetes Center to the next level as we publish the Joslin Clinical Guidelines. Dr Robert A. Gabbay, who serves as editor in chief of *EBDM*™, brought this idea to us last fall, and we shared his enthusiasm for bringing the best practices of the world-renowned Joslin Diabetes Center to physicians, nurses, pharmacists, nutritionists, diabetes educators, and others who care for those learning to manage this disease. Our editorial team worked with Dr Om P. Ganda, chair of the Clinical Oversight Committee at Joslin, to organize updated editions of the guidelines, which have been in use at Joslin for several years. Drs Ganda, Gabbay, and their colleagues have ensured that the guidelines reflect the latest announcements from the FDA, as clinicians have a growing array of therapeutic options for treating people with diabetes.

Most people living with type 2 diabetes receive treatment from their primary care physician, and it is our hope that sharing the Joslin Clinical Guidelines through the leading source of managed care research will serve this group of physicians as well as health plans as they strive to deliver the best care possible.

Sincerely,

Michael J. Hennessy, Sr
Chairman and CEO

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FROM THE EDITORS

Bringing the Joslin Clinical Guidelines to the Diabetes Care Community

GANDA

GABBAY

WITH THIS ISSUE OF *Evidence-Based Diabetes Management*™, we present publication of the first installment of the Joslin Clinical Guidelines, which are the principles that influence our clinical behavior every day at Joslin Diabetes Center and our affiliates and partners around the world. Although some sections of the guidelines have been in use for years, our collaboration with *The American Journal of Managed Care*® represents our first cohesive effort to update and publish the guidelines in a searchable format, one more easily shared with audiences beyond Joslin. It is our hope that publication of the guidelines, in partnership with the leading peer-reviewed journal dedicated to research and leadership in health outcomes, will bring the Joslin Clinical Guidelines into wider use. Through use of these guidelines, patients around the world can benefit from the knowledge, research, and practices developed over more than a century of focus on the care of people with diabetes.

As explained in the overview, the Joslin Clinical Guidelines are developed by the Clinical Oversight Committee at Joslin Diabetes Center, for which we serve as chair and ex-officio members, respectively. Our Clinical Oversight Committee includes physicians, nurses, certified diabetes educators, and behavioral health specialists who are experts in treating individuals with diabetes of all ages. More importantly, our committee members are leaders in developing strategies to help those living with diabetes self-manage their disease. Our process invites the participation of faculty with special expertise who are not on the Clinical Oversight Committee; these experts serve on working groups for individual guidelines. We thank all who have participated in the development of the guidelines over many years for your contributions.

The guidelines are evidence based, and the overview explains our use of a modified form of the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation). For this installment, we present the following: the Clinical Guideline for Adults With Diabetes; the Clinical Nutrition Guideline for Overweight and Obese Adults With Type 2 Diabetes (T2D) or Prediabetes, or Those at High Risk for Developing T2D; the Guideline for Detection and Management of Diabetes in Pregnancy; the Guideline for the Care of the Older Adult With Diabetes; and the Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes. With this installment, we have covered the major issues that most physicians, registered dietitians, certified diabetes educators, nurse practitioners, physician assistants, and pharmacists will encounter in clinical practice. The Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes has been revised to reflect recent scientific advances and regulatory developments that offer more choices than ever for diabetes management. We repeat the position that Joslin Diabetes Center announced earlier this year, when we concurred with the American Diabetes Association, the American Association of Clinical Endocrinologists, the Endocrine Society, and the American Association of Diabetes Educators that those with diabetes should aim for glycated hemoglobin of 7% or lower, not between 7% and 8%.

Is diabetes self-management challenging? Yes. But as these guidelines reflect, and as we see at the Joslin Diabetes Center every day, self-management can succeed through empowering our patients and engaging them alongside appropriate pharmacotherapy. We hope this publication serves as both a resource and an inspiration to providers who are struggling with what to do next for their patients. We invite your feedback and look forward to sharing more of the best practices developed at Joslin—so that individuals with diabetes can live the best lives possible.

Sincerely,

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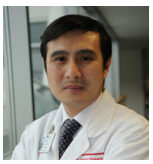

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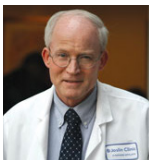

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OVERVIEW

The **Joslin Clinical Guidelines** aim to support clinical practice and influence clinical behaviors in order to improve clinical outcomes and assure that patient expectations are reasonable and informed. The guidelines are developed and approved through the Clinical Oversight Committee, which reports to the chief medical officer of Joslin Diabetes Center. The guidelines are established after careful review of current evidence, medical literature, and sound clinical practice. The Clinical Guideline for Adults With Diabetes will be reviewed periodically and modified as clinical practice evolves and medical evidence suggests.

The guidelines are evidence-based. A modification of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[1] has been adopted to give the user an evaluation of the evidence used to support each standard of care. The **Table** describes the categories in which methodological quality and strength of recommendations have been classified. Evidence levels are graded 1A through 2C, as indicated in brackets. Where evidence is not graded, recommendations are made based on the expertise of the Clinical Oversight Committee.

REFERENCE

1. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Physicians task force. *Chest*. 2006;129(1):174-181.

TABLE. Grading System Used in Joslin Clinical Guidelines

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence
1A Strong recommendation High quality of evidence	Benefits clearly outweigh risk, and vice versa.	Consistent evidence from well-performed, randomized, controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
1B Strong recommendation Moderate quality of evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomized, controlled trials with important limitations (inconsistent results; methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research is likely to have an impact on our confidence in the estimate of the benefit and risk and may change the estimate.
1C Strong recommendation Low quality of evidence	Benefits outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.
2A Weak recommendation High quality of evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well performed, randomized, controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
2B Weak recommendation Moderate quality of evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results; methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
2C Weak recommendation Low quality of evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.

Evidence graded less than "A" is acceptable to support clinical recommendations in a guideline. It is also assumed that for many important clinical recommendations, it would be unlikely that level A evidence be obtained because appropriate studies may never be performed.

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CHAPTER 1.
Clinical Guideline for Adults With Diabetes

Samar Hafida, MD; Om P. Ganda, MD, Chair, Clinical Oversight Committee; Robert A. Gabbay, MD, PhD, FACP; and the members of the Joslin Clinical Oversight Committee

From the Adult Diabetes and Clinical Research sections, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts

The ***Joslin Clinical Guideline for Adults With Diabetes*** is designed to assist primary care physicians and specialists as they individualize the care of and set goals for nonpregnant adults with diabetes. This guideline focuses on the unique needs of the patient with diabetes. It is not intended to replace sound medical judgment or clinical decision making and may need to be adapted for certain patient care situations in which more or less stringent interventions may be necessary. This guideline was approved May 17, 2017, and updated May 25, 2018.

1.1.0 APPROACH TO CARE

1.1.1 Individualizing patient care:

The needs and goals of each patient are unique. A treatment plan must be based on a thorough assessment and requires an understanding of not only the patient's medical needs, but also other factors that may influence the treatment plan such as social history, race, cultural issues, ethnicity, education needs (including literacy and numeracy), comorbidities, and barriers to care. The patient's diabetes management plan should include medical treatment, interventions, follow-up, and ongoing support. Use of the electronic medical record may help facilitate care, by enabling the team to track progress, ensuring goals are met, and facilitating communication flow among team members and the patient.

1.1.2 The patient-centered approach:

Diabetes is a condition that requires considerable self-management. A collaborative counseling model that involves the patient in decisions and goal-setting helps promote behavioral change. Whenever appropriate, with the patient's consent, involving family members and nonclinical caregivers in medical visits and education is valuable.

1.1.3 Working in a team:

Diabetes is best managed by a team, which may include clinicians, diabetes educators (DEs), dieticians, exercise physiologists, and behavioral health specialists. The patient should be informed and fully aware of what roles the various team members play. If access to a team is not possible within the office practice, it is useful to identify community resources. Clear communication among all providers is critical to ensure patients' needs are being met.

1.1.4 Frequency of medical visits:

While the frequency of visits for ongoing care should be individualized, monitoring the patient's progress through medical visits is recommended at least 2 to 4 times/year. Special attention should be given to patients who do not keep scheduled appointments, have frequent hospitalizations, or miss days of work/school. Since many factors contribute to patients' ability to manage their care, the provider should:

- Engage patients in identifying and resolving contributing factors or barriers to underutilization or overutilization of healthcare services. Patients with challenging care may benefit from consultation with endocrinologists focused on diabetes care.
- Refer to a DE, registered dietician (RD), social service professional, or behavioral health professional to address possible barriers and/or psychosocial issues
- Establish a process of follow-up communication regarding adherence to the treatment plan and sustaining behaviors

1.2.0 DIAGNOSIS OF DIABETES MELLITUS

1.2.1 General criteria for diagnosis:

The diagnosis of diabetes mellitus can be made based upon:

- Random plasma glucose ≥200 mg/dl (11.1 mmol/L) and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) *OR*
- Fasting plasma glucose* ≥126 mg/dl (6.9 mmol/L) *OR*
- Results of a 2-hour 75-gram oral glucose tolerance test* ≥200 mg/dl (11.1 mmol/L) *OR*
- Glycated hemoglobin* (A1C) ≥6.5% (46 mmol/mol)**

*These tests should be confirmed by a repeat test, on a different day, unless unequivocally high.

***An A1C level of ≥6.5% on 2 separate days is acceptable for diagnosis of diabetes* [**1B**]. *However, some individuals may have an A1C <6.5% with diabetes diagnosed by previously established blood glucose criteria. Therefore, presence of either criterion is acceptable for diagnosis. Those with an A1C of 5.7%-6.4% (39-46 mmol/mol) are considered to have prediabetes, and they are at high risk for developing diabetes. These patients should be treated with lifestyle changes and followed more frequently.*

The A1C test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay.

A point-of-care (POC) A1C is not acceptable for diagnosis of diabetes.

1.2.2 Hemoglobin A1C (A1C)

Diagnosis:

See above section on Diagnosis of Diabetes Mellitus.

1.2.2a Goals:

The A1C target goal should be individualized for each patient. A goal of <7.0% (53 mmol/mol) is chosen as a practical level for most patients to reduce the risk of long-term complications of diabetes. Achieving this goal is recommended if it can be done safely and practically **[1B].**

Alternative A1C goals may be set, based upon presence or absence of microvascular and/or cardiovascular complications, hypoglycemic unawareness, cognitive status, and life expectancy **[1A].** For patients with longstanding type 2 diabetes (T2D) with preexisting cardiovascular disease (CVD), or high coronary artery disease (CAD) risk (diabetes plus 2 or more additional risk factors), consider revising A1C goals to avoid adverse consequences of tight glycemic control, eg hypoglycemia **[1A]**.

Some clinicians may translate patients' A1C level into their estimated average glucose level, based upon the work of the A1C Derived Average Glucose Study. This metric is also a valid tool that may be used to assess the response of patients to their diabetes treatment plan **[1C]**.

Joslin's A1C target goal for most patients is consistent with that of the American Diabetes Association (ADA). Other expert panels, such as the American Association of Clinical Endocrinologists, suggest that the A1C target goal should be <6.5% in those newly diagnosed with diabetes and without comorbidities. Recent recommendation of 7% to 8% for most individuals with T2D by the Ameican College of Physicians are not endorsed by us (see caveats above).

1.2.2b Caveats:

The A1C may not reflect glycemic control in special patient populations, including pediatric and geriatric populations, patients with anemia or other blood disorders resulting in rapid turnover of red blood cells, in chronic liver and renal disease, following recent blood transfusions, or while patients are hospitalized. It is therefore important to interpret A1C results accordingly when determining treatment plans and goals.

1.2.2c Monitoring:

Monitor the A1C 2-4 times a year as part of the scheduled medical visit **[1C]** to evaluate efficacy of the treatment plan. The A1C may be checked more frequently if the treatment program requires revision, or the advice regarding behavior changes needs reinforcement.

Having the A1C result at the time of the visit can be useful in making timely treatment decisions **[1C].** Alternatively, the A1C may be performed prior to the medical visit POC method.

1.2.2d Treatment:

If A1C is ≥7% and <8%, or above the individualized goal, for 6 or more months:

- Review and clarify the management plan with the patient with special attention given to address:
  - nutrition and meal planning

- physical activity
- medication administration, schedule, and technique
- self-monitoring blood glucose (SMBG) schedule and technique
- treatment of hypoglycemia and hyperglycemia
- sick day management practices

- Reassess goals and adjust medication as needed **[1A]**
- Establish and reinforce individualized glycemic goals with patient
- Refer patient to a certified diabetes educator (CDE) for evaluation, diabetes self-management education (DSME), and support for ongoing consultation **[1C]**
- Consider referral to RD for medical nutrition therapy (MNT) **[1B]**
- Schedule follow-up appointment within 3-4 months or more frequently as the situation may dictate

If A1C is ≥8%:

- Review and clarify the plan as previously noted
- Assess for psychosocial stress as a potential barrier to adequate response to treatment **[1C]**
- Establish and reinforce individualized glycemic goals with the patient
- Intensify therapy
- Refer patient to DE for evaluation, DSME, and support for ongoing consultation. Document reason if no referral initiated
- Refer patient to RD for MNT **[1C]**

If the patient has a history of severe recurrent hypoglycemia or hypoglycemia unawareness (a condition in which the patient is unable to recognize symptoms of hypoglycemia):

- Assess for changes in daily routine such as reduced food intake or increased physical activity **[1C]**
- Refer to DE for evaluation, DSME, and hypoglycemia prevention; encourage family/friend attendance
- Review use of glucagon
- Consider revising A1C goal
- Discuss and reinforce goals with patient
- Adjust medications to minimize hypoglycemia risk **[1B]**
- If insulin-treated, consider use of a more physiologic insulin replacement program, such as basal/bolus therapy
- Consider and screen for other medical causes
- Consider referral for blood glucose awareness training, if available
- Consider use of continuous glucose monitoring [2B]
- Schedule follow-up appointment within 1-2 months. If history of recent, severe hypoglycemia, or change in pattern of hypoglycemia, recommend increase in frequency of communicating blood glucose levels to provider or DE.

1.3.0 SELF-MONITORING OF BLOOD GLUCOSE

SMBG is an important element of the treatment program for all individuals with diabetes. Its benefits are: to gauge treatment efficacy, to help in treatment design, to provide feedback on the impact of nutritional intake and activity, to provide patterns that assist in medication selection, and, for those on insulin, to assist in daily dose adjustments **[1B].**

1.3.1 Goals:

Goals for glycemic control for most individuals with diabetes are:

- Fasting glucose: 80 to130 mg/dl (4.4-7.2 mmol/L)
- 2-hour postprandial glucose: <180 mg/dl (9.9 mmol/L)
- Bedtime glucose: 90 to 150 mg/dl (4.9-8.3 mmol/L)

1.3.2 Frequency:

The frequency of SMBG should be individualized, based on factors such as glucose goals, medication changes, and patient motivation. Most patients with type 1 diabetes (T1D) should monitor 4 to 6 times per day. Some patients may need to monitor even more frequently.

Most patients using intensive insulin therapy should ideally monitor before meals and bedtime, prior to exercise, when they suspect hypoglycemia, after treating hypoglycemia, and prior to driving. In patients with T1D, there is a correlation between increased SMBG frequency and lower A1C. For patients with T2D, the frequency of monitoring is dependent upon such factors as mode of treatment and level of glycemic control **[1C].**

1.3.3 Postprandial monitoring:

To obtain meaningful data for treatment decisions, it is helpful for the patient to monitor for several consecutive days (eg, 2-4 days). In addition to obtaining fasting and preprandial glucose levels, consider obtaining glucose readings 2 to 3 hours postprandial, as postprandial hyperglycemia has been implicated as an additional cardiovascular risk factor **[1B].**

Postprandial monitoring is particularly recommended for patients who:

- Have an elevated A1C but fasting glucose is at target
- Are initiating intensive (physiologic) insulin treatment programs
- Are experiencing problems with glycemic control
- Are using glucose-lowering agents targeted at postprandial glucose levels
- Are making meal planning or activity adjustments

One-hour postprandial glucose monitoring should be considered:

- During pregnancy **[1A]**
- For those patients using alpha-glucosidase inhibitors

Encourage the patient to provide SMBG results (written records or meter for downloading) to each visit for review with provider/educator.

1.3.4 Using alternate sites to monitor:

Blood glucose levels from sites such as the upper arm, forearm, and thigh may lag behind those taken from the fingertips, particularly when glucose levels are changing rapidly. Glucose levels may change rapidly with exercise, eating, or hypoglycemia, or after insulin administration. For this reason, alternate site monitoring is not recommended in the following situations:

- When the blood glucose may be changing rapidly
- For patients using intensive insulin treatment programs
- If hypoglycemia is suspected
- In patients with hypoglycemia unawareness

1.3.5 Continuous glucose monitoring (CGM):

CGM measures interstitial glucose levels and correlates with plasma glucose levels. CGM requires calibration with SMBG at least twice daily. Use of CGM technology has been shown to decrease A1C in adults aged 25 years older using intensive insulin therapy along with CGM, compared with those using intensive insulin therapy with SMBG. The best predictor of A1C lowering was increased frequency of sensor use. CGM can be helpful in insulin-treated patients with hypoglycemia unawareness and/or frequent severe hypoglycemic episodes. The FDA has approved the use of properly calibrated CGM devices (ie, Medtronic 670G pump/sensor and Dexcom G6 sensor) to help make treatment decisions.

Patients with insulin-treated diabetes aged more than 65 years who would benefit from CGM should have access to it with insurance coverage. Intensive diabetes education and support are essential for optimal CGM implementation and ongoing use.

1.4.0 HYPOGLYCEMIA

1.4.1 Classification:

Prompt action is recommended for the treatment of hypoglycemia. When possible, the patient should confirm symptoms with SMBG to document hypoglycemia. All patients with T1D should ensure that a family member/companion/caregiver knows how to administer a glucagon injection in the event that the patient is unable or unwilling to take carbohydrate orally [**1C**].

The International Hypoglycemia Study Group recently recommended that hypoglycemia be classified as:

- *Level 1* (glucose alert level) with glucose less than 70 mg/dL (3.8 mmol/L), which is considered sufficiently low for treatment with fast-acting carbohydrates
- *Level 2* (clinically significant hypoglycemia) with glucose less than 54 mg/dL (2.9 mmol/L), which is considered serious and clinically important hypoglycemia
- *Level 3* (severe hypoglycemia) with no specific glucose threshold but associated with cognitive impairment requiring external assistance.

