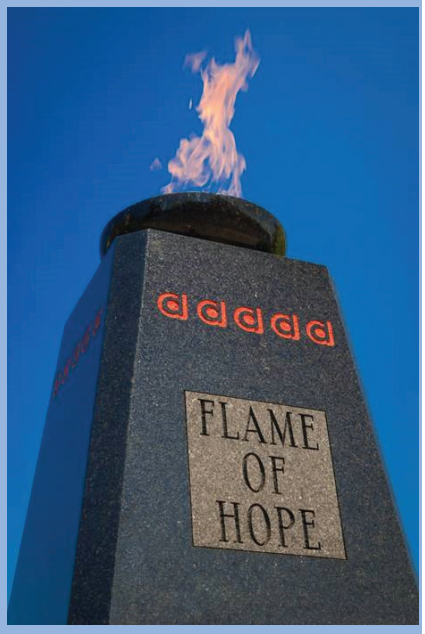
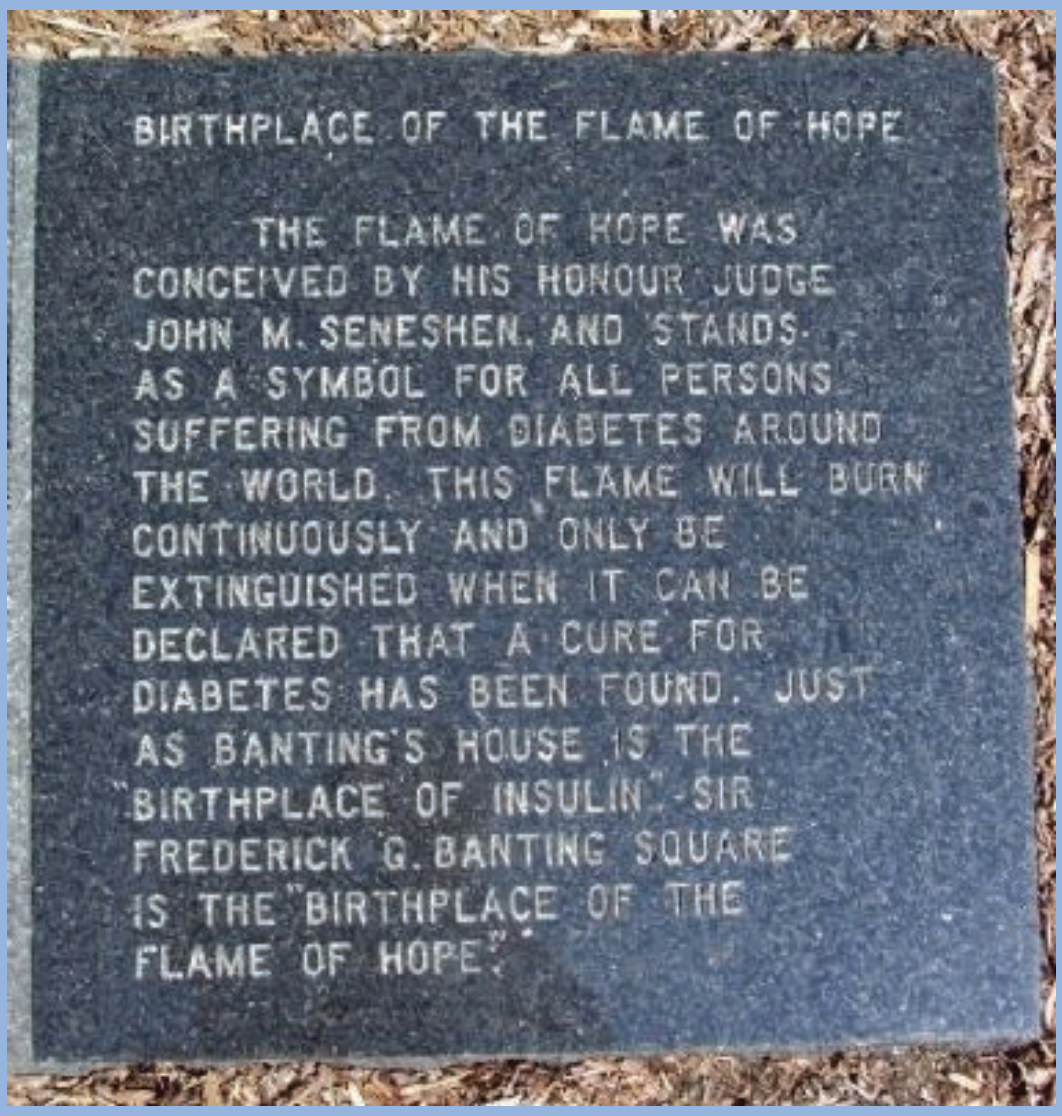
Diabetes in Daily Life

HANDBOOK



Prof. Dr. Khwaja Nazim Uddin



Theme: Flame of Hope

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Prof. Dr. Khwaja Nazim Uddin

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Diabetes in Daily Life
Professor Dr. Khwaja Nazim Uddin

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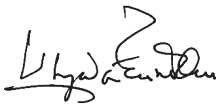
Dedicated to
Martyrs of
National Anti-discrimination
Revolution 2024

Preface

This book is an Inspiration from my practical life.Maximum time of my clinical life is with Diabetes mellitus, dealing diabetic patients in in-patient and outpatient departments and private chamber. Every patient is a chapter to me. This is a huge experience. It is a sincere effort to express this collective knowledge in the format of a book. Tried to explore and share knowledge from text books, journal, seminar and symposium. Most of the data used here are from American diabetic associations (ADA) and EASD (European association for study of diabetes).

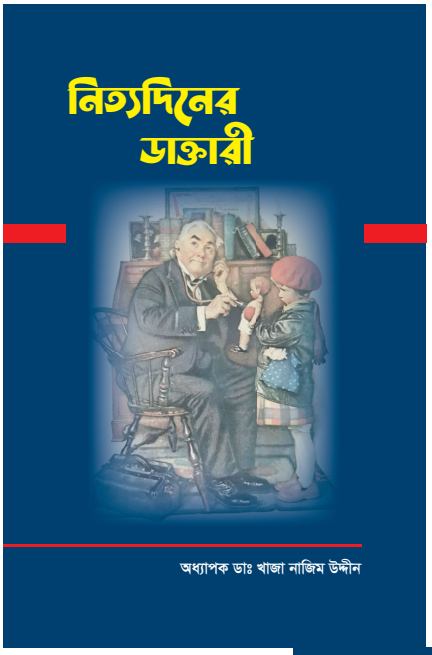
I solemnly acknowledge with sincere thanks to all my patients who are with me for long time through out my clinical career. I am really indebted to them. They enriched my knowledge and works with clinical clues of diabetes mellitus. I thank my daughters Dr. Sarah Nehrina Nazim MBBS MD and Dr. Rifah Najiba Nazim MBBS for their help in manuscript correction.

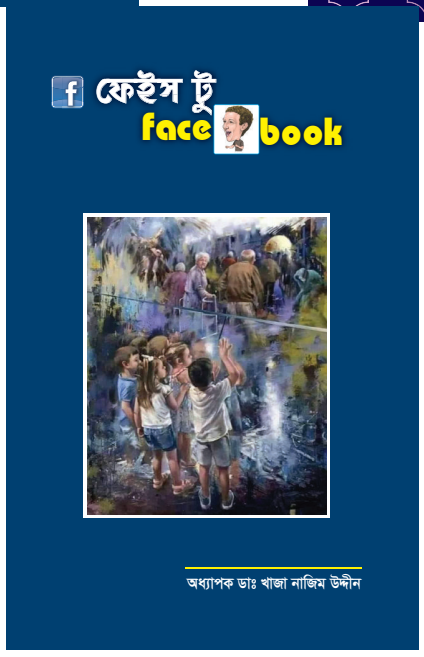
I thank my associate Riyadh who helped me in computer works. The publisher Asian Colour Printing deserves full appreciation and thank.