1.4.2 Treatment:

- Caution patient to avoid alternate site monitoring with blood glucose meter when hypoglycemic
- Treat as mild-to-moderate hypoglycemia if patient is symptomatic or unable to confirm hypoglycemia with SMBG, or if blood glucose levels are >54 mg/dl (2.9 mmol/L) and <70 mg/dL (3.8 mmol/L) and are <90 mg/dL (4.9 mmol/L) at bedtime or overnight
- To treat mild-to-moderate hypoglycemia (plasma glucose 54-70 mg/dL [3.8-2.9 mol/L] most times of the day and <90 mg/ dL (4.9 mmol/L) at bedtime or overnight), begin with 15-20 grams of carbohydrate (1/2 cup juice or regular soft drink; 3-4 glucose tabs) [**1C**]
- If glucose level is ≤54 mg/dl (2.9 mmol/L), consume 20-30 grams of carbohydrate [**1C**]
- Recheck blood glucose after 15 minutes [**1B**]
- Repeat hypoglycemia treatment if blood glucose does not return to normal range after 15 minutes [**1C**]
- Follow with additional carbohydrates if next meal is more than 1 hour away **[1C**]
- If hypoglycemia persists after 2 to 3 treatments, patient or companion should be instructed to contact their healthcare provider or seek emergency care
- In event of severe hypoglycemia (altered consciousness, unable to take carbohydrate orally, or requiring the assistance of another person) treat with glucagon and/or intravenous glucose [**1C**]
- For patients with hypoglycemia unawareness, the threshold for treatment of hypoglycemia needs to be individualized [**1C**]
- For patients using real-time CGM, check 15 minutes post treatment using a finger stick and not the sensor reading. Due to the physiologic lag between blood and interstitial glucose, the sensor will yield a lower result and can lead to overtreatment [**1B**]
- For patients with gastroparesis, treat hypoglycemia with oral glucose gel
- The patient's treatment plan should be revised if hypoglycemic events are frequent, or if they have hypoglycemia unawareness

1.4.3 Education:

- Instruct the patient to obtain and wear or carry diabetes identification
- Instruct patient to carry treatment for hypoglycemia at all times
- Instruct all patients with T1D, and patients with T2D who are at risk for hypoglycemia, to check blood glucose before operating a motor vehicle or other potentially dangerous equipment. In addition, advise them to check blood glucose regularly if driving for 1 or more hours. Hypoglycemia should be treated immediately, and patients should not drive until their blood glucose has reached and remained at a safe range for

at least 30 minutes and/or until cognitive function is restored [**1B**]
- Identify potential causes of hypoglycemia to prevent its occurrence [**1C**]
- Be clear in communicating modified treatment goals in individuals with hypoglycemia unawareness
- Glucagon injections should be prescribed to all patients with severe hypoglycemia. Education on its use should be provided to the patient and to their caregivers/family members if possible

1.5.0 DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSME/S)

Everyone with diabetes should receive DSME/S according to the National Standards for Diabetes Self-Management Education and Support, to facilitate knowledge and to implement and sustain self-care skills and problem-solving [**1B**]. Critical time points recommended for DSME/S are:

- At diagnosis
- Annually for assessment of education, nutrition and emotional needs
- When new complicating factors arise
- When transitions in care occur

Multiple visits with a DE are recommended to evaluate progress toward goals [**1B**].

Group education sessions are encouraged for cost effectiveness and efficiency of staff utilization. Group education is a benefit to patients as it allows them to share ideas and concerns and enables them to learn from one another [**1B**].

1.6.0 MEDICAL NUTRITION THERAPY (MNT)

No one-size-fits-all eating pattern exists for individuals with diabetes. Patients with newly diagnosed diabetes should receive either individualized or group MNT, preferably by a registered dietitian nutritionist who is knowledgeable and skilled in providing diabetes-specific MNT. MNT delivered by a registered dietitian is associated with an A1C decrease of 0.3%-1% for those with T1D and 0.5%-2% for patients with T2D [**1A**]. Goals of MNT are to promote healthy eating patterns while addressing the unique nutrition needs of each patient based on their personal preferences, cultural background, health literacy, barriers to change, and ability to make changes in their eating habits.

Weight management is important for overweight and obese individuals living with T1D and T2D. There is strong evidence that modest and persistent weight loss is beneficial to the management of T2D and can delay the progression from prediabetes to T2D.

For further details please refer to Chapter 2.

1.7.0 PHYSICAL ACTIVITY

All adults should consult their healthcare provider and/or see an exercise physiologist to discuss a safe exercise program that is appropriate to their abilities [**1C**].

1.7.1 Physical activity for healthy adults:

- Physical activity should be an integral component of the diabetes care plan to optimize glucose control, decrease cardiovascular risk factors, and achieve or maintain optimal body weight [**1A**]
- A moderate-intensity aerobic (endurance) physical activity minimum of 30 minutes 5 days per week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes 3 days per week should be achieved unless contraindicated. Activity can be accumulated toward the 30-minute minimum by performing bouts, each lasting 10 or more minutes [**1A**]
- All adults, and particularly those with T2D, should decrease the amount of time spent in daily sedentary behavior. Prolonged sitting should be interrupted every 30 minutes for blood glucose benefits, particularly in adults with T2D.
- A target of 60 to 90 minutes of activity, 6 to 7 days per week, is encouraged for weight loss if overweight or obese [**1A**]
- To increase lean body mass, full body resistance training should be incorporated into the activity plan 3 to 4 days per week. It should include upper-body, core, and lower-body strengthening exercises using free weights, resistance machines, or resistance bands [**1B**]. Beginning training intensity should be moderate, involving 10 to 15 repetitions per set, with increases in weight or resistance undertaken with a lower number of repetitions (8-10) only after the target number of repetitions per set can consistently be exceeded; increase in resistance can be followed by a greater number of sets and, lastly, by increased training frequency
- Stretching exercises should be done when muscles are warm or at the end of the activity plan to loosen muscles and prevent soreness [**1B**]

1.7.2 Physical activity for adults with medical or physical limitations:

- A moderate-intensity aerobic (endurance) physical activity minimum of 30 minutes, 5 days per week, or vigorous-intensity aerobic physical activity for a minimum of 20 minutes, 3 days per week, should be achieved, as feasible, unless contraindicated. Activity can be accumulated toward the 30-minute minimum by performing bouts each lasting 10 or more minutes [**1A**]
- To increase lean body mass, resistance training should be incorporated into the activity plan 3 to 4 days per week, as feasible. It should include upper-body, core, and lower-body strengthening exercises using free weights, resistance machines, or resistance bands [**1B**]
- Incorporate balance exercises to prevent falling and injury

- Functional Fitness Testing is useful to assess patients' functionality and track their progress. Testing such as the 6-Minute Walk Test, 2-Minute Step Test, Balance Assessment, and Hand Strength should be included at baseline and post intervention **[1C]**
- See section on Ocular Health.

1.8.0 CARDIOVASCULAR HEALTH

(Also see sections on Lipids, Blood Pressure, Physical Activity, and Smoking)

1.8.1 Antiplatelet therapy:

A daily enteric-coated aspirin (ASA) (75-162 mg) unless contraindicated* as a **primary** prevention strategy for men aged ≥50 years [**1C**] and for women ≥60 years of age [**1C**] with 1 or more of the following risk factors:

- Family history of premature** CAD or stroke
- Hypertension (HTN)
- Current cigarette smoker
- Albuminuria
- Hyperlipidemia

Recommend a daily enteric-coated ASA (75-162 mg), or clopidogrel (75 mg, if aspirin-intolerant), or another agent of the class as a **secondary** prevention strategy for anyone with 1 or more of the following [**1A**]:

- History of myocardial infarction (MI), angina, or documented CAD
- Vascular revascularization
- Nonhemorrhagic stroke
- Transient ischemic attack
- Peripheral artery disease (PAD)

**Possible contraindications for antiplatelet therapy may include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease. Eye disease is usually not a contraindication for ASA therapy.*

***Premature: 1st-degree male relative aged less than 55 years; 1st-degree female relative aged less than 65 years.*

1.8.2 Other therapeutic considerations:

Consider using beta-blockers in all patients with a history of MI or with documented CAD unless contraindicated [**1A**].

Consider using angiotensin-converting-enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] if ACE inhibitors not tolerated) in patients with known CAD or cardiovascular risk factors and aged ≥55 years [**1B**].

Thiazolidinediones (TZDs) (ie, pioglitazone, rosiglitazone) are contraindicated in patients with heart failure defined as New York Heart Association (NYHA) classes III and IV [and conditions of fluid overload (ie, congestive heart failure). See Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes (Chapter 5) for additional caveats on TZDs [**1A**].

Consider recommending aerobic activity if not clinically contraindicated, and a weight-loss program if patient is overweight or obese. [**1A**]

1.8.3 When to conduct a stress test:

Based on current research and understanding of CAD in diabetes, it is reasonable to screen patients with diabetes who [**1C**]:

- Complain of typical or atypical chest pain
- Have an abnormal electrocardiogram (ECG)
- Have a diagnosis of PAD or carotid artery disease
- Are aged >35 years with sedentary lifestyle about to start a rigorous exercise program

Currently, no strong evidence supports screening asymptomatic patients with T2D for silent myocardial ischemia [**1C**].

Patients with autonomic neuropathy may have increased risk of asymptomatic ischemia and therefore warrant careful attention [**1B**].

If stress testing is performed, either nuclear imaging or echocardiography with ECG monitoring is recommended. An exercise stress test is preferred, if resting ECG is normal and patient is able to exercise, because the response to exercise is an important prognostic factor. If the patient cannot adequately exercise, pharmacologic stress testing is warranted.

1.8.4 Lipid management:

1.8.4a Screening for lipid disorders:

Adults should be screened annually for lipid disorders with measurements of serum cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), preferably fasting [**1B**].

1.8.4b Treatment:

All patients should receive information about a meal plan designed to improve glycemic and lipid control, physical activity recommendations, and cardiovascular risk reduction strategies (with an emphasis on smoking cessation and blood pressure control). Consultation with appropriate education discipline is preferred [**1A**].

Institute therapy after abnormal values are confirmed.

- All patients with any form of clinical diagnosis of atherosclerotic cardiovascular disease (ASCVD), or with LDL-C ≥190 mg/dl: Treat with statin to reduce LDL-C ≥50% [**1A**]
- Patients aged 40 to 75 years without clinical evidence of ASCVD, with LDL-C 70-189 mg/dl: Treat with statin to reduce LDL-C by 30% to 49%. Consider reduction of ≥50% if 1 or more of the following additional major risk factors are present:
  - Calculated 10-year risk of ASCVD ≥7.5% using the American College of Cardiology/American Heart Association risk equation calculator (my.americanheart.org/cvriskcalculator) [**1B**]
  - Family history of premature ASCVD
  - High blood pressure
  - Tobacco use
  - Albuminuria

- In patients aged <40 years, consider statin if LDL-C ≥100 mg/dl and multiple ASCVD risk factors are present [**2B**]
- In patients aged >75 years, no clear evidence exists for benefits of initiating statin therapy in the absence of ASCVD or multiple CV risk factors [**2C**]
- Recheck lipids after drug initiation or dose escalation in 6 to 12 weeks. Thereafter, check lipids every 3 to 12 months to monitor adherence. May down-titrate statin dose if LDL-C <40 mg/dl
- No evidence exists for benefits of statin therapy in patients on hemodialysis or those with heart failure (NYHA class II-IV) [**1B**]
- If adequate reduction in LDL-C as described above has been achieved, a specific LDL-C goal (<70 and <100 mg/dl) or non-HDL-C goal (<100 and <130 respectively) for those with or without ASCVD, respectively, is not recommended
- In patients with ASCVD or with familial hypercholesterolemia, who are unable to achieve LDL-C goal with maximum tolerated statin therapy, add ezetimibe and consider a PCSK9 inhibitor
- For primary prevention of ASCVD, consider use of ezetimibe or bile acid sequestrant or niacin (alone, or in combination therapy) for patients intolerant to multiple statins or who have unacceptable adverse events [**2B**]
- Statins are contraindicated during pregnancy or if contemplating pregnancy

Patients with LDL-C at goal and fasting triglycerides ≥150 mg/dl or HDL-C ≤40 mg/dl:

- Optimize glycemic control [**1A**]
- Refer to RD for dietary modification and therapeutic lifestyle changes [**1A**]
- Consider referral to an exercise specialist for an appropriate exercise regimen
- Recheck lipids within 6 to 12 weeks
- In patients with fasting triglyceride levels 200 to 499 mg/dl and/or HDL-C ≤35 mg/dl after optimal statin therapy; calculate non-HDL-C, intensify statin if non-HDL-C not in goal before considering addition of fibrate [**2B**]
- If triglycerides are persistently ≥500 mg/dl, secondary causes of hypertriglyceridemia should be considered and managed appropriately. Initiate treatment with a very low-fat meal plan and with a fibrate for prophylaxis against acute pancreatitis; reassess lipid status when triglycerides <500 mg/dl [**1A**]
- If fasting triglycerides remain ≥ 500 mg/dl after initiation of fibrate, consider the addition of fish oil (to provide 2 to 4 grams omega-3 fatty acids daily) or niacin [**2B**]

1.8.5 Blood pressure management:

1.8.5a Blood pressure measurement:

- Check blood pressure (BP) at all routine visits after patient has been seated for at least 5 minutes. Use proper-size cuff and arm position. Postural BP (sitting, then standing) should be checked initially, and as clinically indicated:
  - In cases of known or suspected orthostatic hypotension (defined as a fall in systolic BP [SBP] of >20 mmHg or diastolic BP [DBP] of >10 mmHg or an increase in heart rate by more than 20 beats per minute after 3 minutes of standing)
  - In cases where standing upright is associated with lightheadedness, syncope, or signs of brain hypoperfusion [**1C**]
- Initiate lifestyle changes if BP >130/80 mm/Hg
- Consider initiating pharmacologic therapy if the average of 3 blood pressure measurements is >140/90 mmHg
- Schedule for follow-up blood pressure check within 1 month [**1B**]

1.8.5b Blood pressure targets:

- BP goal for each patient aged >18 years is ≤140/90 mmHg [**1B**] **The recent recommendation for achieving BP target of < 130/80 by the American College of Cardiology and others is controversial in patients with diabetes and not endorsed by the Joslin Clinical Oversight Committee or the ADA.**
- SBP <130 mmHg may be appropriate for individuals without CVD or without multiple risk factors [**1B**]
- No clear evidence exists for significant benefits to be gained by lowering SBP to <120 mmHg in those with coronary heart disease or multiple risk factors [**1B**]
- BP goal for patients with albuminuria ≥300mcg/mg is <130/80 mmHg, if tolerated [**1C**]
- Initial goal for patients with isolated systolic HTN (SBP >180 mmHg and DBP <80 mmHg) is a SBP <160 mmHg [**2B**] **or < 140 mmHg if safely achieved.**
- Initial goal for patients with SBP 160-179 mmHg is to lower SBP by 20 mmHg. If well tolerated, lower BP goals may be indicated [**1B**]

1.8.5c Treatment:

If SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, a 3-month trial of lifestyle modification is warranted as follows [1C]:

- Counsel about meal plans, use of Dietary Approaches to Stop Hypertension (DASH), the DASH low-sodium diet, and sodium reduction in general. Also, counsel about activity, weight loss, alcohol use, and stress reduction
- Consider referral to RD for MNT
- Encourage home BP self-monitoring and providing documentation during clinic visits

- Instruct patient to have BP checked 2 times a week prior to the next appointment
- Follow-up with healthcare provider within 2 to 4 weeks
- Initiate or adjust therapy with antihypertensive agents as clinically indicated if BP remains above goal

Studies have shown that aggressive management and control of BP may result in long-term benefits.

- Pharmacotherapy:
  Efficaciousness is the most important consideration in choosing an initial antihypertensive drug. In that sense, any available antihypertensive drug can be an appropriate choice. However, other considerations (eg, presence of albuminuria, coexisting CAD, cost) may dictate a preference for an ACE inhibitor, ARB, calcium channel blocker, or thiazide-type diuretic [**1A**]. In general, ACE inhibitors and ARBs should not be used in combination.

Consider ACE inhibitors or ARBs for patients with persistent urine albumin/creatinine ratio ≥30 mcg/mg. These drugs require monitoring of serum creatinine and K^+ within 1 week of starting therapy and periodically thereafter [**1A**]. (See section on Renal Health.)

ACE inhibitors/ARBs are contraindicated during pregnancy or if contemplating pregnancy.

1.9.0 RENAL HEALTH

1.9.1 Screening for renal health:

Measure serum creatinine at least annually to estimate glomerular filtration rate (eGFR) regardless of degree of urine albumin excretion.) [**1C**]

Measure eGFR using chronic kidney disease epidemiology (CKD-EPI) calculation.

If eGFR is <60 ml/min, evaluate for complications of kidney disease (anemia, hyperparathyroidism, and vitamin D deficiency).

Screen for albuminuria by checking urine albumin/creatinine (A/C) ratio as follows:

- Patients with T1D within 5 years after diagnosis and then yearly [**1C**]
- Patients with T2D at diagnosis (after glucose has been stabilized) and then yearly [**1C**]
- Annually in all patients up to age 70 years [**2C**]
- As clinically indicated in patients aged >70 years

Albuminuria is recognized as a major independent risk factor for CAD in patients with diabetes. Albuminuria may be measured with a spot or timed urine collection. Spot urine is preferred for simplicity.

Continue use of routine urinalysis as clinically indicated [**2C**].

Patients should be advised that BP control, glycemic control, and management of albuminuria may slow the progression of CKD.

1.9.2 Evaluation and treatment of diabetes kidney disease (DKD)

If A/C ratio <30 mcg/mg or timed urine albumin <30 mg/24 hours:

- recheck in 1 year

If A/C ratio 30-299 mcg/mg or timed urine albumin 30-299 mg/24 hours:

- Confirm presence of albuminuria with at least 2 of 3 positive collections done within 3-6 months. In the process, rule out confounding factors that cause a false positive, such as urinary tract infection, pregnancy, excessive exercise, menses, or severe hypoglycemic event [**1C**]
- Consider testing first morning urine
- Consider consult with nephrologist for blood pressure control, successive increases in albumin, and other issues (ie, eGFR <60 ml/min) [**2C**]

Once DKD confirmed:

- Evaluate BP and initiate/modify aggressive blood pressure treatment to achieve a BP of <130/80 mmHg [**2B**]
- Recommend that patient self-monitor BP with portable cuff and maintain a record/log. The monitoring schedule should be determined with the healthcare provider and is based on patient circumstance
- Strive to improve glycemic control with an optimal goal A1C of <7% or as otherwise clinically indicated [**1A**]
- Refer to DE for glucose management
- Initiate/modify ACE inhibitor or ARB treatment if albuminuria persists. Check K^+ and creatinine about 1 week after making these medication changes [**1A**]
- Repeat A/C ratio at least every 6 months. Consider increase in frequency when changes in medication are made [**2C**]

If A/C ratio ≥300 mcg/mg (≥300 mg/24 hours) or persistent albuminuria presents (positive dipstick for protein or ≥30 mg/dl):

- Follow all guidelines as stated for A/C ratio 30-300 mcg/mg
- Consider BP goal of <130/80 mmHg [**2B**]
- Evaluate for patient adherence, with emphasis on avoidance of high sodium and of very high protein intake
- Consider referral to RD for MNT
- Consider referral to nephrologist to:
- Assess cause(s) of impaired kidney function, including assessing for DKD
- Maximize therapies aimed at slowing progression of kidney disease (eg, BP control; reduction of urine protein level)
- Treat complications of kidney disease (hyperphosphatemia, anemia, etc)
- Evaluate any rapid rise in serum creatinine, abnormal sediment, or concomitant hematuria, or sudden increase in albuminuria
- Assess problems with ACE inhibitor use and difficulties in management of high BP or hyperkalemia

- Manage resistant hypertension, defined as BP that remains above goal despite concurrent use of 3 antihypertensive agents of different classes (1 of which should be a diuretic. All should be at maximum dose tolerated)

1.10.0 OCULAR HEALTH

1.10.1 Screening for eye disease:

Refer patient for comprehensive dilated eye exam or validated retinal imaging to determine level of retinopathy.