Prof. Dr. Khwaja Nazim Uddin

Previous books by the author





Diabetes epidemiology: Bangladesh 9th in the world


Pakistan: 30.8%


Kuwait: 24.9%


Egypt: 20.9%


Qatar: 19.5%


Malaysia: 19%


Saudi Arabia: 18.7%


Mexico: 16.9%


Turkey: 14.5%


Bangladesh: 14.2%


Sri Lanka: 11.3%


South Africa: 10.8%


Iraq: 10.7%


United States: 10.7%


Indonesia: 10.6%


China: 10.6%


Spain: 10.3%


Thailand: 9.7%

Source: Public Health 24

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DIABETES WITH COMORBIDITY

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Diabetes in Daily Life

PART - 1
GENERAL

Dr. Khwaja Nazim Uddin
MBBS FCPS FRCP FACP
Professor of Medicine
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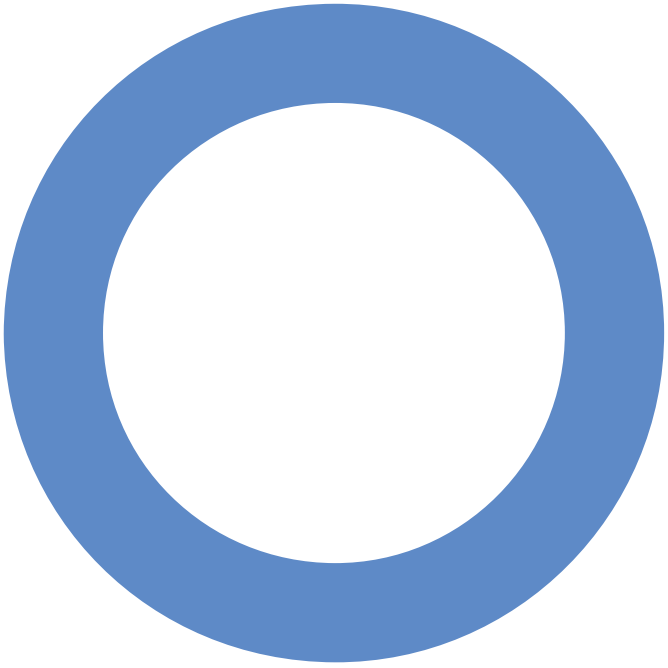


The Global Symbol of Diabetes
IDF

01
CHAPTER

Criteria for Diagnosis of Diabetes and Pre Diabetes

Diagnosis of Diabetes

FPG ≥126 mg/dL (≥7.0 mmol/L). ;1 mmol= 18 mg

Fasting is defined as no caloric intake for at least 8 h.

OR

2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT.

OGTT - The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water -250-300 ml; (children 1.75gm/Kg (max 75g)

OR

A1C ≥6.5% (≥48mmol/mol).

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

OR

RBG: In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (>11.1 mmol)

DCCT, Diabetes Control and Complications Trial; **FPG**, Fasting Plasma Glucose; **OGTT**, Oral Glucose Tolerance Test; **NGSP**, National Glycohemoglobin Standardization Program; **WHO**, World Health Organization; **2-h PG**, 2-h plasma glucose.

** In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

Criteria for diagnosis of Prediabetes

Definition:

- *Pre-Diabetes (IFG -Impaired Fasting Glucose): 6.1 - 6.9 mmol/L
  OR
- *Pre-Debates(IGT- Impaired glucose tolerance): (7.9-11 mmol/L
  OR

*Pre-Diabetes: A1C 5.7-6.4%)

- For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.
- ***Quiz:: if somebody has Fasting glucose-6.4 and/or Random blood glucose 8,9.5 ,11???
- What would be the next step:
- ***Answer: OGTT

Importance of Pre-diabetic:

- Usually symptomless ;higher than normal BG
- Risk of developing overt diabetes
- Risk of heart disease, stroke
- Screening essential to prevent diabetes and its associated complications

Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes. Moreover, the efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

People should consume a mixed diet with at least 150 g of carbohydrates on the 3 days prior to OGTT. Fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

A_1C and its limitations:

A_1C reflects glucose bound to hemoglobin over the life span of the erythrocyte (~120 days) and is thus a “weighted” average that is more heavily affected by recent blood glucose exposure. A_1C is an indirect measure of glucose exposure more so of the immediate previous month. Factors that affect hemoglobin concentrations or erythrocyte turnover can affect A_1C:., Thalassemia or folate deficiency,People with anemia, people treated with erythropoietin, or people undergoing hemodialysis or HIV treatment and in Pregnancy.

02 CHAPTER

Screening for Diabetes Mellitus

American Diabetes Association. Connected for Life. Focus on Diabetes

Proud Sponsor vsp vision care

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. **How old are you?**
   Less than 40 years (0 points)
   40–49 years (1 point)
   50–59 years (2 points)
   60 years or older (3 points)
2. **Are you a man or a woman?**
   Man (1 point) Woman (0 points)
3. **If you are a woman, have you ever been diagnosed with gestational diabetes?**
   Yes (1 point) No (0 points)
4. **Do you have a mother, father, sister or brother with diabetes?**
   Yes (1 point) No (0 points)
5. **Have you ever been diagnosed with high blood pressure?**
   Yes (1 point) No (0 points)
6. **Are you physically active?**
   Yes (0 points) No (1 point)
7. **What is your weight category?**
   See chart at right.

Height	Weight (lbs.)		
4′ 10″	119–142	143–190	191+
4′ 11″	124–147	148–197	198+
5′ 0″	128–152	153–203	204+
5′ 1″	132–157	158–210	211+
5′ 2″	136–163	164–217	218+
5′ 3″	141–168	169–224	225+
5′ 4″	145–173	174–231	232+
5′ 5″	150–179	180–239	240+
5′ 6″	155–185	186–246	247+
5′ 7″	159–190	191–254	255+
5′ 8″	164–196	197–261	262+
5′ 9″	169–202	203–269	270+
5′ 10″	174–208	209–277	278+
5′ 11″	179–214	215–285	286+
6′ 0″	184–220	221–293	294+
6′ 1″	189–226	227–301	302+
6′ 2″	194–232	233–310	311+
6′ 3″	200–239	240–318	319+
6′ 4″	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes.

Talk to your health care team. Your doctor can tell you if additional testing is needed, and through a comprehensive eye exam your optometrist can play a crucial role in the early detection, intervention, and prevention of eye disease and vision loss caused by diabetes.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders. Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

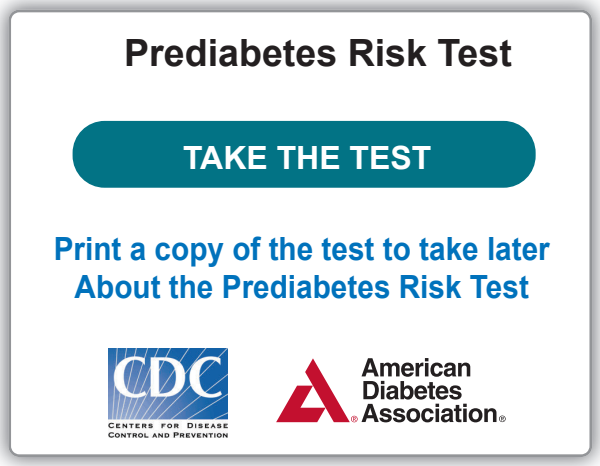
VSP has teamed up with the American Diabetes Association to bend the curve on this epidemic. For more information, go to diabetes.org/risktesteyehealth.

s Risk Test | American Diabetes Association®

Take the Risk Test online and learn more at diabetes.org/risktesteyehealth | 1-800-DIABETES (800-342-2383)

Figure 2.1: Diabetes risk test

Screening Hyperglycemia



Go to googles. Browse Prediabetes Risk test. Click Take the test. Responds to queries. You could know your risks and decide accordingly.

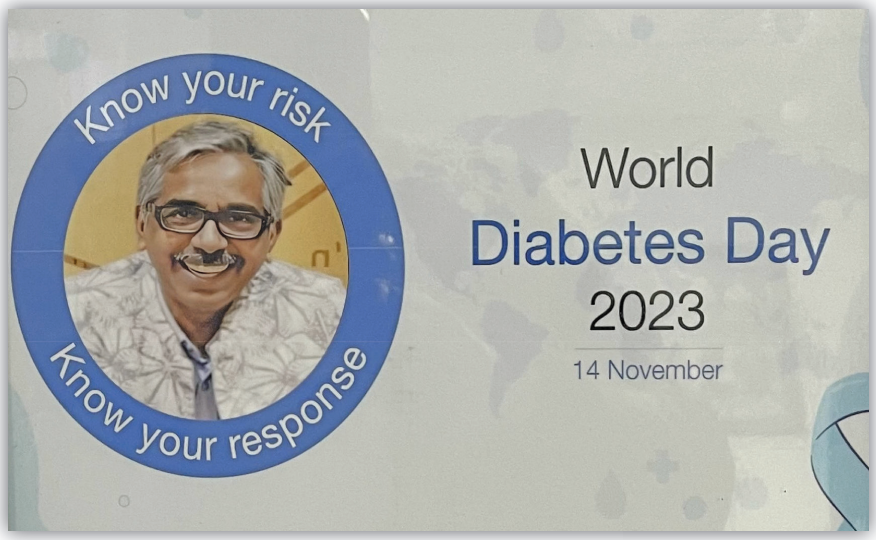


Figure 2.2: World Diabetes Day (WDD); 2023 theme

WORLD DIABETES DAY: World Diabetes Day (WDD) was created in 1991 by IDF and the World Health Organization in response to growing concerns about the escalating health threat posed by diabetes. World Diabetes Day became an official United Nations Day in 2006 with the passage of United Nation Resolution 61/225. It is marked every year on 14 November, the birthday of Sir Frederick Banting, who co-discovered insulin along with Charles Best in 1922.

WDD is the world's largest diabetes awareness campaign reaching a global audience of over 1 billion people in more than 160 countries. The campaign draws attention to issues

of paramount importance to the diabetes world and keeps diabetes firmly in the public and political spotlight.

The World Diabetes Day campaign aims to be the:

Platform to promote IDF advocacy efforts throughout the year.

Global driver to promote the importance of taking coordinated and concerted actions to confront diabetes as a critical global health issue

The campaign is represented by a blue circle logo that was adopted in 2007 after the passage of the UN Resolution on diabetes. The blue circle is the global symbol for diabetes awareness. It signifies the unity of the global diabetes community in response to the diabetes epidemic.

Every year, the World Diabetes Day campaign focuses on a dedicated theme that runs for one or more years. The theme for World Diabetes Day 2021-23 is Access to Diabetes Care – If Not Now, When?..

Theme in 2022-23 was access to diabetes care. The theme for World Diabetes Day 2024-26 is Diabetes and Well-being. In 2024-25 it is Breaking BARRIER BRIDGING GAP.

Screening Prediabetes and Type 2 Diabetes

1. Screening for prediabetes and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults.
   a. Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors eg HTN ,Obesity.,
   b. For all other people, screening should begin at age 35 years.

      **If tests are normal, repeat screening at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain).

      **To screen for prediabetes and type 2 diabetes, FPG, 2-h PG during 75-g OGTT, and A1C are each appropriate. When using OGTT as a screen for prediabetes or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing.

   c. Children and Adolescent: Risk-based screening for prediabetes or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes.
   d. If on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications (screen for prediabetes and diabetes at baseline and repeat 12–16 weeks after medication initiation or sooner, if clinically indicated, and annually)
   e. People with HIV should be screened for diabetes and prediabetes with an FPG test before starting antiretroviral therapy, at the time of switching antiretroviral therapy,

and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, FPG should be checked annually.

f. Dental setting: Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored

g. Health care settings Ideally, screening should be carried out within a health care setting because of the need for follow-up and treatment.

h. for posttransplant DM (PTDM): After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of post transplantation diabetes mellitus (PTDM) is best made once the individual is stable on an immunosuppressive plan and in the absence of an acute infection

2. **NOT in community settings:** Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care

Screening for diabetes and prediabetes in asymptomatic adults (criteria's)

a. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of cardiovascular disease
- Hypertension (≥130/80 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or a triglyceride level >250 mg/dL (>2.8 mmol/L)
- Individuals with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

b. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.

c. People who were diagnosed with GDM should have lifelong testing at least every 3 years.

d. For all other people, testing should begin at age 35 years.

e. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Table 2.1	Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting:

Screening should be considered in youth who have overweight (≥85th percentile) or obesity (≥95th percentile) and who have one or more additional risk factors based on the strength of their association with diabetes:
• Maternal history of diabetes or GDM during the child's gestation
• Family history of type 2 diabetes in first- or second-degree relative
• Race and ethnicity (e.g., Native American, African American, Latino, Asian American, Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)

GDM, gestational diabetes mellitus.

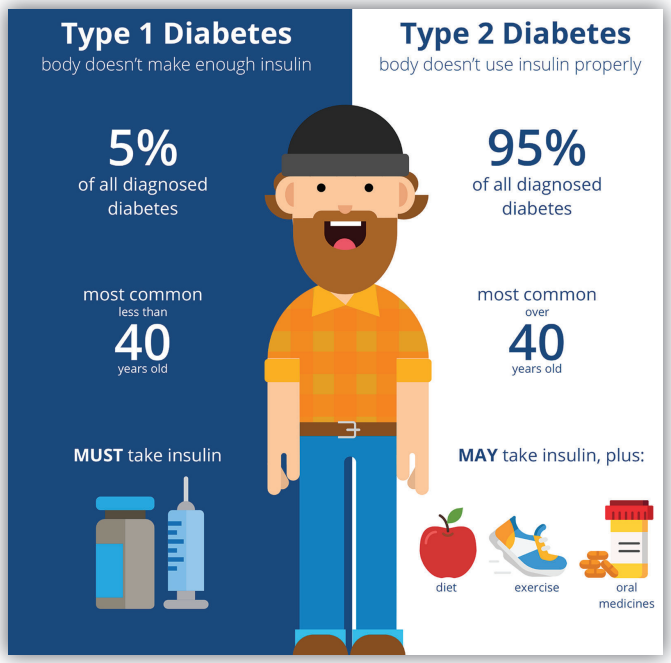
*After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

03
CHAPTER

Classification & Epidemiology

Diabetes is classified conventionally into several clinical categories,

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young-MODY), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of people with HIV, or after organ transplantation)



Source: Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2017. Atlanta, GA: U.S. Department of Health and Human Services; 2017 Accessed from: https://www.cdc.gov/diabetes/library/socialmedia/infographics.html

Figure 3.1:

4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes.