- T1D: initial eye exam at start of puberty or once patient is 10 years of age or older, whichever is earlier, within 3 to 5 years of diagnosis. Annual eye exam thereafter [**1A**]
- T2D: at diagnosis and annually thereafter [**1A**]
- Pregnancy in woman with preexisting diabetes: several exams, including prior to conception; during first trimester; follow-up during pregnancy as determined by first-trimester exam; and 6 to 12 weeks postpartum [**1B**]
- For physiologic insulin therapy (pump therapy or multiple daily injections): Consult with patient's eye care provider or evaluate retinal status with validated retinal imaging to determine level of retinopathy and appropriate follow-up care prior to initiating physiologic insulin therapy [**1A**]

1.10.2 Treatment:

Aggressively treat known medical risk factors for onset and progression of retinopathy:

- Strive to improve glycemic control with optimal A1C goal of <7% [**1A**]
- Monitor eye disease carefully when intensifying glycemic control [**1A**]
- Strive for BP <130/80 mmHg [**1B**]
- Treat albuminuria **[1B]**
- Strive to maintain total cholesterol, LDL-C, HDL-C, and triglyceride levels as per the recommendations outlined in the Lipids section of this guideline **[1A]**
- Treat anemia [**1B**]

Activity programs that involve strenuous lifting; harsh, high-impact components; or activities that place the head in an inverted position for extended periods of time may need to be revised depending on the level of retinopathy.

Reinforce follow-up with eye-care provider for any level of retinopathy, including no apparent retinopathy**.** The frequency of follow-up is dependent upon the level of retinopathy and presence of risk factors for onset and progression of retinopathy and is determined by the eye care provider.

- For high-risk proliferative diabetic retinopathy, prompt scatter (panretinal) laser photocoagulation and/or intravitreal anti–vascular endothelial growth factor (VEGF) injection is indicated [**1A**]
- For clinically significant macular edema (CSME) or center-involved macular edema, focal laser and/or intravitreal anti-VEGF injection is generally indicated regardless of level of retinopathy [**1A**]
- The level of diabetic retinopathy and diabetic macular edema (DME) generally determines follow-up* [**1A**]. See suggested follow-up time spans below:

If No Diabetic Retinopathy:

- 12 months

If Mild Nonproliferative Diabetic Retinopathy:

- Without DME, 12 months
- With DME,** monthly if undergoing anti-VEGF treatment, otherwise 3 to 4 months

If Moderate Nonproliferative Diabetic Retinopathy:

- Without DME, 6 to 9 months
- With DME,** monthly if undergoing anti-VEGF treatment, otherwise 3 to 4 months

If Severe-to-Very Severe Nonproliferative Diabetic Retinopathy:

- Without DME,*** 3 to 4 months
- With DME,** monthly if undergoing anti-VEGF treatment, otherwise 3 to 4 months

If Proliferative Diabetic Retinopathy Less Than High-Risk:

- Without DME,*** 1 week to 3 to 4 months
- With DME,** 1 week to 1 month if undergoing anti-VEGF treatment, otherwise 3 to 4 months

If High-Risk Proliferative Diabetic Retinopathy:

- With or without DME: scatter (panretinal) laser photocoagulation and/or intravitreal anti-VEGF injection with follow-up in 3 months, or 1 month and monthly thereafter if undergoing anti-VEGF treatment

*The presence of known risk factors for onset and progression of retinopathy may suggest follow-up at shorter intervals for all levels of retinopathy.

**Focal laser surgery and/or intravitreal anti-VEGF injection is generally indicated for CSME or center-involved macular edema. If receiving anti-VEGF treatment, follow-up is generally monthly.

***Scatter laser surgery may be indicated, especially for T2D or T1D of long duration

1.11.0 NERVOUS SYSTEM HEALTH

1.11.1 Screening for neuropathy

1.11.1a Methods:

- Ask patient about loss of sensation in the limbs, symptoms of pain, tingling, paresthesia, weakness, or gait instability.
- Evaluate feet for sensation using a 128 Hz tuning fork and Semmes-Weinstein 5.07 monofilament [**1B**]
- Evaluate reflexes
- Laboratory screening with complete blood count, lipid panel, thyroid panel, B12 level (methylmalonic acid and/or homocysteine if low-normal B12), and serum and urine protein electrophoresis, as clinically indicated

- Neurophysiologic testing (electromyogram, nerve conduction studies, or skin biopsy analysis of intra-epidermal nerve fiber density) should be considered in atypical cases
- Assess for symptoms of autonomic neuropathy such as erectile dysfunction, gastroparesis, or postural hypotension. If symptoms of autonomic neuropathy are present, refer for evaluation by formal autonomic testing (including heart rate variability testing, blood maneuver, and the blood pressure response to upright tilt table testing or standing) [**1B**]

1.11.1b Frequency:

- For patients with T1D and T2D without complications, conduct symptom and examination screen at time of diagnosis and at least annually [**1C**]
- For "at-risk patients,"* conduct symptom and examination screen at all routine interval visits [**1C**]
- Laboratory screening at the time of diagnosis of diabetes or with change in symptoms or examination [**1C**]
- Screen for cardiovascular autonomic neuropathy at the time of diagnosis of T2D, or 5 years after diagnosis of T1D. Screening should be repeated yearly or with development of symptoms [**1C**]. If symptoms of autonomic neuropathy are present, refer for evaluation by formal autonomic testing (including heart rate variability testing, blood pressure and heart rate response to a Valsalva maneuver, and the blood pressure response to upright tilt table testing or standing) [**1B**]
- Neurophysiologic testing only for atypical cases [**1C**]

**"At-risk patients" include patients who smoke; who have vascular insufficiency, neuropathy, retinopathy, nephropathy, structural deformities, infections, skin/nail abnormalities, or a history of ulcers or amputations; who are on anticoagulation therapy; or who cannot see, feel, or reach their feet.*

1.11.2 Treatment:

For patients with acute problems or who are "at risk":

- Consider referral to neurologist for:
  - atypical neuropathy
  - rapidly progressive symptoms
  - severe pain unresponsive to first-line therapy
  - weakness suggestive of diabetic amyotrophy

For patients with symptoms related to diabetic peripheral or autonomic neuropathy:

- Consider medications, because they improve quality of life [**1A**]
-

1.12.0 FOOT HEALTH

1.12.1 Screening

1.12.1a Methods:

Screening should include:

- Questions about loss of sensation in the limbs, or symptoms of pain, including claudication, tingling, or other paresthesia
- Foot evaluation for sensory function (Semmes-Weinstein 5.07 monofilament and 128 Hz tunic fork) [**1B**]
- Evaluation of reflexes, skin and soft-tissue integrity, nail condition, callous formation, vascular sufficiency (pedal pulses), and biomechanical integrity
- Examination of shoes for wear and appropriateness

1.12.1b Frequency:

- For patients with T1D and T2D without complications or significant risk factors, conduct foot screen at time of diagnosis and at least annually thereafter [**1C**]
- For "at-risk patients,"* check feet at all routine interval visits [**1C**]

**"At-risk patients" include patients who smoke; who have vascular insufficiency, neuropathy, retinopathy, nephropathy, structural deformities, infections, skin/nail abnormalities, or a history of ulcers or amputations; who are on anticoagulation therapy; or who cannot see, feel, or reach their feet.*

1.12.2 Treatment:

For patients with acute problems or who are "at risk":

- Refer to podiatric physician for routine care and evaluation [**1B**]
- Refer to DE for foot care training** [**1C**]
- Consider referral to neurologist for:
  - atypical neuropathy
  - rapidly progressive symptoms
  - severe pain unresponsive to first-line therapy
  - weakness suggestive of diabetic amyotrophy

For mild current ulcer or infection [**1C**]

** *Mild ulcer or infection is* characterized by: (a) superficial lesion (no foul odor), (b) no significant ischemia, (c) no bone or joint involvement, (d) no systemic toxicity, (e) minimal or no cellulitis (<2 cm)

- Instruct patient in nonweight-bearing, if appropriate
- Apply local dressings with topical antiseptic
- Consider baseline x-ray to evaluate for bone integrity and possible osteomyelitis
- Consider systemic antibiotic therapy
- Refer to podiatric physician for evaluation and treatment
- Refer to DE for foot-care training
- Ensure follow-up appointments are kept

For limb-threatening ulcer or infection* [**1C**]:

*** *Limb-threatening ulcer or infection is* characterized by (a) deep ulcer, (b) bone or joint involvement, (c) gangrene, (d) lymphangitis, (e) cellulitis (>2 cm), (f) systemic toxicity, (g) significant ischemia, (h) no social support system, (i) immunocompromised, (j) foul odor in ulcer.

Osteomyelitis is presumed to be present if able to probe through the ulcer to the bone.

- Urgent hospitalization
- Consult a podiatric physician and vascular surgeon for immediate evaluation and treatment
- Foot care training should address:
  - Avoidance of foot trauma
  - Daily foot inspection
  - Nail care
  - Callous formation
  - Proper footwear
  - Impact of loss of protective sensation on morbidity
  - Need for smoking cessation
  - Action to take when problems arise
  - Importance of glucose control on disease progression

1.13.0 ORAL HEALTH

- Periodontal disease is associated with suboptimal diabetes control and may be a risk factor for cardiovascular disease. There is mixed evidence on the impact of treatment of periodontal disease on glycemic control
- Referral to a dentist should be considered an essential component of a comprehensive diabetes care plan
- At initial visit and annually, discuss need for dental cleaning at *least* every 6 months [**1C**]
- Refer to dental specialist for oral symptoms and findings such as sore, swollen, or bleeding gums, loose teeth, or persistent mouth ulcers [**1C**]
- If edentulous, refer to dental specialist for restoration of functional dentition

1.14.0 BEHAVIORAL HEALTH

A psychosocial evaluation should be an integrated component of the initial assessment and the ongoing care of all patients with diabetes and should be strongly considered in the following situations:

Newly diagnosed diabetes:

- Assess at least the following [**1C**]:
- Ability to cope with the emotional impact and lifestyle changes of diabetes
- Level of social support
- Barriers to treatment and self-management
- Type and degree of nondiabetes-related life stress

During hospitalizations or any intensification in treatment, significant life change, problems with self-management, or metabolic stability. Key areas to assess:

- Diabetes distress: consider using Problem Areas in Diabetes as a screening tool.
- Depression: consider using Patient Health Questionnaire (PHQ)-2 or PHQ-9 as a screening tool
- Anxiety (eg, compulsive SMBG fear of injections).
- Exaggerated fear of hypoglycemia: Consider referral for blood glucose awareness training.
- Disordered eating: Consider inquiry about insulin omission or bingeing if A1C >9% or diabetic ketoacidosis is recurrent
- Family conflict related to diabetes
- Substance abuse: Consider use of the CAGE alcohol screening tool

Newly diagnosed complications from diabetes. Assess at least the following:

- Emotional impact (diabetes distress, depression, anxiety) and lifestyle changes for patient and family
- Barriers to treatment and self-management
- Level of social support
- Type and quantity of nondiabetes-related life stress

Patients using second-generation or atypical antipsychotic medications should be monitored for weight gain with resulting increases in glucose, lipid, and blood pressure levels.

1.15.0 WOMEN'S HEALTH

(Refer to Joslin Guideline for Detection and Management of Diabetes in Pregnancy [Chapter 3]).

- All women of reproductive age should be assessed for the possibility of pregnancy prior to initiating new medications, and they should be counseled on potential risks to the developing fetus.
- Counsel women with the potential for conception about contraception use and relationship of blood glucose control to fetal development and pregnancy outcomes [**1C**]
- At initial and annual visit, discuss sexual function
  - Assess for infectious, hormonal, psychological, or structural etiologies if dysfunction exists
  - Refer to specialist as indicated [**1C**]
- Follow appropriate guidelines for pap/pelvic and mammography screening for primary care patients [**1B**]
- Individualize approach to bone health for women with risk factors for osteoporosis, including surgical and natural menopause [**1B**]
  - Ensure adequate intake of calcium and vitamin D

1.16.0 MEN'S HEALTH

- At initial and annual visit, discuss sexual function and any fertility concerns
  - Assess for hormonal, psychological, or structural etiologies if dysfunction exists [**1C**]
- For men with type 2 diabetes, consider screening for low testosterone [**1B**]
  - Screen for total testosterone and sex-hormone–binding globulin
- Refer to specialist as indicated

1.17.0 ADDITIONAL CONSIDERATIONS

1.17.1 Tobacco dependence:

Screen: Assess patient's use of tobacco and e-cigarettes at initial and follow-up visits.

Treatment (if patient smokes)

- Discuss rationale for and strongly recommend smoking cessation **[1A]**
- Review options available to assist in smoking cessation, including medications and cessation programs [**1B**]

1.17.2 Identifying sleep disorders:

- At initial visit and annually, inquire about sleep quality, level of fatigue, and symptoms such as snoring and restless sleep **[1C]**
- Obstructive sleep apnea is more frequent in the setting of central obesity and is a risk factor for ASCVD
- Refer for sleep study if indicated
- The evidence surrounding the impact of sleep apnea treatment on diabetes control has been so far inconclusive
- Pay special attention to shift workers. An individualized care plan should be tailored to their schedules, and the effect of shift work on glycemic control should be assessed at each visit

1.17.3 Immunizations:

Recommend the following vaccines:

- Influenza vaccine: yearly for all adult patients with diabetes [**1B**]
- Pneumococcal vaccine with pneumococcal polysaccharide vaccine (PPSV23): once for all patients with diabetes [**1B**]
  - Patients ≥65 years of age should receive pneumococcal conjugate vaccine (PCV13) at least 1 year after vaccination with PPSV23, followed by a 1-time revaccination if they received the previous dose ≥5 years earlier **[1C]**
  - Repeat vaccination should be considered for those with nephrotic syndrome, chronic renal disease, and other immunocompromised states
  - Hepatitis B Vaccine 3-dose series: for unvaccinated adult patients with diabetes (age 19-59 years) **[1C].** May also consider for unvaccinated adults ≥60 years **[2C]**

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CHAPTER 2
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CHAPTER 2.

Clinical Nutrition Guideline for Overweight and Obese Adults With Type 2 Diabetes (T2D) or Prediabetes, or Those at High Risk for Developing T2D

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Objective. The Joslin Clinical Nutrition Guideline for Overweight and Obese Adults With Type 2 Diabetes (T2D) or Prediabetes, or Those at High Risk for Developing T2D is designed to assist primary care physicians, specialists, and other healthcare providers in individualizing the care of and setting goals for adult, nonpregnant patients with T2D or individuals at high risk for developing the disease. This guideline focuses on the unique needs of those individuals. Several components complement the *2015-2020 Dietary Guidelines for Americans*. The *Dietary Guidelines for Americans* are jointly developed every 5 years by the US Department of Health and Human Services and the US Department of Agriculture. This Guideline is not intended to replace sound medical judgment or clinical decision making and may need to be adapted for certain patient-care situations where more or less stringent interventions are necessary. This guideline was approved October 19, 2016; updated on January 28, 2018.

2.1.0 TARGET POPULATION

TABLE 1. Individuals Targeted for Intervention Meet 1 Criterion in Each of 2 Categories

Overweight or Obese[a]	Type 2 Diabetes or Prediabetes
BMI ≥25 kg/m^2 or Waistline Men: ≥40 in (102 cm) **[1B]** Women: ≥35 in (88 cm) **[1B]**	Diagnosis of type 2 diabetes (T2D) or prediabetes, determined by IGT or IFG **[1A]** or High-risk of T2D, determined by: • Metabolic syndrome, per AHA/NHLBI criteria **[1B]** • First-degree relative with T2D • Confirmed diagnosis of insulin resistance (eg, high basal insulin)

AHA indicates American Heart Association; BMI, body mass index; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; in, inches; NHLBI, National Heart, Lung, and Blood Institute, T2D, type 2 diabetes.

[a]For Asian populations (South Asian Indians, East Asians, and Malays), a BMI ≥23 kg/m^2 and a waistline ≥35 in/90 cm in men or ≥31 in/80 cm in women **[1B]**.

2.2.0 GENERAL GUIDELINES

- There is strong evidence that weight reduction improves insulin sensitivity and glycemic control, lipid profile, and blood pressure in T2D, and decreases the

risk of developing T2D in prediabetes and high-risk populations **[1A]**.

- Refer individuals to a registered dietitian (RD) experienced in diabetes and weight management for individualized medical nutrition therapy (MNT); care should be coordinated with an interdisciplinary team including the patient's primary care physician (PCP) **[1B]**.
    - To enhance effectiveness of MNT, a series of 3 to 4 encounters with an RD, each lasting 45 to 90 minutes, is recommended to begin at diagnosis
- Priorities for this population include:
    - Weight reduction
    - Glycemic control as well as achieving blood pressure and low-density lipoprotein cholesterol goals
    - Meal-to-meal consistency in carbohydrate distribution for those with fixed medication/insulin programs
    - Individualization for cultural and food preferences (eg, vegetarian)
    - Adoption of a healthy eating pattern that is sustainable over time. The Mediterranean diet, the DASH [Dietary Approaches to Stop Hypertension] diet, and a plant-based or vegetarian diet are examples of healthy dietary patterns
    - Integration of behavior-change therapies to adopt healthy eating behaviors and sustainable weight loss
- The meal plan composition, described below, is for general guidance only and may be individualized by the RD or other healthcare provider according to clinical judgment, individual (patient) preferences and needs, and metabolic response.
- Physical activity is an integral component of a weight loss program for both initial weight loss and for weight maintenance.

2.3.0 WEIGHT REDUCTION

- A structured lifestyle plan that combines dietary modification, activity, and behavioral modification, along with ongoing support, is necessary for weight reduction **[1B]**. To maintain long-term weight loss, ongoing weight-maintenance counseling and support is recommended.
- A modest and gradual weight reduction of 1 to 2 pounds every 1 to 2 weeks should be the optimal target **[2A]**. Reduction of daily caloric intake should be between 250-750 calories **[1C]**. Total daily intake should not be less than 1000 to 1200 calories for women and 1200 to 1600 calories for men, or based on an RD assessment of usual intake **[1C]**.
- A 5% to 10% weight loss may result in significant improvement in blood glucose control among patients with diabetes and may help prevent the onset of diabetes among individuals with prediabetes **[1B]**. Weight reduction should be individualized and continued until an agreed-upon BMI and/or other metabolic goals are reached.
- Target individuals should meet with an RD to discuss a structured MNT plan for weight management that includes menus and snacks as well as education and practice in portion control, all effective components of weight-management plans **[1B]**.
- Diabetes-Specific Meal Replacements (DSMRs) in the form of shakes, bars, ready-to-mix powders, and prepackaged meals that match these nutrition guidelines may be effective in initiating and maintaining weight loss.
    - Meal replacements should be used under the supervision of a RD
    - When meal replacements are initiated, glucose levels should be carefully monitored and, if needed, antihyperglycemic medications should be adjusted
    - Meal replacements should be used with caution by those with hyperkalemia
- Bariatric surgeries, although not without medical and nutrition risks, are effective options and may be discussed when indicated (consider in individuals with BMI ≥40 kg/m^2 and those with BMI ≥35 kg/m^2 with other comorbidities. Reduce calculations by 2.5 kg/m^2 for Asians) **[2B]**. To date, there is limited evidence to support the recommendation of bariatric surgeries for patients with BMI <35 kg/m^2 even if a person has diabetes or other comorbid conditions.
- Anti-obesity medications may be considered for patients who were not able to lose weight through lifestyle modifications, but the long-term risks and benefits of these medications are unclear **[2C]**.
- The effect of diabetes medications should be evaluated throughout the weight loss program and adjusted as necessary to avoid hypoglycemia.

2.4.0 MACRONUTRIENT COMPOSITION

2.4.1 Fat:

Amount. There is general agreement that the type of fat consumed is more important than the quantity (generally 30% to 40% of total calories). Trans fats from partially hydrogenated oil should be eliminated **[1B]**.