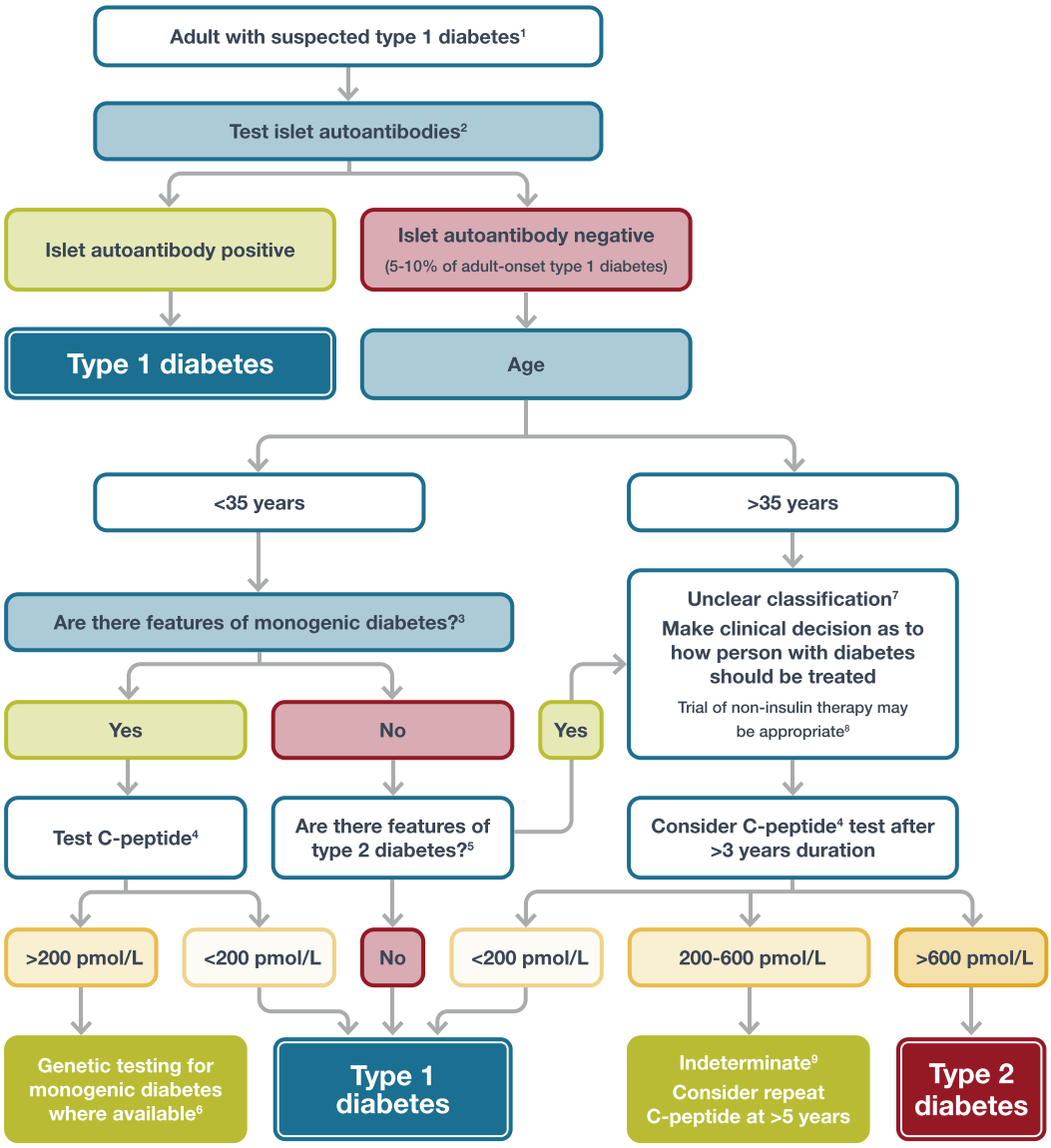


Figure 3.2: Flow chart for investigation of Type 1 diabetes mellitus

Disease burden

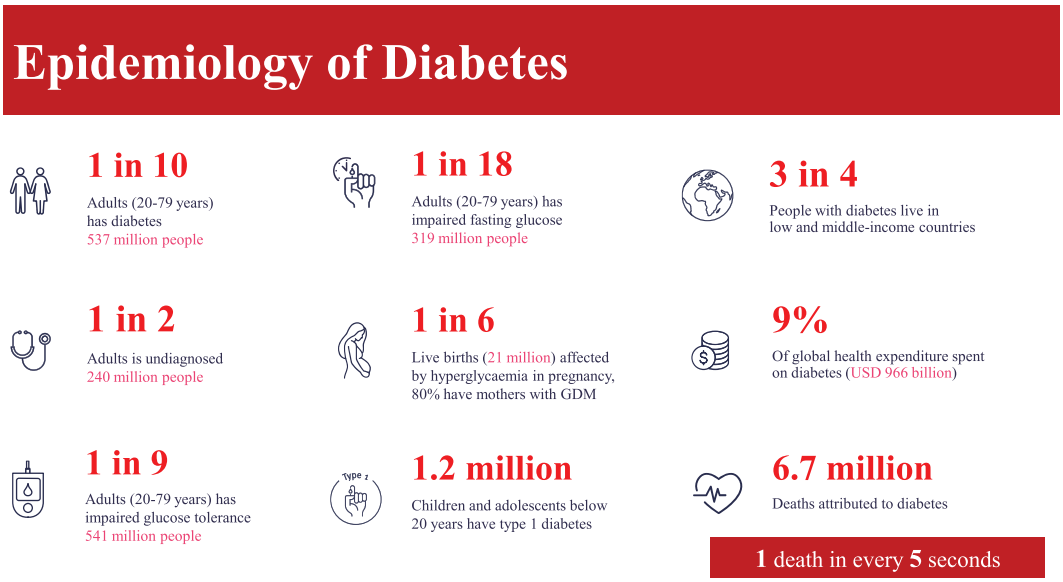


Figure 3.3: 1 in 10 adults (20-79 years of age)-537 million people have Diabetes mellitus

1 in 2 adults (20-79 years of age)-240 million people are undiagnosed

3 in 4 peoples live in low and middle income countries.

1 in6 live births (21 million)affected by hyperglycaemia in pregnancy.80% have mother with GDM.

1.2 million children and adolescents below 20 years have type 1 diabetes

6.7 million deaths attributed to diabetes

One death in every 5 seconds

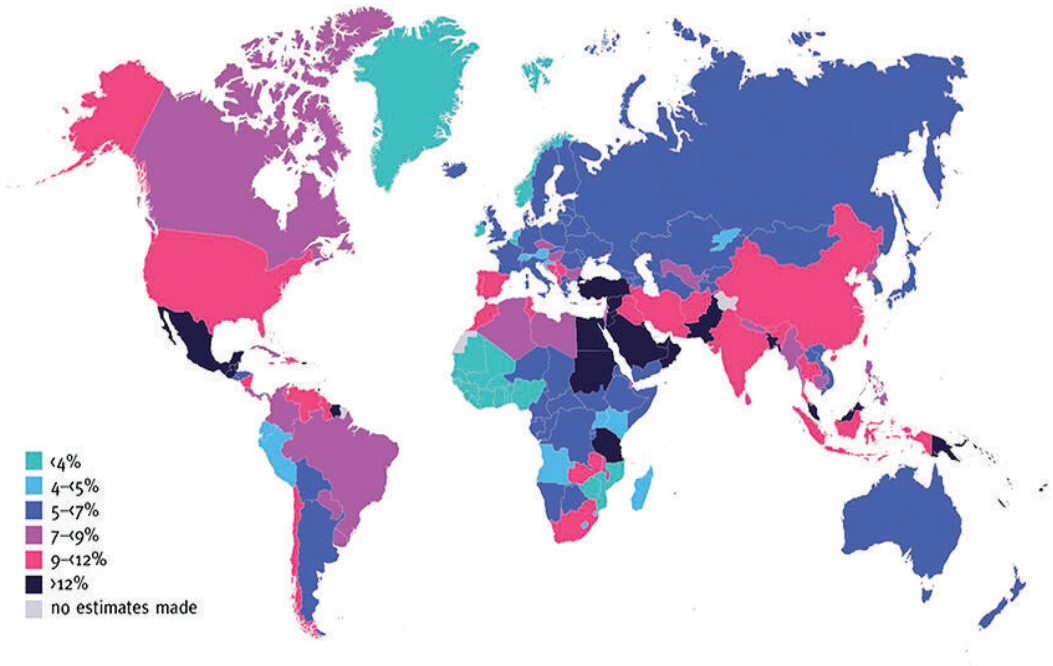


Figure 3.4: Global prevalence of diabetes mellitus

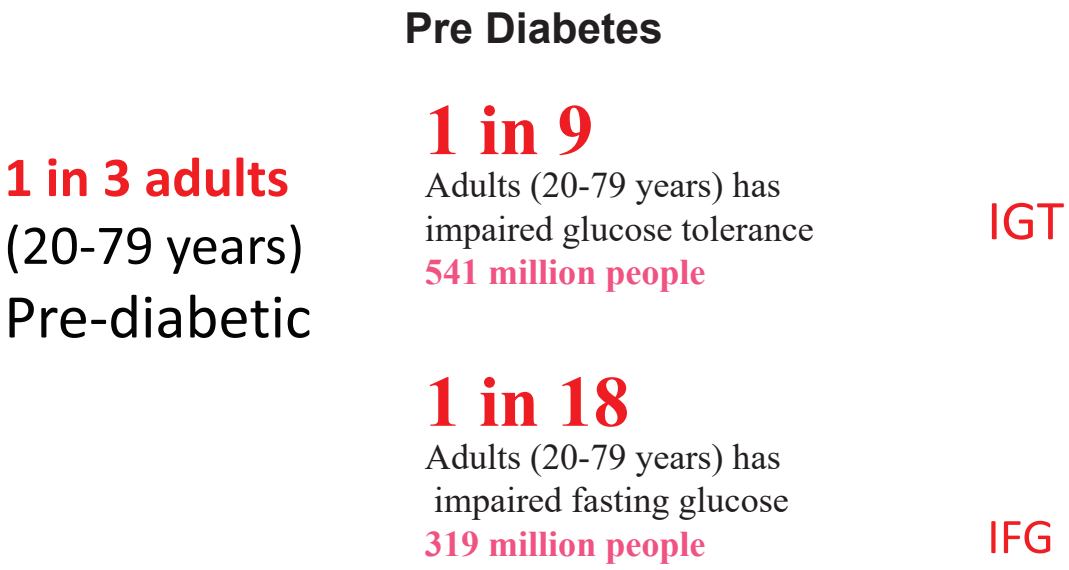


Figure 3.5: Epidemiology of Pre-diabetes:1 in 3 adults(20-79 years) Prediabetes.1 in 9 (adults 20-79 years has impaired glucose tolerance (IGT)-541 million peoples.1 in 18 adults(20-79 years) has impaired fasting glucose(IFG)-319 people.

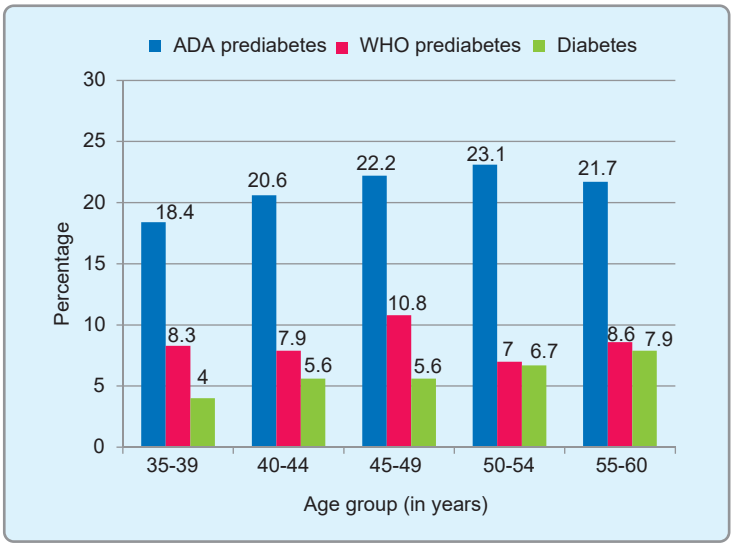


Figure 3.6: Prevalence of Prediabetes and diabetes (Comparison)

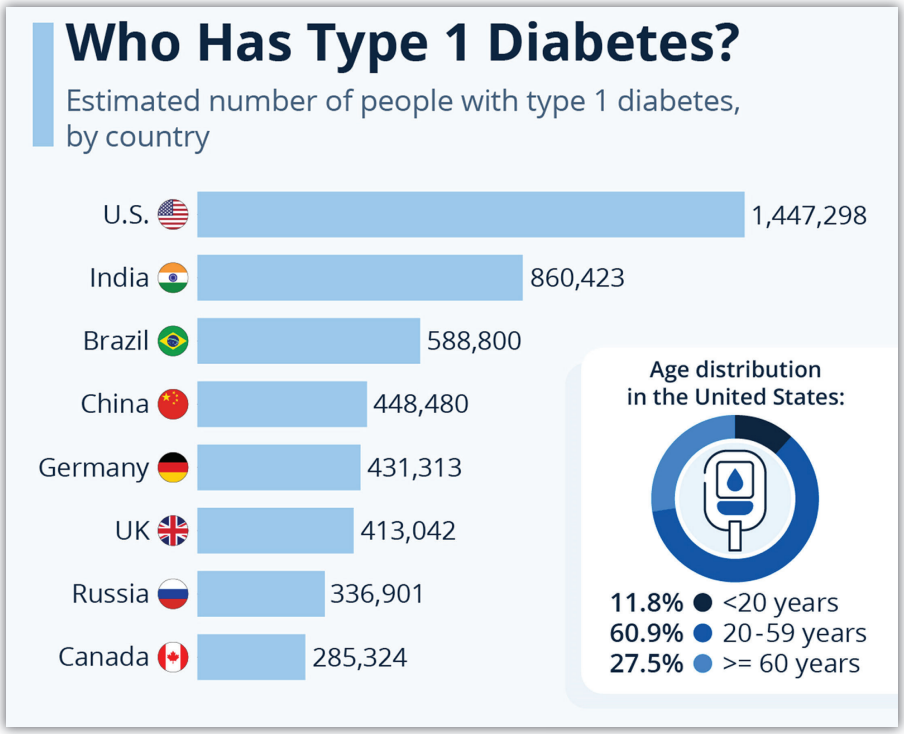


Figure 3.7: Prevalence of Typ1 diabetes

https://cdn.statcdn.com/Infographic/images/normal/31253.jpeg

Suggested citation: American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S20–S42

04
CHAPTER

Management of Diabetes Mellitus

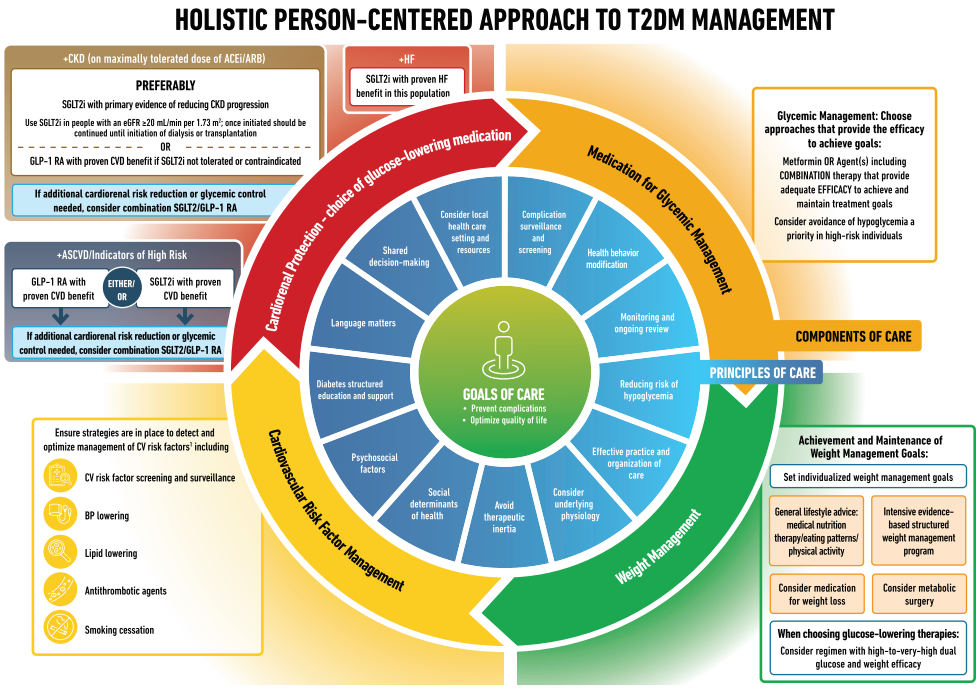


Figure 4.1: Person centred approach to T2DM management

Goal of care is to treat to target of hyperglycemia to prevent complication and optimize quality of life. It should be comprehensive comprising *A*. Complete medical evaluation. *B*. Assessment of a. overall health status,b. diabetes complications,c. cardiovascular risk,d. hypoglycemia risk, and *C*. Shared decision-making: patient-physician-others as and when needed to set therapeutic goals. *D*. Decide a follow-up visit *E*. DSME/S: Diabetes self-management education and support.

DSME/S: On going process of facilitating the knowledge, skill, and ability necessary for diabetes self-care. DSMES focuses on empowering individuals with diabetes by providing them with the tools to make informed of self-management decisions. DSMES should be evaluated by the health care professional and/or interprofessional team, with referrals made as needed: A. at diagnosis; B. when not meeting treatment goals C. when

complicating factors (e.g., health conditions, physical limitations, emotional factors, or basic living needs) that influence self-management develop D. when transitions in life and care occur.

Assessing risk of diabetes complications need to evaluate

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment (google)
- Staging of chronic kidney disease (see Table 11.1)
- Assessment for retinopathy stages
- Diagnosis and sequel of neuropathy and the agony
- Stages NAFLD/NASH and
- Grading and knowledge Hypoglycemia and it's risk

ASCVD, atherosclerotic cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

Goal setting:

- .Blood glucose target: Set target A1C, target Blood glucose target time in range(TIR in CGM).
- If hypertension is present, blood pressure goal to be set.
- Weight management and physical activity goals
- Diabetes self-education and management goals

Therapeutic Treatment Plan of Diabetes

Summary:

- Healthy lifestyle behaviors, DSMES, avoidance of therapeutic inertia both by physicians and patient, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Selecting pharmacotherapy consider the effects on cardiovascular and renal comorbidities; effectiveness; hypoglycemia risk; impact on weight, cost and access; risk for adverse reactions and tolerability of individual.
- Weight management with pharmacotherapy or metabolic surgery, as appropriate. should be considered.
- Treatment modification (intensification or deintensification) for adults not meeting individualized treatment goals should not be delayed.It should be reevaluated at regular intervals (e.g., every 3–6 months) .
- In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include Sodium–glucose cotransporter 2 inhibitor [SGLT2] and/or Glucagon-like peptide 1 receptor agonist [GLP-1 RA).

Insulin obligation:In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if there is evidence of ongoing catabolism (e.g., unexpected weight loss), if symptoms of hyperglycemia are present, or when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L])

Insulin alternatives:In adults with type 2 diabetes, a GLP-1 RA, including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin .Combination therapy and therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with Insulin dosing reassessed..

Insulin & OHA: In adults with type 2 diabetes, glucose-lowering agents may be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits) taking care of the need for and/or dose of glucose-lowering agents with higher hypoglycemia risk (i.e., sulfonylureas and meglitinides).

Cost concern: Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, to support diabetic individuals by implementing strategies to reduce costs. May consider use of lower-cost medications for glycemic management (i.e., metformin, sulfonylureas, thiazolidinediones, and human insulin) within the context of their cardio renal risks and other adverse effects.