- Monounsaturated and polyunsaturated fats should comprise the majority of fat intake **[2B]**.
- Limit saturated fat intake to <10% of total calories.
    - Recent evidence demonstrates that saturated fat from dairy foods (milk, yogurt, cheese) may be acceptable within the total daily caloric intake **[2B]**

- Despite recent evidence suggesting that saturated fat poses a weak or neutral effect on health, further research in this area is warranted

- Low-fat diets are generally less effective than low-carbohydrate diets for weight reduction **[2C]**

Recommended.

- Plant fats rich in mono- and polyunsaturated fats (eg, olive oil, canola oil, soybean oil, nuts/seeds, and avocado) **[2A]**
- Oily fish rich in omega-3 fatty acids (eg, salmon, herring, trout, sardines, fresh tuna) 2 times/week, as a source of these fatty acids **[2B]**

Not recommended.

- Foods high in saturated animal fat, including nonlean pork, lamb, and beef; processed meat; butter and cream
- Foods high in trans fats (eg, most fast foods; most commercially baked goods; margarines from partially hydrogenated oil)

2.4.2 Protein

Amount. Protein intake should range between 1.0-1.5 grams/kg of adjusted body weight. To calculate adjusted body weight, first calculate excess weight: Excess weight = current weight – ideal body weight (IBW). Adjusted body weight = IBW + 0.25 of excess body weight. This amount generally accounts for 20% to 30% of total caloric intake.

- A modest increase in protein reduces appetite and helps achieve and maintain weight reduction **[2B]**. Protein also helps minimize loss of lean body mass during weight reduction **[2B]**.
- No reliable scientific data support a protein intake that exceeds 2 grams/kg of adjusted body weight. Conversely, reduction of protein intake to less than 0.8 grams/kg day may result in protein malnutrition.

Recommended. Fish, skinless poultry, lean meat, dairy, egg whites, nuts, seeds, soy, and other legumes **[2B]**.

Not recommended. Sources of protein that are high in saturated fat (eg nonlean pork, lamb, beef; processed meats) as they may be associated with increased cardiovascular risk **[1B]**. Heme iron in meat is also associated with an increased risk of T2D **[2B]**.

Patients with renal issues. Although reducing total calories may result in a reduction of the total amount of protein intake, any patient with signs of kidney disease (both of the following: proteinuria; estimated glomular filtration rate <60 ml/min) should consult a nephrologist before increasing the total or percentage of protein in their diet **[1B]**. Protein intake for these patients should be modified, but not lowered to a level that may jeopardize their overall health or increase their risk for malnutrition or hypoalbuminemia.

2.4.3 Carbohydrate

Amount. The total daily intake of carbohydrate should be at least 130 grams/day and preferably 40% to 45% of the total caloric intake. Intake should be adjusted to meet the cultural and food preferences of the individual.

Consideration of glycemic index/glycemic load. The glycemic index/glycemic load is an important factor that patients should apply in their daily selection of carbohydrate foods. Foods with a lower glycemic index content should be selected **[2B]** (eg, whole grains, legumes, fruits, green leafy and nonstarchy vegetables, milk, yogurt).

Recommended. Green leafy and nonstarchy vegetables, whole fruits, legumes, whole and minimally processed grains, oats, milk, yogurt **[2B]**.

Not recommended.

- Sugar, or added sugar, especially sugar-sweetened beverages, ice cream, candies, and grain-based desserts. Milk chocolate should be avoided.
- Refined grain products including white bread, white pasta, white rice, low-fiber wheat cereal, cakes, muffins, pizza. White bagels should be limited.
- High glycemic-index carbohydrates, including white potatoes and white rice.

Fiber.

- Approximately 14 grams of fiber/1000 cal (20-35 grams) per day is recommended [**1C**]. If tolerated, approximately 50 grams/day is effective in improving postprandial hyperglycemia; that quantity should be encouraged **[2B].**
- Fiber from unprocessed plant-based food, such as vegetables, fruits, seeds, nuts, and legumes, is preferable. However, if needed, fiber supplements such as psyllium, resistant starch, and β-glucan can be added **[2B]**.

2.5.0 MICRONUTRIENT COMPOSITION

Sodium. Daily consumption should be <2300 mg (about 1 tsp of salt) per day **[1A]**. Further reduction to 1500 mg is recommended in people aged >50 years, especially those including those with hypertension or chronic kidney disease **[2B]**.

Potassium.

- Daily consumption should be a minimum of 4700 mg unless potassium excretion is impaired (eg, patients with chronic kidney disease; patients on certain drugs who retain potassium).
- Potassium helps offset high sodium intake by triggering more sodium excretion by the kidneys.
- Potassium-rich foods include fruits and vegetables like bananas, mushrooms, spinach, and almonds.

2.6.0 VITAMIN AND MINERAL SUPPLEMENTS

- In individuals who are not deficient, there are no significant data supporting the routine use of vitamins or minerals to improve glucose control. However,

some individuals may benefit from multivitamin supplementation, as calorie-restricted diets may be inadequate in some nutrients, such as calcium.
- No significant data support the use of herbal supplements or spices to improve glucose control.

2.7.0 NONNUTRITIVE SWEETENERS

All FDA-approved nonnutritive sweeteners are permissible in moderate quantities.

2.8.0 ALCOHOL

- If alcohol is consumed, consumption must remain moderate: no more than 1 drink per day for women and no more than 2 drinks per day for men (1 drink is equal to 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled alcohol).
- Alcoholic beverages contain calories and are low in nutritional value. They may contribute to hypoglycemia or, in the case of high-carbohydrate alcoholic beverages, hyperglycemia.
- It is not advisable to increase alcohol consumption for the purpose of deriving purported health benefits.

2.9.0 HEALTHY DIETARY PATTERN

The following dietary patterns have been shown to be effective in the prevention and management of diabetes:

- Mediterranean diet
- DASH diet
- Plant-based, vegetarian, and vegan diets
- Moderately low carbohydrate consumption; high consumption of plant-based protein; fats from plants

The following specific foods have been shown in some study results to be associated with a reduced risk of developing T2D:

- Oat cereal
- Yogurt
- Dairy products
- Tea, coffee, and decaffeinated coffee
- Green leafy vegetables
- Fish and seafood (only in Asia)
- Red grapes, apples, blueberries
- Nuts (especially walnuts)

2.10.0 PHYSICAL ACTIVITY

- Physical activity should be an integral component of the weight loss and diabetes care plan to optimize glucose control, decrease cardiovascular risk factors, and achieve or maintain optimal body weight.
- All adults should consult their healthcare provider and/or see an exercise physiologist to discuss a safe exercise program appropriate to their abilities **[1C]**.
- To increase lean body mass, full-body resistance training should be incorporated into the activity plan 3 to 4 days per week. The training should include upper-body, core, and lower-body strengthening exercises using free weights, resistance machines, or resistance bands **[1B]**.

Guidelines for healthy adults with diabetes or prediabetes:

- Moderate-intensity aerobic (endurance) physical activity performed a minimum of 30 minutes 5 days per week, or vigorous-intensity aerobic physical activity performed a minimum of 20 minutes 3 days per week, should be achieved unless contraindicated. Activity can be accumulated toward the 30-minute minimum by performing bouts, each lasting 10 or more minutes **[1A]**.
- A target of 60 to 90 minutes of moderate-intensity aerobic activity per day, 6 to 7 days per week, is encouraged for weight loss if overweight or obese **[1B]**.
- Stretching exercises should be done when muscles are warm or at the end of the activity plan to loosen muscles and prevent soreness **[1B]**.

Additional guidelines for adults with medical or physical limitations:

- Incorporate balance exercises to prevent falls and injuries.
- Functional Fitness Testing is useful to assess patients' functionality and to track their progress. Testing such as 6-Minute Walk Test, 2-Minute Step Test, Balance Assessment and Hand Strength should be included at baseline and post intervention **[1C]**.
- For those with proliferative diabetic retinopathy, retinal traction, or severe nonproliferative diabetic retinopathy, activity programs that involve strenuous lifting; harsh, high-impact components; or components that place the head in an inverted position for extended periods of time may need to be revised, depending on the level of retinopathy and other retinal disease. Consultation with an eye specialist in diabetes eye care is advised.

Appendix A.

TABLE 2. Suggested Approximate Macronutrient Distribution According to Clinical Guideline

Daily Calorie Level	Carbohydrate		Protein		Fat	
	Grams	%	Grams	%	Grams	%
1000	130	~50[a]	75	30	22	20
1200	135	45	75-90	25-30	40	30
1500	150-170	40-45	75-110	20-30	50	30
1800	180-200	40-45	90-135	20-30	60	30
2000	200-225	40-45	100-150	20-30	70	~30

[a]A minimum of 130 grams of carbohydrate per day, in a 1000-calorie meal plan, calculates to ~50% of the total daily calories.
NOTE: The diets within the rectangle represent most common diet plans for weight loss.
Source: American Diabetes Association

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CHAPTER 3. Guideline for Detection and Management of Diabetes in Pregnancy

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Objective: The Joslin Guideline for Detection and Management of Diabetes in Pregnancy is designed to assist internal medicine specialists, endocrinologists, and obstetricians in individualizing the care of and setting goals for women with preexisting diabetes who are pregnant or planning pregnancy. It is also a guide for managing women who are at risk for or who develop gestational diabetes mellitus (GDM). This guideline is not intended to replace sound medical judgment or clinical decision making. Clinical judgment determines the need for adaptation in all patient care situations; more or less stringent interventions may be necessary.

The objective of the Joslin Guideline for Detection and Management of Diabetes in Pregnancy is to support clinical practice and to influence clinical behaviors in order to improve clinical outcomes and assure that patient expectations are reasonable and informed. This guideline was approved November 13, 2016, and updated February 12, 2018.

3.1.0 SCREENING FOR GESTATIONAL DIABETES MELLITUS

FIGURE. See at end of Chapter 3.

3.2.0 PRECONCEPTION CARE. For preexisting type 1 diabetes (T1D) or type 2 diabetes (T2D)

3.2.1 Glucose goals prior to conception:

- Fasting and pre-meal glucose: plasma 80 to 110 mg/dL [**1C**]
- 1-hour postprandial blood glucose: plasma 100 to 155 mg/dL [**1C**]
- Glycated hemoglobin (A1C): <7% and as close to 6% as possible, without severe hypoglycemia [**1B**]
- Avoid severe hypoglycemia [**1B**]

3.2.2 Counseling:

- Educate women of childbearing age about the importance of near-normal blood glucose control prior to conception.
- Refer to a specialist in maternal–fetal medicine and/or endocrinology/diabetes for counseling, assessment

of maternal and fetal risk, and guidance in achieving management goals. This includes all women who are planning pregnancy and women who are not planning pregnancy but are using inadequate contraception and have A1C greater than 7%.

- Assess diabetes self-management, including meal planning, insulin care and use, activity program, medication schedule, self-monitoring of blood glucose (SMBG), treatment for hypoglycemia and hyperglycemia, and sick day management, utilizing diabetes educators (DEs) as appropriate. Review maternal and fetal health issues.
- Begin a multivitamin with 400 mcg of folic acid to supplement average daily intake of 400 mcg for a total daily intake of 800 mcg to 1 mg of folic acid to decrease the risk of neural tube defects. Patients with a prior pregnancy affected with a neural tube defect should take folic acid 4 mg daily.
- Strongly advise smoking and alcohol cessation.
- Refer overweight and obese women with and without known diabetes or polycystic ovary syndrome (PCOS) for medical nutrition therapy with a goal of 5% to 10% weight loss based on 2009 Institute of Medicine recommendation.

3.2.3 Medical assessment:

- Take thorough medical and obstetrical history, including comprehensive review of diabetes history and management.
- Eye evaluation: dilated comprehensive eye exam and pregnancy clearance by an ophthalmologist; should also include a discussion about the risk of developing and/or the progression of diabetic retinopathy during pregnancy.
- Kidney function assessment: random urine albumin/creatinine ratio and serum creatinine. Refer to nephrology if urine protein ≥1 gram.
- Thyroid evaluation: Check thyroid stimulating hormone level.
- Gynecology evaluation: Make sure pelvic exam and Pap smear are up to date.
- Cardiac evaluation: If asymptomatic and ≥ 35 years of age with 1 or more additional risk factors (hypertension, smoking, family history of coronary artery disease, hypercholesterolemia, albuminuria, or nephropathy), recommend 1 or more of the following: electrocardiogram (ECG), echocardiogram, or exercise tolerance test (ETT). If symptomatic, recommend ECG and echocardiogram or ETT and consider referral to cardiologist.
- Check vitamin B12 level in patients consuming more than 1 mg folic acid daily, as high-dose folic acid may mask a B12 deficiency.

3.2.4 Diabetes medications:

- Discontinue oral antihyperglycemic therapy; start insulin. An exception is metformin, which may be continued during anovulatory infertility and in the first trimester in patients with PCOS or T2D. Prior to the first prenatal visit, the patient should begin increasing doses of insulin as necessary to control blood glucose while metformin is tapered off or discontinued. Metformin should not be used beyond the first trimester or in lieu of insulin based on safety and efficacy data available at this time
    - Metformin crosses the placenta and achieves therapeutic levels in the fetus. Presently, there are no long term randomized controlled trials (RCT) regarding outcomes in offspring of mothers with preexisting diabetes treated with metformin during pregnancy. (See 3.3.3b regarding outcomes in infants exposed to metformin in utero in PCOS and GDM.).
    - Other oral medications have not been adequately studied for the treatment of preexisting T2D in pregnancy.
- The rapid-acting insulin analogs lispro and aspart lower postprandial blood glucose and decrease the risk of nocturnal hypoglycemia. Patients on lispro and aspart prior to conception may continue them during pregnancy. Patients on regular insulin may be switched to lispro or aspart if 1-hour postprandial blood glucose levels are above target and/or the patient is also experiencing pre-meal or nocturnal hypoglycemia.
- No information exists on the safety of using the insulin analogs glulisine and degludec in pregnancy. We cannot recommend their use at this time.
- A rapid-acting insulin, lispro or aspart, may be delivered either through multiple daily injections or an insulin pump.
- Detemir is a long-acting insulin analog that has been studied in T1D and is noninferior to isophane insulin in terms of safety, efficacy, and outcomes.
- Glargine, a long-acting insulin analog, is not recommended in women who are planning a pregnancy or who are currently pregnant. There is no RCT data comparing it to detemir or isophane insulins. A specific concern in the pregnant population is related to the 6- to 8-fold increased insulin-like growth factor receptor affinity and mitogenic potency compared with human insulin.
- There is inadequate safety information about the use of glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, and sodium glucose co-transporter-2 inhibitors in pregnancy. Therefore, they should not be used in pregnancy.

3.2.5 Other medications

3.2.5a Hypertension and/or albuminuria management:

- Angiotensin-converting-enzyme (ACE) inhibitors

and angiotensin receptor blockers (ARBs) should be stopped preconception except as cited in 3.2.5b below, due to the increased risk of fetal injury or demise with second or third trimester use and inconsistent teratogenicity data.

- The nondihydropyridine calcium channel blocker diltiazem in extended release forms may be a useful substitute for ACE inhibitors and ARBs.
- Switch to antihypertensive agents that are safe in pregnancy (see section **3.5.0** below).

3.2.5b Diabetic nephropathy/chronic kidney disease management:

- Data on teratogenicity of ACE inhibitors and ARBs are inconsistent; therefore, risks and benefits of continuing them during preconception should be weighed. **[1B]** The benefits of preconception use of ACE inhibitors for renal protection may outweigh the uncertain risk of birth defects. In this case, ACE inhibitors should be stopped as soon as pregnancy is diagnosed in the first trimester.

3.2.5c Lipid management:

- Stop all cholesterol-lowering agents before conception, including statins. **[1B]**
- Hypertriglyceridemia: Omega-3 fatty acids may be started or continued in pregnancy. **[2B]**

3.3.0 DIABETES MANAGEMENT DURING PREGNANCY

3.3.1 Self-monitoring of blood glucose and urine ketones: preexisting diabetes and GDM:

- For gestational diabetes, check glucose levels 4 times/day: once before breakfast and 1 hour after each meal.
- For preexisting diabetes, check glucose levels before every meal and 1 hour after each meal.
- Nocturnal monitoring (around 3 am) may be necessary on an intermittent basis.
- Check fasting urine ketones daily.

3.3.2 Treatment goals

3.3.2a Preexisting diabetes:

- Fasting and pre-meal plasma glucose: 60 to 99 mg/dL. [**1C**]
- 1-hour post meal or peak postprandial plasma glucose: 100 to 129 mg/dL. [**1C**]
- Urine ketones: negative.
- Normalization of A1C to <6% if possible without resulting in severe hypoglycemia. [**2B**]
- Use standard hypoglycemia treatment for blood glucose less than 60 mg/dL: Consume 15 grams of carbohydrate, and recheck glucose in 15 minutes. If blood glucose remains less than 60 mg/dL, consume an additional 15 grams of carbohydrate.
- Avoid severe hypoglycemia (an episode in which the patient experiences coma, seizure, or suspected seizure, or impairment sufficient to require the assistance of another person). Blood glucose goals must be relaxed for patients with hypoglycemia unawareness or recurrent hypoglycemia.

3.3.2b Gestational diabetes mellitus (GDM):

TABLE 1. Diagnosing GDM

	Plasma Glucose Hadlock AC <75th percentile	Plasma Glucose Hadlock ≥75th percentile
Fasting and pre-meal glucose	60-90 mg/dL	60-79 mg/dL
1 hour post meal or peak postprandial	100-129 mg/dL	90-109 mg/dL

- Urine ketones: negative.
- Initiate insulin therapy if above levels are not maintained.
- Use standard hypoglycemia treatment for blood glucose less than 60 mg/dL: Consume 15 grams of carbohydrate, and recheck glucose in 15 minutes. If blood glucose remains less than 60 mg/dL, consume an additional 15 grams of carbohydrate.

3.3.3 Diabetes monitoring and visits

3.3.3a Preexisting diabetes:

- Medical visits (endocrinologist preferred) every 1 to 4 weeks, with additional phone contact as needed, depending on level of self-management skills and stability of blood glucose control. At each visit, review SMBG and urine ketone results; measure blood pressure; measure urine protein and ketones by dipstick.
- Check A1C level every 4 to 8 weeks.
- Education utilizing a DE, preferably a certified diabetes educator (CDE), as needed; suggest nutrition therapy (NT) by registered dietitian (RD).
- Ophthalmology exam early in first trimester; repeat dilated exam every trimester and for 1 year postpartum as indicated by the degree of retinopathy.
- Consider providing mental health counseling to assist women and/or their partners cope with the psychological and relationship changes that may result from pregnancy.

3.3.3b Gestational diabetes mellitus:

- Medical visits (endocrinologist preferred) every 1 to 4 weeks, with additional phone contact as needed, depending on level of self-management skills and stability of blood glucose control. At each visit, review SMBG and urine ketone results; measure blood pressure; measure urine protein and ketones by dipstick.
- If newly diagnosed with gestational diabetes, patient should be started on insulin, not metformin or glyburide (glibenclamide), if medication is required. **[2C]**

- Education utilizing a DE (preferably a CDE) as needed, especially for review of SMBG to increase adherence; NT should be provided by an RD.
- Glyburide is associated with a 2-fold or greater increased risk of macrosomia and neonatal hypoglycemia compared with insulin, in meta-analyses and an increased risk of neonatal hypoglycemia, in an RCT powered for neonatal outcomes. **[2B]**
- Glyburide should not be used in pregnancy, except in rare situations when insulin is not an option. **[2B]**
- Metformin is associated with high treatment failure rates and increased preterm delivery, but also with lower neonatal hypoglycemia. Infants exposed to metformin in utero, during prior PCOS or GDM RCTs, may weigh more, and demonstrate larger waist circumferences and greater fat mass at 4 and 9 years of age. **[2B]**

3.4.0 DIABETES MEDICATIONS

For **preexisting diabetes** the only diabetes medication currently used throughout pregnancy is insulin (see **Preconception Care**). Insulin does not cross the placenta. Oral agents are often insufficient and ineffective in both T1D and T2D.**[1B]**

3.5.0 HYPERTENSION MANAGEMENT

- Maintaining blood pressure in nonpregnant patients with diabetes at below 130/80 mmHg decreases end organ damage. [**2A**]
- During pregnancy, blood pressure targets are 110 to 129 mmHg systolic and 65 to 79 mmHg diastolic in women with chronic hypertension.[**2C**] These targets are lower than in those without diabetes. Antihypertensives are initiated in pregnant patients with known or suspected chronic hypertension if blood pressure is ≥130/80 mmHg 3 times during pregnancy.
- Preeclampsia requires special treatment; therefore, these guidelines and treatment strategies do not apply to preeclampsia, for which other treatment options are preferred, nor do they apply to gestational hypertension.
- Antihypertensives used during pregnancy are:
  - Alpha methyldopa
  - Beta-blockers:
    - acebutolol, betaxolol, bisoprolol, labetalol, levatol, metoprolol, nadolol, sotalol, timolol
    - NOTE: atenolol ; should not be used as it may cause fetal growth restriction)
  - Calcium channel blockers Nifedipine extended release. The nondihydropyridine calcium channel blocker diltiazem in extended-release form may be preferred in patients with microalbuminuria or nephropathy.
  - Hydralazine as second-line agent.
- Aspirin 81 mg daily is recommended from 12 weeks gestation until delivery to help reduce risk for preeclampsia in patients with T1D or T2D. **[2B]**

3.6.0 NUTRITION THERAPY

Recommendations are the same for preexisting diabetes and GDM except where noted.

3.6.1 Counseling and education:

- All pregnant women should receive NT counseling by a RD, preferably an RD/CDE.
- All pregnant women should receive SMBG training by a DE (CDE preferred).
- Daily food records and SMBG records are required to assess effectiveness of NT.
- Carbohydrate counting skills are taught for either a consistent carbohydrate intake or a personalized insulin-to-carb ratio, so the patient can adjust insulin based on carbohydrate intake.
- At least 3 encounters with a CDE are recommended:
  - Visit 1 (60-90 minute individual or group visit with RD) for assessment and meal planning. This could include SMBG instruction if RD has received appropriate training.
  - Visit 2 (30-45 minutes) with RD or RN 1 week after initial visit to assess and modify plan.
  - Visit 3 (15-45 minutes) with RD or RN in 1 to 3 weeks to further assess and modify plan, as needed.
- Additional visits every 2 to 3 weeks and, as needed, with RD or RN until delivery, and one visit 6 to 8 weeks after delivery.

3.6.2 Calories:

TABLE 2.

WHO BMI Range (kg/m²)	Energy Needs (kcals/kg) Based on Pre-Gravid kg		Total Weight Gain Range (pounds)		Rates of Weight Gain (pounds/week) 2nd & 3rd Trimesters
	Single	Multiple	Single	Multiple	
Underweight (<18.5)	36-40	42-50	28-40	[a]	1.0 (1-1.3)
Normal (18.5-24.9)	30	40-45	25-35	37-45	1.0 (0.8-1)
Overweight (25-29)	24	30-35	15-25	31-50	0.6 (0.5-0.7)
Obese (>30)	insufficient information[b]		11-20	25-42	0.5 (0.4-0.6)

BMI indicates body mass index; kcal, kilocalorie; kg, kilogram; WHO, World Health Organization

[a]Insufficient information was available to develop a provision guideline for underweight women with multiple fetuses.

[b]Insufficient information was available to address needs (kcal/kg) in the obese category.

Guide to Calculating Energy Needs

Estimated Energy Requirements (EER) for pregnancy:
EER in pregnancy = EER pre-pregnancy (see below) + additional energy expended during pregnancy + energy dispostion, as follows:

First trimester:	EER prepregnancy + 0
Second trimester:	EER prepregnancy + 340 singleton
Third trimester:	EER prepregnancy + 452 singleton

Calculate EER prepregnancy, for women aged 19 years and older, as follows:
EER = 354 – (6.91 x age [years] + PA x [(9.36 x weight in kg + 726 x height in m), where PA is physical activity coefficient (see below).

PA = 1.0 for sedentary (physical activity level [PAL] is >1.0 but <1.4)
PA = 1.12 for low activity (PAL is ≥ 1.4 but < 1.6)
PA = 1.27 for active (PAL is ≥1.6 but < 1.9) PA = 1.45 for very active (PAL is ≥1.9)

3.6.2a Distribution of calories:

- Individualize distribution of calories based on usual intake, preferences, and medication regimen.
  - Consistent timing of 3 meals and 2 to 4 snacks per day; smaller frequent meals decrease postprandial hyperglycemia.
- Weight should be monitored at each visit; each patient's weight gain should be tracked on prenatal weight gain chart.

TABLE 3. Calorie Distribution

	GDM	Preexisting T1D or T2D
Carbohydrate	40% to 55% total calories	40% to 55% total calories
Breakfast	15-30 g[a,b]	consistent carb intake or individualized, per usual intake and BG levels
Lunch/Dinner	45 g each	consistent carb intake or individualized, per usual intake and BG levels
Daytime snacks (mid-morning/ mid-afternoon)	15-20 g each	
HS Snack	15-30 g	15-30 g
Fiber	Calculate 14 g of fiber/1000 kcals per day (25-30 g/ day) based on provider assessment	
Protein	Calculate 1.1 g of protein/kg/day, based on provider assessment Multiple-fetus pregnancies: an additional 50 grams of protein/day, above nonpregnant DRI for protein, during 2nd and 3rd trimesters	
Fat	30% to 40% total calories with <10% total calories from saturated fat for both GDM and preexisting diabetes Encourage use of monounsaturated and polyunsaturated fats such as olive oil, canola oil, soybean oil, nuts, seeds, avocado, and fish, particularly those high in omega-3 fatty acids; discourage intake of saturated fats	

BG indicates blood glucose; DRI, daily reference intake; GDM, gestational diabetes mellitus; g, grams; HS, bedtime; kcal, kilocalorie; kg, kilogram; T1D, type 1 diabetes; T2D, type 2 diabetes.

Other Dietary Guidelines for Pregnancy

Nutritive and nonnutritive sweeteners. The safety of nonnutritive sweeteners has not been established.

Vitamin and mineral supplements. Prenatal multivitamin and mineral supplements should include: (1) iron, 30 mg/ day; (2) potassium iodide 150 mcgs (3) folic acid, 400 mcg to supplement 400 mcg from daily dietary intake. Start the prenatal vitamin preconception, ideally, to boost folic acid to decrease the risk of neural tube defects; (4) added calcium to reach 1000 mg/day, or 1300 mg/day if aged 18 years or less; (5) vitamin D, 600 IUs/day, with tolerable upper intake of 4000 IU/day for 12 weeks.

Caffeine/Fluids. Limit caffeine to <200 mg/day (equivalent of 1 cup of coffee or 4 cups of black tea). Excess caffeine consumption during pregnancy may increase the risk of miscarriage. Three liters of water per day for adequate hydration, or about 10 cups per day, in total beverage intake is recommended.

3.7.0 PHYSICAL ACTIVITY

Regular physical activity is recommended after a provider gives clearance.

- 30 minutes of moderate exercise on most days, for 150 minutes per week
- Unless contraindications are present, women who were previously inactive or active should be encouraged to be active.

Benefits of exercise include reducing insulin resistance postprandial hyperglycemia, and excessive weight gain.

Activity after meals can reduce postprandial hyperglycemia.

3.8.0 ALCOHOL AND TOBACCO USE

Alcohol and tobacco use should be discouraged during pregnancy.

3.9.0 POSTPARTUM CARE

Breastfeeding is encouraged in patients with preexisting or gestational diabetes.

Enalapril and captopril may be used to treat hypertension and albuminuria in nursing mothers of full-term infants.

Appointments with the following specialists should be completed 6 to 8 weeks postpartum: ophthalmology, RD or registered nurse, and endocrinology.

For women who developed GDM

- A 2-hour, 75-gram oral glucose tolerance test (OGTT) should be performed at 6 weeks to evaluate for persistent diabetes.
  - Normal: fasting glucose level <100 mg/dl
  - Impaired: fasting glucose level 100 to 125mg/dl
  - Diabetes: fasting glucose level ≥126 mg/dl
  - Normal glucose tolerance: 2-hour OGTT value <140 mg/dl
  - Impaired glucose tolerance: 2-hour OGTT value 140 to 199mg/dl
  - Diabetes: 2-hr OGTT value ≥200mg/dl

- Counsel women with GDM on the roles of lifestyle management and weight loss to reduce the risk of future T2D; approximately 50% of women with GDM will develop T2D in the next 7 to 10 years.
- Review nutrition guidelines and establish exercise goals. For women with BMI greater than 25 (or BMI >23 in Asians), target a 5% to 7% weight loss from the preconception weight.
- Discuss family planning/contraceptive issues. Medroxyprogesterone (Depo-Provera) and progestin-only oral contraceptives are less preferred in patients who have had gestational diabetes, as they can accelerate the development of T2D. In patients with preexisting diabetes, medroxyprogesterone may worsen glycemic control. The intrauterine device is preferred in monogamous partnerships because it is a metabolically neutral and highly effective form of contraception.
- Assist women with GDM with the transfer of care back to the primary care physician for longer-term diabetes screening and diabetes risk reduction interventions. This includes a 75-gram, 2-hour OGTT at 1 year postpartum and every 3 years, a fasting glucose or A1c yearly on alternate years, , and a yearly discussion of risk reduction options and lifestyle management strategies afterwards.

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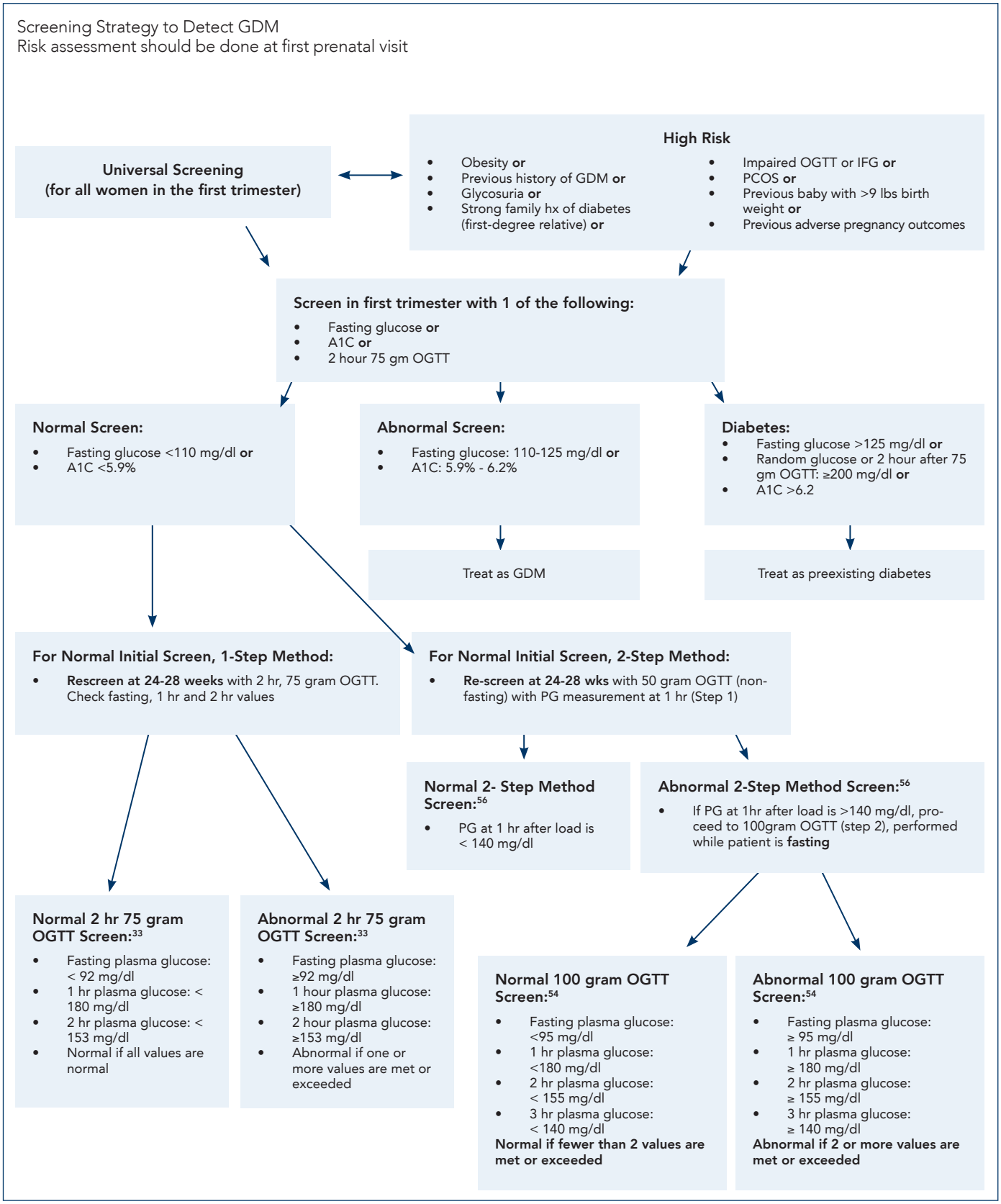
FIGURE. Gestational Diabetes Mellitus (GDM)



A1C indicates glycated hemoglobin; hx, history; lbs, pounds; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PG, plasma glucose; wks, weeks.

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CHAPTER 4.

Guideline for the Care of the Older Adult With Diabetes

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Objective: The Joslin Guideline for the Care of the Older Adult with Diabetes is designed to assist primary care physicians, specialists, and other healthcare providers in addressing the unique challenges and issues of the older person with diabetes. The guideline should be used in conjunction with Joslin's Clinical Guideline for Adults with Diabetes as well as Joslin's Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes (T2D).

The primary goal of diabetes management in older adults is to achieve balance between optimal glycemic control to prevent and/or slow the onset and progression of acute and chronic complications, while avoiding hypoglycemia and its consequences. Hypoglycemia can result in worse outcomes in older adults as it can lead to traumatic falls and worsening of chronic conditions such as cognitive dysfunction. Therefore, in many cases, aggressive treatment may not be appropriate if the older adult's comfort, safety, and overall quality of life are thereby compromised, or if aggressive treatment may not improve outcomes. Recent consensus on the management of diabetes recommends individualization of treatment goals based on coexisting medical conditions, cognitive status, functionality, and available resources. The older adult's view on illness, health, and aging should also be considered. Appropriate support systems for complex diabetes are not uniformly available nationwide. As a result, treatment decisions become more complex as the capacity to cope with self-care declines.

To assist with self-care, education strategies also require adaptation for aging. Learning new diabetes self-management skills may be difficult for older people, increasing the need for education to proceed in a simple, step-like manner. Cognitive dysfunction, depression, and functional disabilities (such as vision and hearing deficits and a decline in dexterity) are important issues to consider when assessing the older adult's ability for self-care. Involvement of family members or friends may be required to assure appropriate self-care and adherence to treatment programs.

Portions of this guideline are based upon recommendations of the International Diabetes Federation's Global Guideline for Managing Older People with Type 2 Diabetes and the American Diabetes Association/American Geriatrics Society Consensus Report on Diabetes in Older Adults.

4.1.0 GENERAL CONSIDERATIONS

- In determining treatment plans and goals, individualized patient assessment is required, being cognizant of the following:
  - Chronological age versus actual health status
  - Duration of disease and age of onset (for example, older-age onset of T2D is more prominent in non-Hispanic whites and is associated with a lower likelihood of insulin use than middle-age onset; retinopathy is more likely to occur in middle-age–onset diabetes rather than older-age–onset diabetes. There is no difference in coronary artery disease or neuropathy prevalence in middle vs older age onset)
  - Presence of complications and comorbidities
  - Life expectancy
  - Social support system
  - Financial status
  - Patient preferences
- Treatment programs should be simplified to decrease

TABLE 1. Geriatric Syndrome: Screening and Modifications

Condition	Clinical Presentation	Shorn Screening Test	Modification to Treatment Plans and Goals
Cognitive dysfunction	• Decline in self-care and/or worsening of glycemic control without clear etiology • Appears stubborn or not able to follow instructions • Seems uninterested in helping him/herself • Makes errors, especially when problem-solving	• Clock drawing test • MiniCog test[a] • Montreal Cognitive Assessment Test[b]	• Avoid tight glucose control and complex diabetes medication programs • Educate caregivers and seek their support in managing the patient's diabetes • Repeat important education topics at each visit, eg, how to recognize and treat hypoglycemia • Avoid diabetes medications that have a risk of hypoglycemia, as the hypoglycemia may go unnoticed and untreated • Recommend reminders, such as alarms, notes, and pill boxes, for taking medications or eating meals
Depression	• Seems uninterested in helping him/herself • Is less interested in activities • Seems overwhelmed with life events • Has a decline in self-care and/or worsening of glycemic control without clear etiology	• Patient Health Questionnaire (PHQ-2) • Geriatric Depression Scale	• Assess and treat depression
Physical disabilities • Vision impairment • Hearing loss • Gait abnormality	• Dosing errors • Discrepancies between log book and meter download • Disinterest in conversation • Inactivity, lack of follow-up with exercise recommendations • Reports of falls	• Vision and hearing screening • Physical exam to evaluate for peripheral neuropathy • Ask about recent falls and fear of falls • Assess for risk factors for falls • Bone-density study to evaluate bone heath and fracture risk	• Recommend use of assistive devices for vision and hearing impairment, such as hearing aids, talking glucose meters, glucose meters with large readouts, magnifiers • Recommend use of assistive devices such as cane or walker for balance and gait issues • Recommend safe-venue, supervised exercise program/physical therapy • Recommend an exercise program that is suitable for the patient's current level of activity, eg, wheelchair exercises, exercise pedals, etc
Malnutrition/ weight loss	• Weight loss • Dental issues	• Nutrition assessment tools, eg, DETERMINE survey	• Avoid restrictive diets; encourage adequate calories, hydration, protein intake, nutrition supplements - Consider Meals on Wheels if unable to shop/cook for self - Consider communal meals at senior centers if socially isolated - Consider community food pantries if finances impede healthy food purchases. • Encourage regular dental checkups
Polypharmacy/ medication nonadherence	• Fluctuations in glucose, blood pressure, and/or cholesterol levels • Inability to accurately list names and doses of medications • Voices lack of trust in medication safety or efficacy • Appears overly medicated	• Carefully reconcile medication list at each visit • Assess for lack of resources	• Ask patient to carry current medication list with them • Ask patient what he/she actually takes on the list of medications they carry • When possible, discontinue medications that have no clear benefit • Look for medication adverse effect or drug–drug interaction as the possible cause of any new symptoms • If needed, review patient's medication refill history with their pharmacy • Refer patient/family to financial resources to assist with obtaining needed medications

[a]MiniCog. Screening for impairment in older adults. [b]Montreal Cognitive Assessment Test.

the potential of medication errors and to avoid overwhelming the patient and their caregivers.
- Treatment goals should be reassessed at frequent intervals as health status can change quickly in older adults.

4.2.0 GERIATRIC SYNDROME

The table in this guideline (**Table 1**) lists a group of conditions collectively called *geriatric syndrome*, which occurs more frequently in older adults with diabetes. These conditions can interfere with a patient's ability to perform self-care activities and make healthcare more challenging for the older adult and for their caregivers. The table below includes the condition, possible clinical presentations, commonly used short clinical screening tests, and suggested modifications to treatment plans and goals to compensate for the condition.