Referrals for initial care management:

- Eye care professional for annual dilated eye exam
- Family planning for individuals of childbearing potential
- Registered dietitian nutritionist for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Behavioral health professional, if indicated
- Audiology, if indicated
- Social worker/community resources, if indicated
- Rehabilitation medicine or another relevant health care professional for physical and cognitive disability evaluation,
- Whenever indicated Other appropriate health care professionals

Essential things for success in treating the chronic condition of Diabetes:

1. **Life style behavior change**: Aim is to have a disciplined, patient& knowledgeable patient having accomplished ideas of diabetes, diet and exercise and their inter relationship in his life.
2. **The pharmacotherapy**: Oral hypoglycemic agent (OHA) and/or, Injections
3. ***Follow up*:** Assessment and treatment planning are essential components of initial and all follow-up visits. Smoking cessation must be stressed and implemented in every visit.

05
CHAPTER

Diet in Diabetes

Diet: Diet is for nutrition and weight management.

Essentials:

Targets:

BMI(body mass index): ≤25. For Asians ≤23 :

Calorie/Day: less to reduce weight, more to gain weight, adequate to maintain weight

Components of a meal: CHO:50-60%, Protein 15-20%, Fat 20-30%

Diabetics must take (daily):one egg with yolk, one cup of milk, one sweet fruit

- **Diabetic should not take** sugar, glucose
- **Diabetic may take** any other food with moderation
- **Rhetorics**: Believe it and follow these :Nothing like diabetes diet, diabetic recipe .
- **Safe Sweetener**: Sucralose (Splenda), Dextrans, Saccharine (Sweet 'N low).Aspartum (Splenda).Stevia

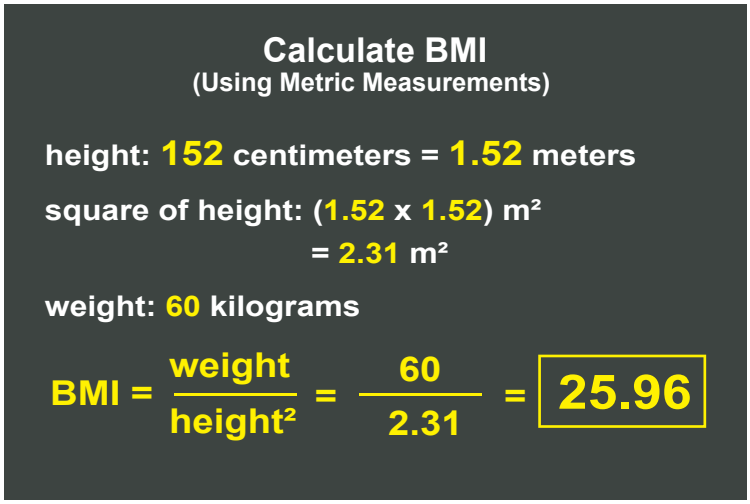


Figure 5.1: BMI calculation

BMI Number Mean?

Body mass index (BMI) is a measure of your weight relative to your height.

For all men and women 20 years old and older, the BMI measurement is classified into one of four main weight categories:

Below 18.5: Underweight

18.5 – 24.9: Healthy Weight

25.0 – 29.9: Overweight

30.0 and above: Obesity

People of Asian descent may have greater health risks at a lower BMI. People in this group may be placed in the overweight range if their BMI is between 23 and 25 and may have obesity if their BMI is 25 or greater.

Type of Diet:

- Mediterranean
- DASH
- Atkin / Keto

Diet: Diet is for nutrition and weight adjustment.

Every person has individual calories requirements. Easiest way to decide is height in cm and weight as per height..Some one with height 165 cm, ideal weight is 65 Kg. A diabetic person should reduce weight if it is overweight and increase it if less weight. BMI chart can be used or calculated to decide grade of overweight.Dietary adjustments should be done as needed for the individual. After deciding daily requirements of calorie one should calculate the quantity of carbohydrates, Protein and Fat requirements.Ideally 50-60% should be carbohydrates,15-20 should come from Protein and contribution of fat to be 20-30%. So if some one goes for no or less/least carbohydrates or fat that is not a healthy attitude.

Ideal daily food for a diabetic person: There is no diabetic diet neither any diabetic recipe. One should Not to take sugar or glucose.If some one have very good control of blood glucose he may have the taste of sweets on occasion of unavoidablity; definitely keeping in mind of blood glucose. During the month of Ramadan a piece jilapi or a little sweet meat in a party is allowed if he or she has very good control of blood glucose. Every one should take (if otherwise not contraindicated) one egg with yolk, one cup of milk and one sweet fruit everyday. The remaining foods he or she may take with moderation.A non diabetic person can take whole pineapple but diabetic one should take only a piece. A diabetic will take four piece of lichi but the person who has no diabetes can take 50-100 pieces.

Sweetner:Diabetic Jam Jelly or other commercial products are not really sugar free.The sugar alcohol (sorbitol etc.) used here if used in excess has potential to increased blood

glucose and may cause diarrhoea. Sweetner (so called low calorie, Sugar less) is not safe either. Best is to avoid tham. One tab or one drop or one teaspoon is sweet like that of one teaspoon of sugar but no or less calorie.There are about 9 (nine) different artificial sweeteners) in the market. They are many times sweeter than sugar (sucrose). There are many gossips about safety particularly about carcinogenic effect. The FDA and European medical associations have justified the safety of use of these. But even if you choose a calorie-free sweetener, enjoy sugar substitutes in moderation. According to a study, artificial sweeteners can alter your brain's response to sweetness and affect your ability to feel satisfied when you eat sweet-tasting food or drink, putting you at risk for consuming too much of it. In fact, the American Diabetes Association (ADA) recommends that in the case of beverages, it's best not to rely on zero- or low-calorie options as a replacement for ones that contain sugar beyond the short term; but instead, to drink as little of any type of sweetener as you can and to simply drink more water.

Measurement of Diet:

Plate formula-

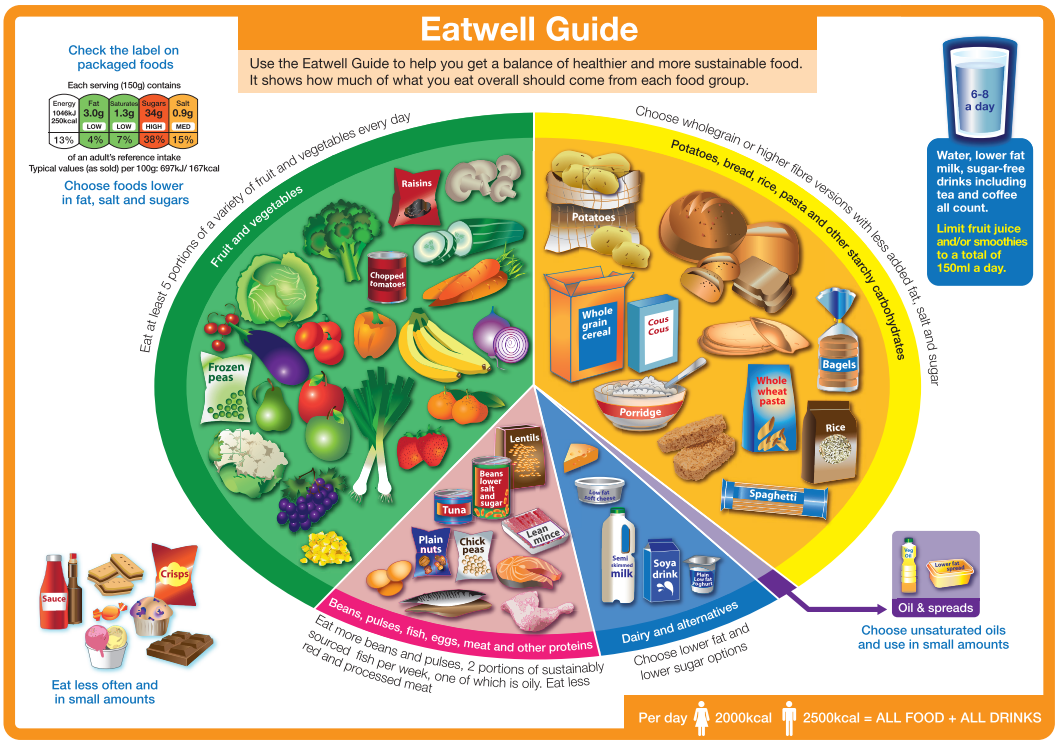
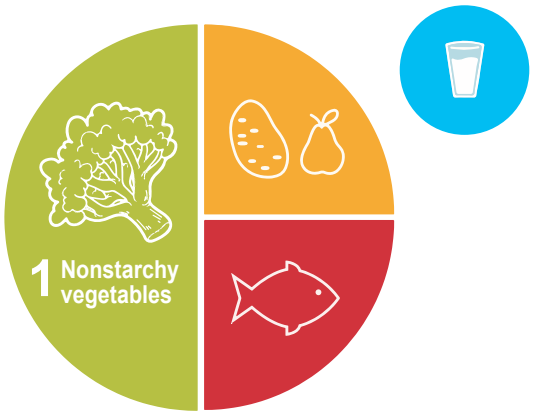


Figure 5.2: Plate formula for diabetic diet

Building a Healthy Plate:

Choose Nutrient-Rich Foods. Planning a healthy diet using the MyPlate approach is not difficult. Half of the plate should have fruits and vegetables, one-quarter should have whole grains, and one-quarter should have protein. Dairy products should be low-fat or non-fat. Plate is to be 9 inches accross.

1. Fill half the plate with nonstarchy vegetables.



Nonstarchy vegetables are lower in carbohydrate, high in vitamins, minerals, and fiber.

Examples of nonstarchy vegetables:

- Asparagus
- Broccoli or Cauliflower
- Cabbage (Green, Red, Napa, Bok choy, Chinese)
- Carrots
- Celery
- Cucumber
- Eggplant
- Leafy greens such as Kale, Collards, Mustard Greens, or Swiss Chard
- Mushrooms
- Okra/ladies fingure
- Green beans, Peas
- Peppers
- Salad greens such as Lettuce, Spinach, Arugula, Endive, and other salad mixes
- Squash such as Zucchini, Yellow squash, Chayote, Spaghetti squash
- Tomatoes

2. Fill one quarter of your plate with lean protein foods

There is no evidence that adjusting the daily level of protein intake (typically 1–1.5 g/kg body weight/day or 15–20% of total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk. Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety. Reducing the amount of dietary protein below the

recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines and may increase the risk for malnutrition.

Foods high in protein such as fish, chicken, lean beef, soy products, and cheese are all considered “protein foods.”Proteins foods (especially those from animal sources) usually contain saturated fat, which may increase risk of heart disease. Lean proteins are lower in fat and saturated fat, making them a healthier choice. Keep in mind that some plant-based protein foods (like beans and legumes) are also high in carbohydrates.Examples of lean protein foods include:

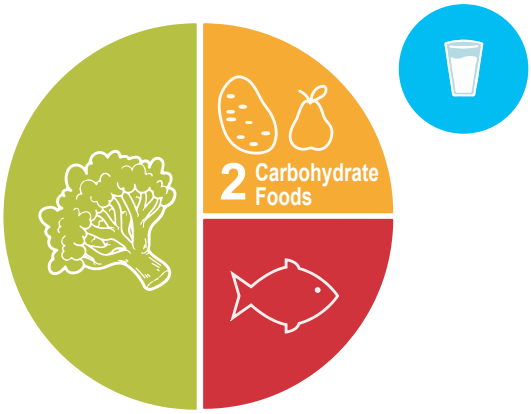
- Chicken, turkey, and eggs
- Fish like salmon, cod, tuna, tilapia, or swordfish
- Shellfish like shrimp, scallops, clams, mussels, or lobster
- Lean beef cuts such as chuck, round, sirloin, flank, or tenderloin
- Lean pork cuts such as center loin chop or tenderloin
- Lean deli meats
- Cheese and cottage cheese

Plant-based sources of protein:

- Beans, lentils, hummus, and falafel
- Nuts and nut butters
- Edamame
- Tofu and tempeh
- Plant-based meat substitutes

3. Fill one quarter of the plate with carbohydrate foods

Carbohydrate: Systematic reviews and meta-analyses of RCTs found carbohydrate-restricted eating patterns, particularly those considered low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year. A systematic review and meta-analysis of RCTs investigating the dose-dependent effects of carbohydrate restriction found each



10% decrease in carbohydrate intake had reductions in levels of A1C, fasting plasma glucose, body weight, lipids, and systolic blood pressure at 6 months, but favorable effects diminished and were not maintained at follow-up or at greater than 12 months. This systematic review highlights the metabolic complexity of response to dietary intervention in type 2 diabetes as well as the need to better understand longer-term sustainability and results , very-low-carbohydrate eating plans are not currently recommended for individuals who are pregnant or lactating, children, people who have renal disease, or people with or at risk for disordered eating, and these plans should be used with caution in those taking sodium–glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant impact on A1C while others demonstrated A1C reductions of 0.15% to 0.5%.

Foods that are higher in carbohydrate include grains, starchy vegetables, beans and legumes, fruit, yogurt, and milk. These foods have the greatest effect on blood sugar.Examples of carbohydrate foods:

- Whole grains such as brown rice, bulgur, oats/oatmeal, polenta, popcorn, quinoa, and whole grain products (bread, pasta, tortillas)
- Starchy vegetables such as acorn squash, butternut squash, green peas, parsnips, plantain, potato, pumpkin, and sweet potato/yam.
- Beans and legumes such as black, kidney, pinto, and garbanzo beans.
- Fruits and dried fruit.
- Dairy products like milk, yogurt, and milk substitutes (*i.e.* Soy milk)

Fat: Evidence suggests that there is not an optimal percentage of calories from fat for people with or at risk for diabetes and that macronutrient distribution should be individualized according to the individual's eating patterns, preferences, and metabolic goals. The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and it is recommended that the percentage of total calories from saturated fats should be limited. Multiple RCTs including people with type 2 diabetes have reported that a Mediterranean eating pattern can improve both glycemic

management and blood lipids. The Mediterranean eating pattern is based on the traditional eating habits in the countries bordering the Mediterranean Sea. Although eating styles vary by country or culture, they share a number of common features, including consumption of fresh fruits and vegetables, whole grains, beans, and nuts/seeds; olive oil as the primary fat source; low to moderate amounts of fish, eggs, and poultry; and limited added sugars, sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid and docosahexaenoic acid) supplements for all people with diabetes for the prevention or treatment of cardiovascular events.

A balanced diet and a good health

A healthy diet is good for physical and mental health.

It can reduce the risk and severity of obesity, heart disease, diabetes, hypertension, depression and cancer.

Why a balanced diet?

Sometimes we eat because we enjoy the taste and experience of different foods. Sharing food and meals are important social events.

But other than for pleasure, we need food to get nutrients, vitamins, minerals and energy.

Very few foods are either all good or all bad. By having an idea of the balance in your diet, it should be easier to enjoy food and be healthy.

There are seven essential factors for a balanced diet: carbs, protein, fat, fibre, vitamins, minerals and water.

The rough percentage of daily calories that should come from each factor is shown in Table below.

Table 5.1 Essential nutrients for a healthy balanced diet

Nutrient	% of daily calories	Function	Source
Carbs	45–55%	Energy	Grains (refined & unrefined): wheat, maize, corn, millet, oats, rice, flour, pasta, noodles; potatoes; sweet potatoes, yam. Fruit (sugar).
Protein	10–35%	Tissue growth and maintenance	Meat, fish, nuts, eggs, soya, beans and pulses.
Fat	20–35% from fat	Energy, energy storage, hormone production	Nuts, seeds, plant oils, dairy products (milk, cheese).
Fibre	Included in carbs.	Regulates blood sugar levels, bowel function and bowel health.	Peas, beans, vegetables, fruit, oats, whole grains, brown rice, nuts, seeds.
Vitamins & minerals	trace	Metabolism regulation, aiding cell growth, other biochemical functions	Specific to each vitamin/mineral. A range of vegetables, lean meat, nuts and seeds will cover most people's needs.
Water	0	Maintaining hydration	Drinking water, other beverages. About 20% of water intake comes from food.

Table 5.2 Healthy eating:(Diabetic & non diabetics): Eat more, eat less…

	Food types	Comments
Eat more	Raw and cooked vegetables & fruit ("5-a-day"), nuts, seeds, beans & pulses, whole grain cereals/bread, lean white meat (chicken without skin), fish (especially oily)	Linked to many aspects of better health including reducing LDL.
Eat in moderation	Lean cuts of beef, lamb, pork, shellfish, dairy products (low fat), unsaturated fats (olive oil, vegetable oil). Dried fruit, jams. Sucrose, honey, fructose, chocolate.	These foods can all be an important part of your diet.
Eat less and in limited amounts	Saturated fat (butter, margarine, lard, cheese, cream, high fat milk), trans fat & salt (less than 5g daily). Processed meats/fatty cuts of meat (sausages, salami, bacon, ribs etc).Processed meals (high in fat, sugar and salt). Pastries, muffins, pies, cakes, sweets, etc. Alcohol is high in sugar and calories and is only recommended in moderation.	These foods are not good for your health.Some guidelines include specific recommendations.