4.3.0 DIAGNOSIS

See Joslin's Clinical Guideline for Adults with Diabetes (Chapter 1) for more details.

CDC data indicate that about half of older adults have prediabetes. It is recommended that all adults ≥45 years of age be screened for diabetes every 1 to 3 years using a glycated hemoglobin (A1C), fasting glucose, or oral glucose tolerance test. This recommendation should be modified for those with shorter life expectancies and those with multiple comorbidities.

4.4.0 TREATMENT GOALS

See Joslin's Clinical Guideline for Adults with Diabetes for more details. Treatment goals are modified for health status, based on recommendations from the American Diabetes Association.

Treatment goals for A1C, glucose, blood pressure, and lipid levels should be modified for the older adult based on patient characteristics and on health status. See **Table 2** below.

4.5.0 EDUCATION

Education strategies require adaptation for aging. Simplify and focus programs:

- Use focused educational material that is easy to follow and excludes extraneous information.
- Provide individual rather than group education if the patient has cognitive or physical deficits.
- Focus on 1 to 2 topics at a time. Repetition and re-education are needed for many older adults.
- Education sessions should be slow-paced, with instruction occurring in steps.
- Multiple sessions may need to be scheduled, to prevent "information overload."
- Use memory aids (eg, personalized handouts) to reinforce points made during face-to-face sessions.
- When possible, simplify the patient's medication program especially for those who have multiple medical problems, cognitive dysfunction, or functional disability (eg, changing insulin to 2 injections per day from 4 injections per day).
- When discussing medications, focus education on medication adherence by using charts, pill boxes, and other reminders.
- Caregivers should be instructed in how to track amounts of medication used.
- Educate the patient that uncommon symptoms such

TABLE 2. Treatment Goals for the Older Adult

Patient Characteristics/ Health Status	Rationale	A1C	Fasting or Postprandial Glucose (mg/dL)	Bedtime Glucose (mg/dL)	Blood Pressure (mmHg) (see hypertension section in this guideline for details)	Lipids Treatment (see lipid section in this guideline)
Healthy • Few coexisting chronic illnesses[a] • Intact cognitive status • Intact functional status	• Longer life expectancy	<7.5% **[1C]**	80-130	90-150	<140/90 **[2B]**	Statins (unless not tolerated) **[1B]**
Complex/intermediate • Multiple coexisting chronic illnesses[a] • Mild to moderate cognitive impairment • 2+ Instrumental Activities of Daily Living (IADL)[b]	• Intermediate life expectancy • High treatment burden • Hypoglycemia vulnerability • Fall risk	<8% **[2C]**	90-150	100-180	<150/90 **[2C]**	Statins unless not tolerated **[1C]**
Very complex/poor health • Long-term care residents • End-stage chronic illnesses • Moderate-to-severe cognitive impairment • 2+ Activities of Daily Living (ADL) dependenciesc	• Limited life expectancy • Benefits uncertain	<8.5% **[2C]**	100-180	110-200	<150/90 **[2C]**	Consider stopping statin use if expected longevity is less than 1 year **[2C]**

Source: American Diabetes Association; [a]Coexisting chronic illnesses: conditions serious enough to require medication or lifestyle management. They may include arthritis, cancer, congestive heart failure, depression, chronic obstructive pulmonary disease, falls, and chronic renal failure.
[b]IADL: measures functioning in traveling, shopping, housework, managing finances, using the telephone, and taking medications.
[c]ADL: measures the 5 basic functions of bathing, toileting, dressing, transferring, and eating.
A1C indicates glycated hemoglobin.

as confusion, dizziness, and weakness can be manifestations of hypoglycemia.
- Involve the patient's caregiver or arrange for visiting nurse evaluation if medication adherence is an issue.
- Provide very specific guidelines on when the patient and/or caregiver should call the healthcare provider for assistance.

4.6.0 DEVICES
- Recommend equipment that is easy to hold, easy to read, and requires the least number of steps.
- Insulin pens, pens that contain noninsulin glucose-lowering medication, and prefilled syringes may be easier for older patients to use than manipulating a syringe and vial. Syringe magnifiers are available if vision is impaired.
- For some patients, inhaled insulin may be another option for prandial insulin.
- Choose blood glucose meters that have a large display, are easy to hold and use, and that minimize handling of strips and lancets. "Talking meters" are available for those with vision impairment.

4.7.0 MONITORING
- Emphasize the importance of regular self-monitoring of blood glucose (SMBG), especially before driving or using power tools.
- Checking glucose levels at different times of the day, on different days of the week, will allow the provider to assess glucose patterns throughout the day without having the patient check the glucose several times each day. For example, check the fasting and presupper glucose levels one day, and prelunch and bedtime levels another day.
- Some older adults may not be able to perform SMBG due to physical or cognitive impairment. To decrease the risk of hypoglycemia in these situations, glycemic goals may need to be adjusted and medication programs may need to be simplified. In T2D, if appropriate, use diabetes medications that have a low risk for hypoglycemia.
- Develop a plan to treat hypoglycemia. Encourage the patient to carry a source of glucose on their person and to have one at the bedside at all times.
- Develop a sick day plan.
- Encourage caregivers to accompany patients to education sessions and receive appropriate education in glucose monitoring and blood glucose interpretation.

4.8.0 DRIVING
- A referral for education and counseling should be advised if the patient's ability to drive is in question. Organizations such as local elder services, the American Geriatric Society, and the various state motor vehicle registries may have additional information for patients as well as family members.
- Drive-wise programs, where available, can be useful to assess the patient's ability to drive.

4.9.0 NUTRITION CHALLENGES (see Appendix for examples of nutrition prescriptions)
Although diabetes nutritional guidelines for the older adult are no different than for younger adults, unique challenges often exist due to:
- Lack of motivation
- Impaired food shopping or preparation capabilities
- Omission of meals due to cognitive dysfunction or depression
- Compromised dentition
- Altered taste perception
- Altered gastrointestinal function
- Weight loss and malnutrition
- Coexisting illnesses
- Limited finances

4.9.1 Nutritional recommendations:
Consider referral to a dietitian to work with the older adult patient and caregivers to:
- Assess nutritional needs
- Avoid making unnecessary dietary changes in life-long eating habits, remembering that to treat coexisting illnesses multiple changes may be required, such as reducing potassium, sodium, and dietary fats
- Minimize the complexity of meal planning and engage the spouse, or others living with the patient, in creating a home environment that supports positive lifestyle change
- Educate how consistency in carbohydrate intake and meal timing can help minimize fluctuations in blood glucose levels as well as help maintain or achieve a reasonable weight
- Consider giving prandial insulin after the meal rather than before, based on carbohydrate intake
- Assess the ability to buy and prepare healthy meals
- Help maximize a limited food budget
- Suggest community resources such as Meals on Wheels

4.9.2 Weight loss/potential malnutrition:
- Weight-loss diets commonly recommended to younger adults should be prescribed with great caution to the older adult, since undernutrition/malnutrition is often more of a problem than obesity in the older adult.
- Weight loss and the potential for malnutrition should be carefully monitored, especially after acute illness, hospitalization, and social stress.
    - Use serial weight measurements to monitor changes.
- To avoid weight loss, it may be necessary to let patients

eat what they enjoy and adjust diabetes medications accordingly.

4.9.3 Chronic care settings:

- In chronic care settings, there is no need for a rigid and restrictive meal plan. A regular meal plan with consistent, moderate carbohydrate intake may be sufficient and may help avoid undernutrition.

4.10.0 PHYSICAL ACTIVITY

(see Appendix for examples of activity prescriptions)

4.10.1 Benefits of activity:

Physical activity should be stressed in all older adults as it is crucial in maintaining functionality, independence, and acceptable quality of life.

- Regular exercise program offers other benefits to older adults, such as:
  - Reduced glucose levels
  - Improved lipid profile
  - Improved blood pressure
  - Increased muscle tone and strength
  - Improved gait and balance
  - Overall physical conditioning
  - Decreased depression, and an overall sense of improved well-being.

4.10.2 Types of activity:

- Types of physical activities that may be appropriate for the older adult should take into account the current level of physical fitness/disability. It is important to develop an activity program to increase mobility, endurance, and strength, and to increase the duration of the activity gradually. Common activities to achieve these goals include:
  - Aerobic activities
  - Walking
  - Swimming or water aerobics
  - Stationary bicycle riding
  - Resistance training
  - Armchair exercises
  - Weight lifting
  - Balance exercise
  - Tai chi
  - Yoga
  - Flexibility exercises
  - Other physical activities:
    - Gardening
    - Household chores

4.10.3 Challenges to consider:

- Challenges to maintaining a regular physical activity program include:
  - Fluctuations in health
  - Comorbidities, such as cardiovascular disease, osteoarthritis, and osteoporosis
  - Risk and fear of falls
  - Finding a safe environment for exercise
  - Issues with transportation
  - Hypoglycemia
    - The risk of hypoglycemia is increased among those using insulin and other diabetes medications that can cause hypoglycemia. More frequent SMBG may reduce this risk.
- An exercise physiologist or a physical or occupational therapist can provide a supervised environment to help a patient perform exercises safely.

4.11.0 MEDICATIONS: GENERAL CONSIDERATIONS

General principles to consider when prescribing medications to an older adult include:

- "Start low and go slow" when dosing and titrating medications
- Agents with low risk of hypoglycemia are preferred in this age group
- Deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia

4.11.1 Overtreatment of diabetes is common in older adults and should be avoided.

- Consider drug–drug interactions carefully, as most older adults are on multiple medications as well as supplements
- Evaluate renal function using the estimated glomerular filtration rate (eGFR) rather than serum creatinine because low muscle mass in the older population may result in a "normal" creatinine level despite significant renal dysfunction-
- Monitor liver and kidney function with periodic tests
- Assess financial resources when using newer, generally more expensive agents

4.11.2 Oral glucose-lowering medications: (Table 3)

Please also refer to Joslin's Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes (Chapter 1) for more detailed information on diabetes medications.

4.11.3 Injectable noninsulin antidiabetic medications (Table 4)

4.11.4 Insulin products (Table 5)

4.12.0 HYPERTENSION: GENERAL CONSIDERATIONS

The goals of therapy for hypertension in the older adult are the same as those for younger adults with diabetes. The target blood pressure should be less than 140/90 mmHg as tolerated. Isolated systolic hypertension is much more common in the older adult.

Systolic blood pressure <150 is acceptable in patients with multiple comorbidities or limited life expectancy. Care should be taken to treat with antihypertensive agents to bring systolic blood pressure to goal, if feasible. Blood pressure should be lowered gradually in order to reduce the risk of hypotensive symptoms. Older adults are prone to "white coat" hypertension. If suspected, patients should be asked to measure blood pressure at home and keep a log for periodic evaluation.

4.12.1 Antihypertensive drugs (Table 6)

4.13.0 LIPIDS (for more detail please see Joslin's Clinical Guideline for Adults with Diabetes Chapter 1)

GENERAL CONSIDERATIONS

- **All individuals with preexisting cardiovascular disease (CVD):** Based on a large body of clinical-trial evidence, all individuals with preexisting CVD should be treated with high-intensity statin therapy designed to lower low-density lipoprotein cholesterol (LDL-C) by ≥50% from baseline, regardless of baseline cholesterol. The adherence to statin therapy should be monitored at 4 to 12 weeks after initiation, and every 3 to 12 months thereafter, as indicated.
- If age >75 years, or if adverse events occur while on a high-intensity statin dose, treat with moderate-intensity statin therapy, designed to lower LDL-C between

TABLE 3. Oral Antidiabetic Medications

For additional details see Joslin's Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes (Chapter 5)				
Medication Class	**Mechanism of Action**	**Advantages**	**Disadvantages**	**Caveats in the Older Population**
Biguanides • liquid metformin* (Riomet) • metformin (Glucophage) • metformin extended release (Glucophage XR, Fortamet, Glumetza) *Liquid formulation for patients unable to swallow large tablets	Decrease hepatic glucose production, increase GLP-1 secretion	Low risk for hypoglycemia Low cost Well understood AEs	Contraindicated in advanced liver disease, alcohol excess, decompensated congestive heart failure, acute intercurrent illness, dehydration AEs include gas, diarrhea, B12 deficiency, lactic acidosis	Use as initial therapy unless contraindicated Initiate at low dose, increase dose slowly, and take with food to decrease gas, diarrhea Extended release formulation may decrease GI symptoms May cause weight loss May cause GI symptoms initially or symptoms may develop after prolonged use Measure liver functions, serum creatinine, and eGFR initially, then periodically and with any increase in dose Avoid initiating and stop use if eGFR <45
Insulin secretagogues **Sulfonylureas** • glimepiride (Amaryl) • glipizide (Glucotrol) • glipizide extended release (Glucotrol XL) • glyburide (Micronase, Diabeta) • micronized glyburide (Glynase) **Meglitinides** • repaglinide (Prandin) **D-phenylalanine derivatives** • nateglinide (Starlix)	Stimulate beta-cell insulin secretion	Many sulfonylureas are available at lower cost Shorter-acting agents like glipizide, or the nonsulfonylurea insulin secretagogues repaglinide and nateglinide, may lower the risk of nocturnal hypoglycemia. In patients with erratic oral intake, these drugs may lower the risk of daytime hypoglycemia	Contraindicated in severe liver or renal disease Risk of hypoglycemia, especially with longer-acting sulfonylureas such as chlorpropamide (first-generation sulfonylurea) and glyburide	Consider use of short-acting sulfonylurea in the setting of renal disease to reduce the risk for hypoglycemia Repaglinide or nateglinide may be useful for those with postprandial hyperglycemia or hypoglycemia on sulfonylurea Watch for increased risk of hypoglycemia in those with memory issues, or that may accompany acute illness, hospitalization, weight loss, lack of appetite, and skipped meals
TZDs • pioglitazone (Actos) • rosiglitazone (Avandia)	Improve glucose transport; decrease hepatic glucose production	TZDs can be well tolerated in healthy older adults as they do not cause hypoglycemia Can be used in renal impairment but may increase fluid retention	Fluid retention and CHF are common comorbidities in the elderly, preventing the use of TZDs Should be avoided in patients with Class III and Class IV CHF See footnotes 1-3 for CV and other risks Contraindicated in liver disease Increases bone loss and risk for bone fracture May increase risk for macular edema	AEs of fluid retention can be limiting factors in using this class of medications Concerns re: bladder cancer are fewer in the elderly with shorter life expectancy See footnotes 1-3 for CV and other risks

table continued SP246

TABLE 3 (cont.). Oral Antidiabetic Medications

Medication Class	Mechanism of Action	Advantages	Disadvantages	Caveats in the Older Population
Alpha-glucosidase inhibitors • acarbose (Precose) • miglitol (Glyset)	Delay absorption and breakdown of carbohydrates	Use if postprandial hyperglycemia predominates Low risk of hypoglycemia if used as monotherapy	Contraindicated in chronic intestinal disorders May cause gas, diarrhea Acarbose is contraindicated in cirrhosis Do not use in renal impairment (creatinine >2.0)	Modest glucose-lowering effect Ideally, use pure glucose to treat hypoglycemia when used in combination therapy, because the drugs decrease absorption of other forms of carbohydrate Initiate at low dose and increase slowly to decrease flatulence
DPP-4 inhibitors • sitagliptin (Januvia) • saxagliptin (Onglyza) • linagliptin (Tradjenta) • alogliptin (Nesina)	In a glucose-dependent manner, these medications slow the inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels	Helpful in controlling postprandial glucose elevations Lower risk of hypoglycemia	AEs include occasional diarrhea and stomach discomfort Safety of use in the setting of prior pancreatitis is unknown. Stop medication if pancreatitis is suspected when a DPP-4 inhibitor is in use High cost Lower glucose-lowering efficacy may result in the need for a multidrug program Increased risk for CHF with saxagliptin	Low risk of hypoglycemia Assess kidney function prior to initiating and periodically thereafter Reduce dose in renal disease with some members of the class Good drug for frail elderly with newly diagnosed diabetes Postmarketing reports of hepatic failure with alogliptin
SGLT2 inhibitors • canagliflozin (Invokana) • dapagliflozin (Farxiga) • empagliflozin (Jardiance) • ertugliflozin (Steglatro)	Block the reabsorption of glucose by the proximal tubule of the kidney, thereby increasing excretion of glucose in the urine	Low risk of hypoglycemia	Do not use in moderate-to-severe renal disease as it may worsen renal function May reduce blood pressure Increased risk for genital mycotic infections and for urinary tract infection May result in dehydration, weight loss, hyperkalemia, increased low-density lipoprotein cholesterol High cost Little data available for safety in the older population	Adjust dose in mild kidney disease To decrease the risk of hypotension and dehydration, consider adjustment of antihypertensive medication, especially diuretics, when starting this medication class Do not use dapagliflozin in setting of bladder cancer; use with caution with a history of bladder cancer
Many of the oral diabetes medications are available in fixed combinations. Please see Joslin's Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes. Fixed combinations have the advantage of 1 versus 2 co-payments. Adherence may improve as there are fewer tablets to administer and to remember. The disadvantage to fixed combinations is decreased flexibility in dosing. Colesevelam, a bile acid sequestrant, and quick-release bromocriptine are approved by the FDA for the treatment of diabetes, but there is very limited use in the older population.				

AE indicates adverse effect; CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose co-transporter-2; TZD, thiazolidinedione.

Footnotes

[1]There is an increased risk for edema when insulin and a TZD are used together. Rosiglitazone should not be used in combination with insulin.

[2]FDA requirements for liver function tests with TZDs: If initial alanine aminotransferase (ALT) is >2.5 times normal, do not start this medication. Once TZD is started, monitor ALT periodically thereafter according to clinical judgment. If ALT is >2.5 times normal during treatment, check weekly. If rise persists or becomes >3 times normal, discontinue TZD.

[3]TZDs cause or exacerbate congestive heart failure in some patients. After initiation of TZDs and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain; dyspnea; and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of the TZD must be considered. TZDs are not recommended in patients with symptomatic heart failure or in patients with established New York Heart Association Class III or IV heart failure.

[3i]On September 23, 2010, the FDA announced regulatory actions with respect to products containing rosiglitazone: Avandia (rosiglitazone maleate) tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets, and Avandaryl (rosiglitazone maleate and glimepiride) tablets. These FDA actions required GlaxoSmithKline to implement restrictions on the use of these products through a Risk Evaluation and Mitigation Strategy (REMS) program to assure their safe use and through additional labeling changes in response to the agency's review of data that suggested an elevated risk of CV events. However, based on additional data review, the REMS program was removed as of May 2014. Rosiglitazone now has the same indications for prescribing as pioglitazone.

[3ii]According to an FDA advisory issued on June 15, 2011, on potentially increased risk of bladder cancer with pioglitazone use: a) do not use pioglitazone in patients with active bladder cancer; b) use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

4.11.3. Injectable Noninsulin Antidiabetic Medications (**TABLE 4**)

Medication Class	Mechanism of Action	Advantages	Disadvantages	Caveats in the Older Population
Incretin mimetics • exenatide (Byetta) • liraglutide (Victoza) • extended release exenatide (Bydureon) • dulaglutide (Trulicity) • semaglutide (Ozempic)	In a glucose-dependent manner, increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety	Use may be associated with weight loss, which is helpful in the overweight/obese person Low risk of hypoglycemia	Medications must be injected Dosing frequency is dependent on the medication and can range from twice a day to once weekly Adverse effects include nausea, diarrhea, and increased satiety, which can affect nutritional status in the older adult Increased risk for pancreatitis Risk for acute renal impairment High cost Limited data on safety in the older population	Low risk of hypoglycemia, and formulation that can be used once weekly, makes this an attractive agent to use in elderly Consider the person's cognitive abilities, dexterity, and visual acuity before considering use of any injectable medication To decrease risk of hypoglycemia if using with a sulfonylurea or basal insulin, consider initially decreasing sulfonylurea or insulin dose

30% and 49% from baseline. If the baseline LDL-C is not known, the minimum target should be LDL-C <70 mg/dl, or non–HDL-C <100 mg/dl.

For primary prevention in older people aged ≤75 years: Statin therapy should be based on 10-year CVD risk as calculated by the revised risk calculator (my.americanheart.org/cvriskcalculator).

If the 10-year risk is <7.5%, a moderate-to-intensive statin therapy is indicated, designed to lower LDL-C by 30% to 50% from baseline. If the baseline LDL-C is not known, the minimum target should **be LDL-C <100 mg/dl, or non–HDL-C <130 mg/dl.**

If the 10-year risk is ≥7.5%, intensive statin therapy should be instituted, designed to lower LDL-C by ≥50% from baseline, regardless of baseline cholesterol. If the baseline LDL-C is not known, the minimum target should be LDL-C <70 mg/dl, or non–HDL-C <100 mg/dl**.**

For primary prevention in older people aged >75 years: Initiation of statin therapy is of uncertain value, and should be individualized, based on comorbidities, life expectancy, safety considerations, and priorities of care. Consider stopping statin therapy if life expectancy is less than 1 year.

4.13.1 Lipid-lowering medications (Table 7)

4.14.0 FOOT CARE

- Recommendations for foot examinations and treatment in older adults with diabetes are the same as those for younger individuals. Older adults may require additional education and devices such as mirrors to examine their feet due to decreased mobility and dexterity. See Joslin's Clinical Guideline for Adults With Diabetes for more detail.
- Older adults should be encouraged to see a podiatrist regularly. Medicare provides coverage for podiatrist visits every 9 weeks, along with special footwear for patients with diabetes-related qualifying foot problems.

4.15.0 EYE CARE

Recommendations for eye examinations and treatment in older adults with diabetes are the same as those recommended in Joslin's Clinical Guideline for Adults with Diabetes.

- Providers should also consider eye conditions commonly seen in older adults, including glaucoma, macular degeneration, and cataracts, which may be present without evidence of diabetic eye disease or coincident with diabetic eye disease.
  - Nondiabetic ocular conditions such as cataracts may complicate evaluation and treatment of diabetic retinopathy
  - Interventions for nondiabetic ocular conditions may be risk factors for progression of diabetic retinopathy
  - Interventions for diabetic eye disease may pose risk factors for progression of nondiabetic eye conditions such as cataracts and glaucoma
- Although tighter glycemic control has been shown to lower the risk of eye complications, the overall risk of hypoglycemia and increased mortality risk with tight control in the older population should be considered when setting the glycemic goals.

4.11.4. Insulin Products (**TABLE 5**)

Medication Class	Mechanism of Action	Advantages	Disadvantages	Caveats in the Older Population
Injectable U-100 insulins **Rapid-acting:** • Insulin aspart analog (Novolog) • Insulin glulisine analog (Apidra) • Insulin lispro analog (Humalog) **Short-acting:** • Human Regular • Humulin R • Novolin R **Intermediate-acting:** • Human NPH insulin • Humulin N • Novolin N **Long-acting:** • Insulin detemir (Levemir) • Insulin glargine (Lantus) • Insulin degludec (Tresiba) **Premixed insulins:** • 70% NPH; 30% Regular (Humulin 70/30) • 70% NPH; 30% Regular (Novolin 70/30) • 50% lispro protamine suspension, 50% lispro (Humalog Mix 50/50) • 75% lispro protamine suspension, 25% lispro (Humalog Mix 75/25) • 70% aspart protamine suspension, 30% aspart (Novolog Mix 70/30)	Allow glucose to enter cells for an energy source; decrease hepatic glucose production	Improved glucose control in type 2 diabetes when used in combination with other antidiabetic medications, or when other programs do not give adequate control. Insulin can be used as monotherapy Insulin is the only treatment choice in treating T1D	Older adult patients taking insulin often face difficulties with self-administration because of reduced dexterity, impaired vision, and cognitive deficits Risk of hypoglycemia	Consider the person's type of diabetes, cognitive abilities, dexterity, and visual acuity before considering the use of insulin Long-acting insulin can be used safely with other noninsulin diabetes medications to control postprandial glycemia. When deciding on the timing and dose of basal insulin, consider the individual's glucose pattern. In general, older adults have a higher contribution of postprandial hyperglycemia compared with fasting hyperglycemia. Thus, starting basal insulin in the morning in this population may decrease the risk of nocturnal hypoglycemia and improve postprandial glucose control It is often beneficial to use simpler insulin regimens with fewer daily injections, such as premixed insulin preparations and easier injection systems (eg, insulin pens with easy-to-set dosages). If syringe and vial are to be used, a careful assessment of the individual's ability to draw up and give an injection needs to be made prior to devising the insulin and self-monitoring program The risk for hypoglycemia when using premixed insulins is lessened when meal times are more fixed There is a potential increased risk for nocturnal hypoglycemia when taking a premixed insulin at the evening meal Other self-management skills, such as treating hypoglycemia and eating on a regular schedule, will need to be assessed prior to determining the person's insulin program and reassessed periodically thereafter
Injectable U-300 Insulin				Limited experience May be used in patients with large insulin requirement (greater than 200 units daily)
Injectable U-500 Insulin				May be used in patients with large insulin requirement (greater than 200 units daily)
Inhaled insulin Afrezza inhalation insulin		May be used instead of prandial insulin.	Older adult patients taking insulin often face difficulties with self-administration because of reduced dexterity, impaired vision, and cognitive deficits. Risk of hypoglycemia Need to ensure normal pulmonary function periodically	Limited experience

NPH indicates neutral protamine Hagedorn; T1D, type 1 diabetes.

4.12.1. Antihypertensive Drugs (**TABLE 6**)

Medication Class	Mechanism of Action	Advantages	Disadvantages	Caveats in the Older Population
ACEI/ARB Examples: **ACEIs:** lisinopril, ramipril, benazepril, trandolapril **ARBs:** losartan, valsartan irbesartan	Inhibition of the renin-angiotensin system	Evidence for cardiovascular benefits Evidence for renal protection	Dry cough with ACEI Hyperkalemia Drop in eGFR (contraindicated in renal vascular disease) Angioneurotic edema with ACEI (rare)	Before initiating therapy, check-baseline renal function and serum potassium; recheck within 1-2 weeks of initiation of therapy, with each medication dose increase, and at least yearly thereafter
Diuretics Include hydrochlorothiazide, chlorthalidone, furosemide, torsemide, bumetanide, indapamide	Sodium excretion; limit volume expansion	May be effective as monotherapy; also additive blood-pressure–lowering effect with other agents	Hypokalemia Volume depletion Dehydration (dose- related)	Before initiating therapy, check-baseline electrolytes; recheck electrolytes within 1-2 weeks of initiation of therapy, with each medication dose increase, and at least yearly thereafter
Calcium channel blockers Include diltiazem, verapamil, amlodipine	Direct vascular effects by inhibition of calcium channels	Potent antihypertensive effect May have greater effect in stroke prevention	Fluid retention with certain agents in class (amlodipine, diltiazem) Bradycardia with certain agents in class (diltiazem, verapamil)	Some evidence suggests that treatment with calcium channel blockers, diuretics, and ACE inhibitors are more effective than beta blockers in this population
Beta blockers Include metoprolol, atenolol, propranolol, carvedilol	Reduce cardiac output	Evidence for cardiovascular benefits after acute coronary events	Bradycardia, fatigue	May be less effective in older adults and African Americans
Mineralocorticoid receptor antagonists Include spironolactone, eplerenone	Inhibit mineralocorticoid receptor	Additive effects as antihypertensives or in heart failure	Hyperkalemia	Before initiating therapy, check-baseline renal function and serum potassium; recheck within 1-2 weeks of initiation of therapy, with each medication dose increase, and at least yearly thereafter
Combination therapy				Most patients require more than 1 antihypertensive medication to reach goal

ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

4.13.1. Lipid-Lowering Medications **(TABLE 7)**

Medication Class	Mechanism of Action	Advantages	Disadvantages	Caveats
HMG CoA-R reductase inhibitors (statins) • atorvastatin (Lipitor) • fluvastatin (Lescol) • lovastatin (Altoprev, Mevacor) • pitavastatin (Livalo) • pravastatin (Pravachol) • rosuvastatin (Crestor) • simvastatin (Zocor)	Reduce cholesterol synthesis and promote cholesterol excretion by enhancing the activity of LDL receptors	Drug class of choice for lowering LDL-C on the basis of many clinical trials Reduce LDL-C ~20%-60%, depending on drug and dose Reduce CVD events in both primary prevention and in patients with preexisting CVD	3%-6% probability of liver toxicity; 10%-15% probability of myalgia or muscle weakness; rarely myositis or rhabdomyolysis May precipitate new-onset diabetes, especially in those with prediabetes or metabolic syndrome Rarely result in GI AEs Rarely result in cognitive disturbances (reversible)	Check ALT within 4-12 weeks of initiation of the medication, with each dose increase, and with any signs or symptoms of liver dysfunction Routine CK measurements are not necessary unless symptoms warrant Older adults on medications for hyperlipidemia should have periodic evaluation of liver enzymes
Ezetimibe	Reduces cholesterol absorption	Well tolerated Additive efficacy in lowering LDL-C, beyond statin effects	Modest effect; lowers LDL-C by 15%-20% Rare AEs	May improve CVD event reduction when added to moderate-dose statin, if statin intensification not feasible Not preferred in monotherapy, but may be useful as adjunct to statin, if statin alone cannot be intensified
Bile acid sequestrants	Bind to bile acids and promote excretion of cholesterol in gut	Dose-dependent reduction in LDL-C, 15%-30% Can be combined with statins	Adherence issues due to GI AEs	Limited data on CVD event reduction Not preferred in monotherapy unless other agents can't be used
Niacin	Inhibits lipolysis, and has multiple lipid effects via diverse mechanisms	Dose-dependent lowering of LDL-C by 10%-20%; raises HDL-C by 15%-25%; lowers TG 15%-30% Additive efficacy with statins in achieving lipid goals	Adherence issues due to multiple AEs, including flushing, pruritus, liver toxicity, hyperuricemia, and raised glucose levels	Effects on CVD prevention unproven
Fibrates	Inhibit lipolysis and VLDL production; enhance triglyceride clearance	Drug of choice to lower TG; raises HDL-C; minimal effect on LDL-C	Myalgia in combination with other drugs, including statins Caution in presence of CKD; may promote gallstones	Limited data on CVD event reduction Indicated in preventing pancreatitis, if TG >500 mg/dL Additional studies on CVD events underway
Omega-3 fatty acids	Inhibit triglyceride synthesis in liver	Well tolerated. 25%-30% reduction in TG levels; modest effects on HDL-C; may raise LDL-C	Adherence issues May prolong bleeding time	No data on CVD event reduction; studies ongoing Currently approved to lower TG if >500 mg/dl; may reduce risk of pancreatitis
PCSK 9 inhibitors		Antibody to PCSK9 further reduces LDL-C in combination with statin or if statin intolerant	Expensive	Limited data in elderly

AE indicates adverse effect, ALT, alanine aminotransferase; CK, creatinine kinase; CVD, cardiovascular disease; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.

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Appendix

Examples of Exercise Prescriptions

For inactive or frail patients
Do the items checked below. If an item is not checked, ignore it.

- Walk 5 minutes inside the house or in the hallway, every day
  - Start with 1-3 times a day before meals
  - Increase a little each week to 10 minutes 3 times every day
- Pedal with legs and arm
  - Start with what you can do and increase a little each week up to 15-20 minutes every day
- Stationary bike
  - Start with 5 minutes, 1-3 times a day
  - Increase a little each week up to 30 minutes every day

For active patients
Do the items checked below. If an item is not checked, ignore it.

- Aerobic activity: Do 1 of these at least 5 days each week. You can do the same one each time or pick a different one for variety. Start with short periods of time and increase to 30-60 minutes a day.
  - Walking (use pedometer to increase activity as tolerated)
  - Stationary bike
  - Swimming
  - Water aerobics
- Resistive training: Do 1 of these at least 2 days each week. You can do the same one each time or pick a different one for variety. Start with no/low weights and increase weights and repetitions as tolerated, up to 8-10 reps for 2-3 cycles for each muscle group
  - Hand weights (or 8-ounce water bottle)
  - Resistance bands
  - Use machines at gym
- Stretching: Do 1 of these daily. You can do the same one each time or pick a different one for variety. Again, start low and go slow. Avoid excessive stretching and injury.
  - Yoga
  - Stretching

Examples of Nutrition Prescriptions

To avoid low blood sugar

- ☐ Do not skip or delay meals
- ☐ Have some carbohydrate/starch to eat at each meal
- ☐ Keep glucose tablets/gel or hard candy with you at all times
- ☐ Check your blood sugar anytime you feel unwell, sick, or confused
- ☐ Eat a snack before any significant activity

Nutrition prescriptions

Do the items checked below. If an item is not checked, ignore it.

- ☐ Do not skip or delay meals
- ☐ Have some carbohydrate/starch to eat at each meal
- ☐ Have at least 1500 mg of calcium and 800 units of vitamin D every day
- ☐ Eat a snack at bedtime
- ☐ Eat a snack between meals
- ☐ Eat a snack before any physical activity

DETERMINE Nutritional Assessment
For each statement, circle the response in the YES/NO column that applies to you.

I have an illness or condition that made me change the kind and/or amount of food I eat.	YES	NO
I eat fewer than 2 meals per day.	YES	NO
I eat few fruits or vegetables, or milk products (less than 3 fruits/vegetables, 2 dairy).	YES	NO
I have 3 or more drinks of beer, liquor, or wine almost every day.	YES	NO
I have tooth or mouth problems that make it hard for me to eat.	YES	NO
I don't always have enough money to buy the food I need.	YES	NO
I eat alone most of the time.	YES	NO
I take 3 or more different prescribed or over-the-counter drugs a day.	YES	NO
Without wanting to, I have lost or gained 10 pounds in the last 6 months.	YES	NO

Basic Activities of Daily Living

- **Bathing**: includes grooming activities such as shaving, and brushing teeth and hair
- **Dressing**: choosing appropriate garments and being able to dress and undress, having no trouble with buttons, zippers or other fasteners
- **Eating**: being able to feed oneself
- **Transferring**: being able to walk, or, if not ambulatory, being able to transfer oneself from bed to wheelchair and back
- **Continence**: being able to control one's bowels and bladder, or manage one's incontinence independently
- **Toileting**: being able to use the toilet

Instrumental Activities of Daily Living

- **Using the telephone**: being able to dial numbers, look up numbers, etc
- **Managing medications**: taking the appropriate medications and correct dosages on time
- **Preparing meals**: making appropriate food choices and preparing meals safely
- **Maintaining the home**: doing or arranging for housekeeping and laundry
- **Managing finances**: budgeting, paying mortgage/rent and bills on time, etc
- **Shopping**: being able to shop for groceries and other small necessities, and transport purchases from store to home
- **Using transportation**: being able to drive or use public transportation for appointments, shopping, etc

Depression Screening

Over the past 2 weeks, how often have you been bothered by any of the following problems?

a. Little or no interest or pleasure in doing things

0: not at all

1: several days

2: more than half the days

3: nearly every day

a. Feeling down, depressed, or hopeless

0: not at all

1: several days

2: more than half the days

3: nearly every day

Total score (Add a. and b.): _____

(If patient scores >0, administer full Geriatric Depression Scale)

CHAPTER 5
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CHAPTER 5.

Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes

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From the Adult Diabetes and Clinical Research Sections, Joslin Diabetes Center, Harvard Medical School. ***Approved May 10, 2016; updated April 24, 2018.***

Objective: The objective of the Joslin Diabetes Center Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes is to support clinical practice, influence clinical behavior to improve outcomes, and to assure quality of care according to accepted standards. The guideline was established after careful review of current evidence, literature, and clinical practice. This guideline is reviewed periodically and modified to reflect changes in clinical practice and available pharmacological information.

This guideline is not intended to serve as a mandatory standard, but rather to provide a set of recommendations for patient care management. These recommendations are not a substitute for sound and reasonable clinical judgment or decision making and do not exclude other options. Clinical care must be individualized to the specific needs of each patient and interventions must be tailored accordingly. The guideline has been created to address initial presentations and treatment strategies in the adult nonpregnant patient population. The guideline is not a substitution for full prescribing information. Refer to Joslin's Clinical Guideline for Adults with Diabetes (Chapter 1) as well as Joslin's Guideline for the Care of Older Adults With Diabetes (Chapter 4) for additional, more comprehensive information on diabetes care and management.

5.1.0 DIABETES MELLITUS: DIAGNOSTIC CRITERIA (NONPREGNANT ADULTS)

- Random plasma glucose (PG) ≥200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) **or**
- Glycated hemoglobin (A1C) ≥6.5%[a] **or**
- Fasting plasma glucoseb ≥126 mg/dl **or**
- Results of a 2-hour 75-g oral glucose tolerance test ≥200 mg/dL at 2 hours

[a]Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes. Consider evaluation for hemoglobin variant if A1C is discordant from PG values.
[b]These tests should be confirmed by a repeat test, on a different day, unless unequivocally high.

5.2.0 GOALS OF GLYCEMIC CONTROL FOR INDIVIDUALS WITH DIABETES (TABLE 1)

TABLE 1.

Biochemical Index	Normal	Goal[1]
FPG or preprandial glucose (mg/dL)	<100	80-130
2 hours postprandial glucose (mg/dL)	<140	<180 [**2C**]
Bedtime glucose (mg/dL)	<120	90-150
A1C (%) sustained	<6%	<7% [**1A**] A1C target goal should be individualized for each patient. A goal of <7% is chosen as a practical level for most patients to reduce the risk of complications. Achieving normal blood glucose and A1C is recommended, if it can be done practically and safely. Less stringent goals may be considered for older adults or those with advanced comorbidities (see Joslin's Guideline for Older Adults With Diabetes, Chapter 4).

See notes to table on SP259
A1C indicates glycated hemoglobin; FPG, fasting plasma glucose. mg/dL

5.3.0 INITIAL TREATMENT STRATEGY (FIGURE)

5.3.1 Advancing antidiabetes medications:

TABLE 2. Considerations for Selecting Noninsulin Glucose-Lowering Medications

Start With Metformin Unless Contraindicated [1B]

Action: Decreases hepatic glucose production, increases GLP-1 secretion. Use as initial therapy unless contraindicated.
Adverse effects: Gas, diarrhea, lactic acidosis; B-12 deficiency (long-term). Initiate at low dose, increase dose slowly and take with food to decrease gas, diarrhea. Extended release formulation may decrease gastrointestinal symptoms.
Dosing:

- Metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Starting metformin in patients with an eGFR <45 mL/min is not recommended.
- Obtain eGFR at least annually in all patients taking metformin. In patients at increased risk for renal impairment, such as the elderly, assess renal function more frequently.
- If eGFR later falls below 45 mL/min, assess benefits and risks of continuing treatment. Discontinue metformin if eGFR later falls below 30 mL/min.
- Discontinue metformin at time of or before an iodinated contrast imaging procedure if eGFR is 30-60 mL/min; in patients with a history of liver disease, alcoholism, or heart failure; or who will undergo intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is back to baseline level.

table continued SP256

5.4.0 CONSIDERATIONS FOR SELECTING NONINSULIN GLUCOSE-LOWERING MEDICATIONS

5.4.1 First-line add-on to metformin or use as monotherapy if metformin is contraindicated: *see table SP256*

5.5.0 PREFERRED CONSIDERATIONS IN PATIENTS WITH T2D AND ESTABLISHED CARDIOVASCULAR DISEASE

TABLE 3. Preferred Considerations in Patients With T2D and Established Cardiovascular Disease

Clinical Setting	History of ASCVD	History of HF
Consider drugs with CV safety and superiority	GLP-1 RA with evidence to reduce CVD events (eg, liraglutide **[1B],** semaglutide)	SGLT2 inhibitors with evidence to reduce HF and mortality, (eg, empagliflozin **[1B],** canagliflozin)
Other considerations and caveats	Avoid use with advancing CKD Recent data indicate a small increase in biliary disease and need for cholecystectomy Increased risk of retinopathy progression with semaglutide	Avoid use perioperatively and/or in the presence of risk factors for DKA (eg, LADA, dehydration, infection, major trauma) Avoid use with advancing CKD Distal lower limb amputations increased with canagliflozin

ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; LADA, latent autoimmune diabetes of adults; T2D, type 2 diabetes.
Notes:
In several recent trials in patients with CVD, DPP-4 inhibitors were found to be safe (noninferior to) but also nonsuperior to other antihyperglycemic drugs from CV point of view; a secondary outcome, heart failure, was significantly increased with saxagliptin. In clinical trials, liraglutide and empagliflozin reduced CV mortality. [**1B**]

See **Table 2** for additional details on various classes of noninsulin drugs.

5.6.0 ORAL GLUCOSE-LOWERING MEDICATIONS (TABLE 4)

5.6.1 Examples of fixed-dose medications (TABLE 4):

5.7.0 INJECTABLE ANTIDIABETES MEDICATIONS (INCRETIN MIMETICS AND NONINSULIN ANALOGUES) (TABLE 5)

5.8.0 INSULIN PRODUCTS (TABLE 6)

5.8.1 Premixed insulin combinations:

TABLE 7. Premixed Insulin Combinations

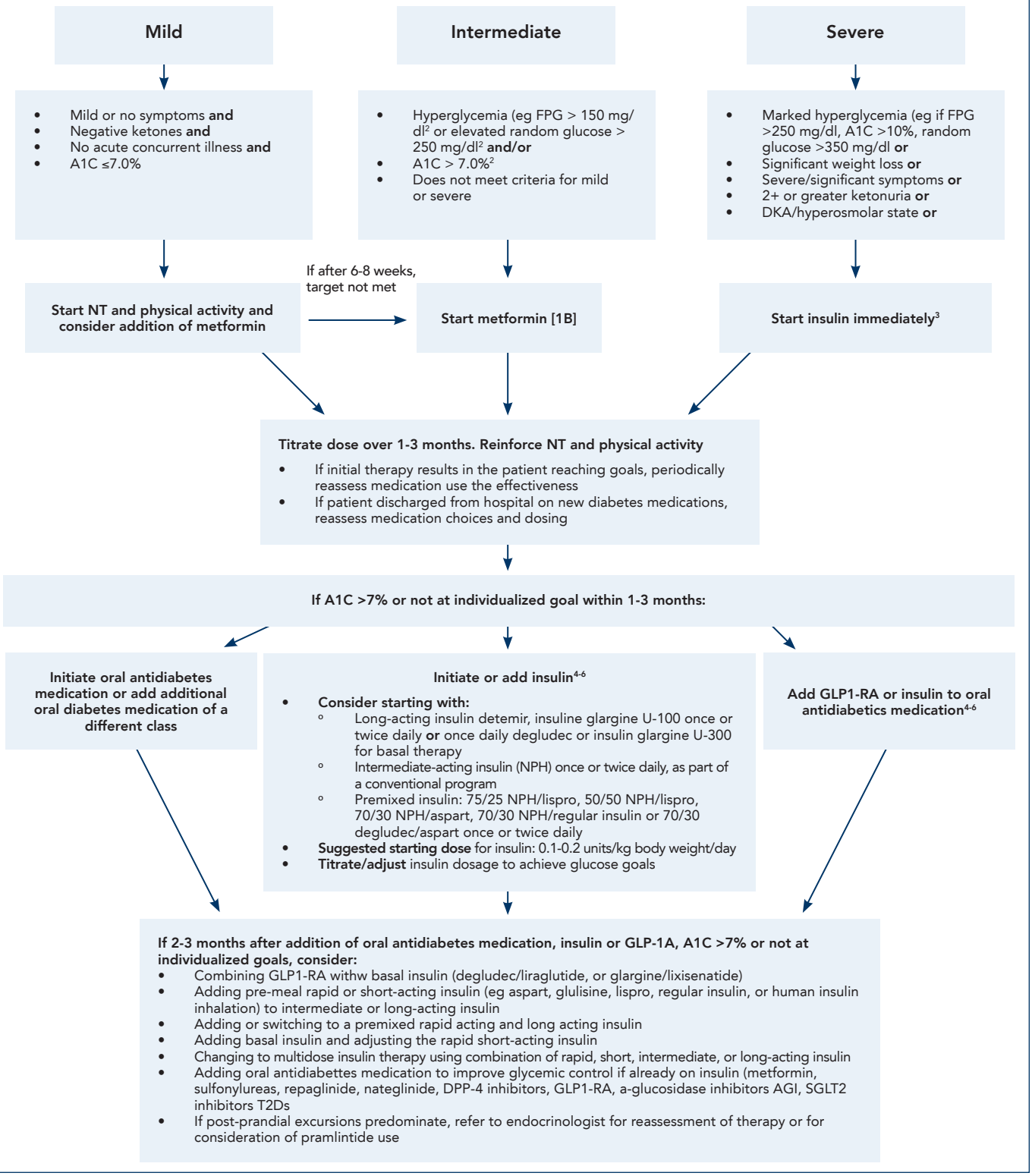
Insulin Type	Product
70% NPH, 30% regular	Humulin 70/30
70% NPH, 30% regular	Novolin 70/30
50% lispro protamine suspension, 50% lispro	Humalog Mix 50/50
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25
70% aspart protamine suspension, 30% aspart	Novolog Mix 70/30
70% degludec, 30% insulin aspart	Ryzodeg 70/30 (approved by FDA, but not yet available)

NPH indicates neutral protamine Hagedorn.

FIGURE 1. Advancing Antidiabetes Medication Therapy

Nutrition therapy (NT), physical activity, blood glucose monitoring and patient education are the cornerstones of diabetes management for all patients. Pharmacological management should be used in combination with nutrition therapy and physical activity. Current weight status and lifestyle should be considered when choosing initial pharmacological therapy.

Initial Presentation (Based on characteristics listed within each box) —



A1C indicates glycated hemoglobin; AGI, α-glucosidase inhibitor; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; SGLT2, sodium glucose co-transporter-2; TZDs, thiazolidinediones. See notes to table on SP259.

TABLE 2 (cont.). Considerations for Selecting Noninsulin Glucose-Lowering Medications

First-Line Add-On To Metformin Or Use As Monotherapy If Metformin Is Contraindicated

Insulin Secretagogues (sulfonylurea, repaglinide, nateglinide)

Action: Stimulates beta cell insulin secretion.

Adverse effects: Potential for hypoglycemia.

Contraindications: Sulfonylurea use is contraindicated in severe liver or renal disease.

Notes: Metabolites of glipizide are less active than other sulfonylureas. Consider the use of short-acting sulfonylureas, such as glipizide or glimepiride, in setting of renal disease.

Glyburide is not preferred due to the increased risk of hypoglycemia.

Repaglinide or nateglinide may be useful for those with postprandial hyperglycemia or with hypoglycemia on a sulfonylurea.

DPP-4 Inhibitors

Action: In a glucose-dependent manner, slows inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels.

Adverse effects: UTI-like symptoms.

Notes: Reduce dose in renal disease with all members of the class except linagliptin.

- Postmarketing reports of hepatic failure with alogliptin.

- Clinical trials reported no adverse CV outcomes, except increased secondary outcome of heart failure with saxagliptin.

-It is unknown if DPP-4 inhibitors increase the risk for pancreatitis.[10]

GLP-1 RAs

Action: In a glucose-dependent manner, increases insulin secretion, decreases glucagon secretion, slows gastric emptying, and increases satiety.

Adverse effects: Nausea, diarrhea, renal impairment if low eGFR.

Contraindications: Gastroparesis requiring treatment with metoclopramide.

Personal or family history of medullary thyroid cancer or patients with MEN2.

Notes: Use may be associated with weight loss. To avoid hypoglycemia when using a GLP-1 RA with a sulfonylurea or insulin, consider initially decreasing sulfonylurea or insulin dose.

- Increased risk of biliary disease and gallstones.

- Liraglutide reduced major CV events in 2 large clinical trials in patients with CVD or high risk of CVD.

- It is unknown if GLP-1 RAs increase the risk for pancreatitis.[10]

SGLT2 Inhibitors[11]

Action: Blocks reabsorption of glucose by the kidney, thereby increasing excretion of glucose in the urine.

Adverse effects: Hypotension, genital mycotic infections, UTI, dehydration, hyperkalemia, increased LDL cholesterol, ketoacidosis in the absence of severe hyperglycemia.[11]

Contraindications: Do not use in moderate to severe renal disease as it may worsen renal function.[12]

Notes: Use may be associated with modest decreases in BP and in weight.

Adjust dose in mild renal disease.

Mechanism of action results in positive test for urine glucose.

- Dapagliflozin is contraindicated in setting of bladder cancer; use with caution if there is a history of bladder cancer.

- A small increase in fracture rate has been reported with canagliflozin and dapagliflozin.

- Cases of acute kidney injury have been reported with canagliflozin and dapagliflozin. Promptly discontinue these drugs if this occurs and treat the renal impairment.

- Empagliflozin and canagliflozin reduced major CV events and heart failure in clinical trials, in those with preexisting CVD as well as risk of renal disease progression (**see Table 3**).

AGIs

Action: Delays absorption and breakdown of carbohydrates.

Adverse effects: Gas, diarrhea.

Contraindications: Chronic intestinal disorders, acarbose in cirrhosis, acarbose and miglitol in renal impairment (creatinine >2.0).

Notes: Use if postprandial hyperglycemia predominates.

Ideally use pure glucose to treat hypoglycemia when used in combination therapy as the drug decreases absorption of other forms of carbohydrate.

Initiate at low dose and increase slowly to decrease flatulence.

TZDs[7-9]

Action: Improves glucose transport and decreases hepatic glucose production.

Adverse effects: Weight gain, fluid retention.

Contraindications: Liver disease, severe LV dysfunction at risk for CHF.

Do not use pioglitazone in setting of bladder cancer (**see footnotes**)

Notes: Full effect of initiation or titration of therapy may take 2-4 weeks.

May increase risk for macular edema.

Increases bone loss and risk for bone fracture.

Can be used in renal impairment but may increase fluid retention.

A recent trial with pioglitazone showed reduced CVD events in nondiabetic patients with insulin resistance.

Other Therapy

Bile Acid Sequestrant (colesevelam)

- Mechanism of action re: glucose lowering is unclear
- Modest effect on A1C. Also lowers LDL-C.

Note: Reduces gastric absorption of some drugs. If known interaction or unknown interaction with narrow therapeutic index drug, administer 1 hour prior or 4 hours after colesevelam.

Contraindications:

- Bowel obstruction
- Serum triglycerides >500mg/dl
- History of hypertriglyceridemia-induced pancreatitis

Centrally Acting Agent (bromocriptine mesylate)

- Mechanism of action re: glucose lowering is unclear
- Most effective when used in combination with other antidiabetes medications
- Modest effect on A1C

Contraindications:

- Should not be taken by patients who are nursing mothers, take ergot medicines, or have syncopal migraines

Source: American Diabetes Association

A1C indicates glycated hemoglobin; AGI, α-glucosidase inhibitor; BP, blood pressure; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; MEN2, multiple endocrine neoplasia type 2; SGLT2, sodium glucose co-transporter 2; UTI, urinary tract infection, TZD, thiazolidinedione.

See notes to tables on SP259.

TABLE 4. Oral Glucose-Lowering Medications

Biguanides	Insulin Secretagogues	DPP-4 Inhibitors	SGLT2 Inhibitors	AGIs	TZDs[9]
• liquid metformin* (Riomet) • metformin (Glucophage) • metformin extended release (Glucophage XR, Fortamet, Glumetza) Glucophage, Glucophage XR, and Fortamet are available as generic medications *Liquid metformin formulation can be used for patients unable to swallow large tablets and/or who are post gastric bypass.	**Sulfonylureas** • glimepiride (Amaryl) • glipizide (Glucotrol) • glipizide extended • release (Glucotrol XL) • glyburide (Micronase, Diabeta) • micronized glyburide • (Glynase) *Glimepiride, glipizide, and glyburide are available as generic medications. **Meglitinides** • repaglinide (Prandin) **D-phenylalanine Derivatives** • nateglinide (Starlix) *Repaglinide and nataglinide are available as generic medications.	• sitagliptin (Januvia) • saxagliptin (Onglyza) • linagliptin (Tradjenta) • alogliptin (Nesina) • vildagliptin (Galvus; not available in the United States)	• canagliflozin (Invokana) • dapagliflozin (Farxiga) • empagliflozin (Jardiance) • ertugliflozin (Steglatro)	• acarbose (Precose) • miglitol (Glyset) *Acarbose is available as a generic medication.	• pioglitazone (Actos) • rosiglitazone (Avandia) *Pioglitazone and rosiglitazone are available as generic medications.

Examples of fixed-dose combination medications in the United States

- metformin and glipizide (Metaglip)
- metformin and glyburide (Glucovance)
- sitagliptin and metformin (Janumet)
- sitagliptin and metformin ER (Janumet XR)
- saxagliptin and metformin ER (Kombiglyze XR)
- alogliptin and metformin (Kazano)
- linagliptin and metformin (Jentadueto)
- linagliptin and metformin ER (Jentadueto XR)
- alogliptin and pioglitazone (Oseni)
- dapagliflozin and metformin (Xigduo)
- empagliflozin and metformin (Synjardy)
- empagliflozin and linagliptin (Glyxambi))
- dapagliflozin and saxagliptin (Qtern)
- canagliflozin and metformin (Invokamet)
- ertugliflozin and metformin (Stegluromet)
- ertugliflozin and sitagliptin (Steglujan)

Others

Bile Acid Sequestrants
- colesevelam (Welchol) ; cholestyramine (Questran)

Centrally Acting
- bromocriptine (Cycloset)

AGI indicates a-glucosidase Inhibitor; DPP-4, dipeptidyl peptidase-4; ER, extended release; SGLT2, sodium-glucose co-transporter 2; TZDs, thiazolidinediones.
See notes to tables on SP259.

TABLE 5. Injectable Noninsulin Antidiabetes Medications Available in the United States

Incretin Mimetics And Synthetic Analogues			
Product	**Mechanism of Action**	**Diabetes Type**	**Injection Frequency**
exenatide (Byetta)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	2/day
lixisenatide (Adlyxin)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with short-acting insulins	2	1/day
liraglutide (Victoza)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/day
extended release exenatide (Bydureon)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Not approved for use with insulin	2	1/week
dulaglutide (Trulicity)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/week
semaglutide (Ozempic)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/week
pramlintide (Symlin)	Synthetic analogue of human amylin, a naturally occurring hormone made in the beta cells, which slows gastric emptying, suppresses glucagon secretion, and regulates food intake. A significant reduction in insulin dose may be required when insulin is used in conjunction with pramlintide	1 and 2	1-4/day (with meals)

TABLE 6. Insulin Pharmacodynamics

Insulin Type/Generic	Brand Name	Onset	Peak	Duration
Ultra–Rapid-Acting				
Faster insulin aspart	Fiasp	10-20 minutes	30 minutes-2 hours	3-5 hours
Insulin human inhalation	Afrezza	12-30 minutes	30-90 minutes	3 hours
Rapid Acting				
Insulin aspart	Novolog	15-30 minutes	30 minutes-3 hours	3-5 hours
Insulin glulisine	Apidra			
Insulin lispro U-100 Insulin lispro U-200	Humalog/Admelog Humalog			
Short-Acting				
Insulin human regular	Humulin/Novolin R	30-60 minutes	2-5 hours	up to 12 hours
Insulin human regular concentrated	Humulin R U-500	30-60 minutes	2-5 hours	6.5-10 hours
Intermediate-Acting				
Human NPH (neutral protamine Hagedorn) insulin	Humulin/Novolin N	90 minutes-4 hours	4-12 hours	up to 24 hours
Long-Acting				
Insulin detemir	Levemir	45 minutes-4 hours	Minimal peak (depending on dose)	up to 22 hours
Insulin glargine	Lantus/Basaglar			
Insulin glargine U-300	Toujeo	6 hours		>24 hours
Insulin degludec U-100 or U-200	Tresiba	1 hour		>42 hours

Notes for Figure and Tables

1. Goals should be individualized based on factors that include the following: comorbidities, age, duration of diabetes, hypoglycemic awareness.
2. If diet history reveals markedly excessive carbohydrate intake, consider initial trial of nutrition therapy and physical activity before initiating oral antidiabetes medications, even if glucose levels are above the thresholds listed.
3. Some patients with T2D initially stabilized on insulin may be considered for transition to noninsulin antidiabetes medications as blood glucose control permits.
4. May need to taper and discontinue some or all oral antidiabetes medications as insulin is initiated and adjusted, particularly if using short- or rapid-acting and basal insulins.
5. Pre- *and* postprandial blood glucose should be checked. Frequency of checking may vary; it can be 1 to 4 times/day depending on individual patient and status of glycemic control.
6. There is an increased risk for edema when insulin and a thiazolidinedione are used together. Rosiglitazone should not be used in combination with insulin.
7. FDA requirements for LFT monitoring for thiazolidinediones (TZDs): If initial alanine aminotransferase (ALT) is >2.5 times normal, do not start this medication. If ALT is >2.5 times normal during treatment, check weekly. If rise persists or becomes >3 times normal, discontinue TZD.
8. Thiazolidinediones cause or exacerbate congestive heart failure in some patients. After initiation of TZDs and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive or rapid weight gain; dyspnea; and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of the TZD must be considered. TZDs are not recommended in patients with symptomatic heart failure or in patients with established NYHA Class III or IV heart failure.

9a. On September 23, 2010, the FDA announced regulatory actions with respect to products containing rosiglitazone: Avandia (rosiglitazone maleate) tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets, and Avandaryl (rosiglitazone maleate and glimepiride) tablets. These FDA actions required GlaxoSmithKline to implement restrictions on the use of these products through a Risk Evaluation and Mitigation Strategy (REMS) program to assure their safe use and through additional safety labeling changes in response to the agency's review of data that suggested an elevated risk of cardiovascular events. However, based on additional data review, the REMS program was removed as of December 16, 2015. Rosiglitazone now has the same indications for prescribing as pioglitazone.

9b. According to the FDA advisory issued on June 15, 2011, regarding potential increased risk of bladder cancer with pioglitazone use: (1) Do not use pioglitazone in patients with active bladder cancer. (2) Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

10. Risks of acute pancreatitis or pancreatic cancer have not been confirmed in clinical trials. The FDA is currently monitoring clinical reports via the Adverse Event Reporting System
11. Diabetic ketoacidosis (DKA) with SGLT-2 inhibitors: Rare but sometimes serious cases have been reported. Check for DKA if symptoms develop, even if glucose levels are not elevated
12. The potential benefits of SGLT-2 inhibitors in preventing progression of early renal disease are being investigated.

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