Eating a wide range of different foods will give your body the nutrients and micronutrients that it needs. Diabetics should avoid sugar & sweets

Keto diet: (courtesy: Prof.Saifuddin - saifk56dmc@yahoo.com)

Keto diet is an extremely carbohydrate restrictive, high fat diet. The Keto diet typically recommends that only 5% of calories come from carbohydrates along with 75% from fat and 20% from protein. While a balanced diet contains carbohydrate 40-60%, protein 15-30 and fat 25-30%. There are different types of keto diets according to content and consumption.

Dietary assimilation in the body-On a balanced diet with high/normal carbohydrates: Glucose increases in blood, pancreas secrets insulin in response,glucose is pushed into cells metabolized and there is energy production. While on the Keto diet,higher fat diet.Sugar falling,lipase realeases triglyceride,liver uses it to produce energy and ketones.

Risks of the Keto diet: Keto diet is so restrictive it is very difficult to follow long term, once stopped there is a rapid regain of weight. Keto diet associated weight loss is 4-6 pounds in the first week while healthy weight loss is one pound per week.

It increases saturated (allowance < 7% of daily calorie) fat and bad cholesterol (LDL) increases the risk of heart diseases and others. Studies showed lowest carbohydrate intake (39%), increases death from coronary heart disease by 51% cerebrovascular disease by 50% and cancer by 35%.

It increases the dangerous risk of diabetic ketoacidosis in T1 and T2 DM and for those with SGLT2 users.It causes constipation, mood swing and fuzzy thinking. Liver and kidney problems are frequent. So there are lipid/cholesterol disoreders, bone disorders, hair fall and gastro esophageal reflux disorders (GERD) with keto diet.

Diet plan should be individualized depending on diversity of people affected by diabetes and prediabetes, their cultural backgrounds, personal preferences, comorbidities and socioeconomic settings in which they live.American diabetic association (ADA) also state balanced diet with appropriate proportion of carbohydrates, proteins, fats, vitamins and minerals is the best option.

06
CHAPTER

Weight management and exercise

Summary:

- In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss.
- For many individuals with overweight and obesity with type 2 diabetes, 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and blood pressure (1,2).
- It should be noted, however, that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety.

Physical activity and exercise: Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important.

Youth with type 1 diabetes or type 2 diabetes is to engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.

Adults with type 1 diabetes and type 2 diabetes is to engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals. With 2–3 sessions/week of resistance exercise on nonconsecutive days.

For older adults Recommend flexibility training and balance training 2–3 times/week with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.

For all people with diabetes:

Baseline physical activity and time spent in sedentary behavior (i.e., quiet sitting, lying, and leaning) should be evaluated.

- Who do not meet activity guidelines, needs to encourage increase in physical activities (e.g., walking, yoga, housework, gardening, swimming, and dancing) above baseline (type 1 diabetes and type 2 diabetes).
- Prolonged sitting should be interrupted every 30 minutes for blood glucose benefits.
- Health care professionals should counsel people with diabetes to engage in aerobic and resistance exercise regularly.
- Aerobic activity bouts should last at least 10 min, with the goal of ~30 min/day or more most days of the week for adults with type 2 diabetes. Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise.
- Adults able to run at 6 miles/h (9.7 km/h) for at least 25 min can benefit sufficiently from shorter durations of vigorous-intensity activity or interval training (75 min/week)

Types of Exercise

1. Aerobic (cardio)
2. Muscle-strengthening or resistance exercise
3. Stretching or bone strengthening (yoga, tai-chi)

Resistance activities: Undertake muscle strengthening activities on at least 2 days each week. Strengthening activities include anything that requires your body to move against a weight or gravity. This would include activities such as lifting tins of food, repeated sitting and standing from a chair or seated leg raises.

How long

- Minimum 30 minute/day, 5 days a week (150 minutes/week)
- More is better as per the health allows
- No omission for 2 consecutive days
- Same times every day
- Target weight: Reduce >10% not less than 7.5%, <5% not appropriate.
- Target heart rate: 220 minus weight in Kg & (70-100%) of that

Exercise programs for people with diabetes

ADA: The American Diabetes Association (ADA) recommends that most adults with type 2 diabetes get 150 minutes or more of moderate-to-vigorous aerobic activity per week, which can be spread throughout the week.

WHO: Recommend 150 minutes/week at moderate to vigorous intensity for most adults with diabetes. For adults able to run steadily at 6 mph/9.7 kmph for 25 min/ml, 75 min/week of vigorous activity may provide similar cardioprotective and metabolic benefits.

A guide to BGLs (blood glucose levels) and exercise

- < 4mmol/L: Exercise should be postponed until hypoglycemia has been treated.
- 4mmol/L – 5mmol/L: Have a small amount of carbohydrate. i.e., a piece of fruit or a small glass of milk before starting exercising.

- 5mmol/L – 10mmol/L: This is the ideal BGL range to exercise.
- 10mmol/L – 14mmol/L: consistently over 10mmol/L, consider gentle exercise and see GP discuss ongoing treatment.
- 15mmol/L: If BGL is more than 15mmol/L better to postpone exercise.

Warning signs to stop exercising

If anyone experience any of the following during exercise, should stop it and rest.

- Chest, abdominal, neck, jaw, or arm pain or tightness
- Palpitations, irregular or racing heart beat
- Feeling faint, lightheaded or dizzy
- Leg cramps or pain
- Symptoms of hypoglycemia (stop immediately and treat!)

If the pain/symptom does not go away within five minutes, seek urgent medical attention.

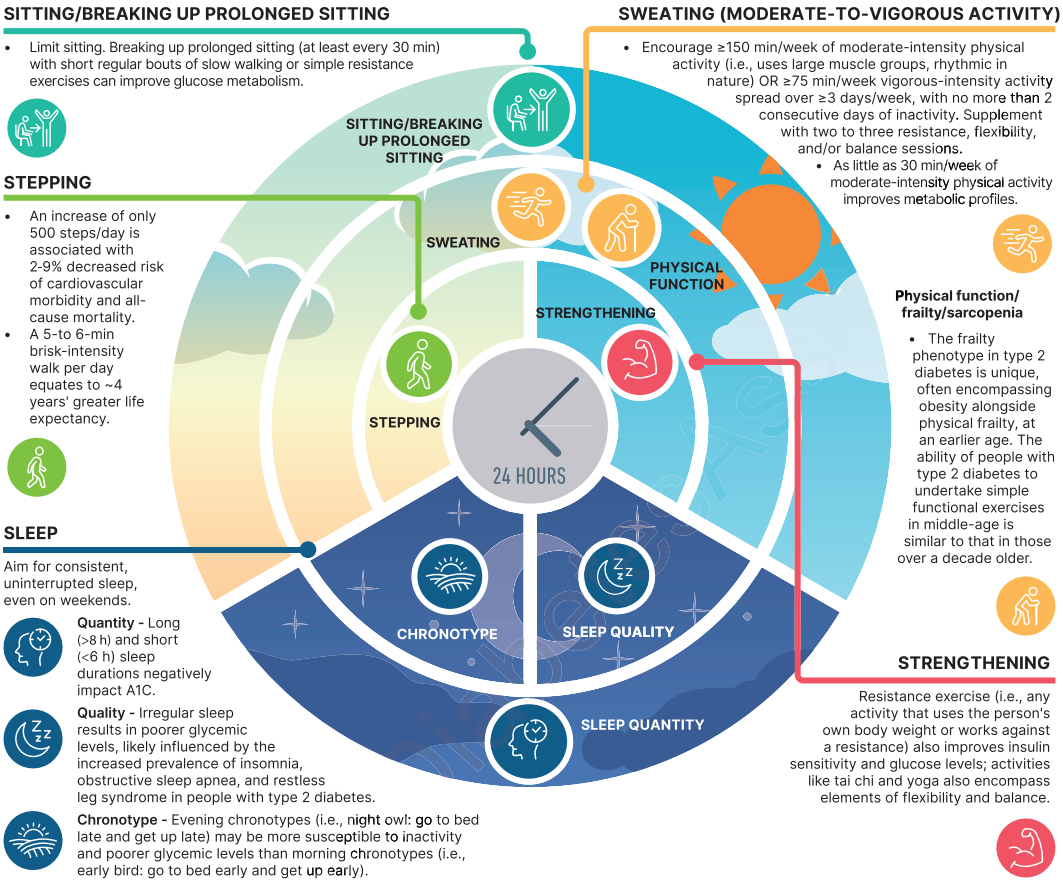
Timing of exercise: In general, the best time to exercise is one to three hours after eating, when the blood sugar level is likely to be higher. If you use insulin, it's important to test your blood sugar before exercising. The study says 145 pm to 5 pm is the ideal time. The body's metabolism also tends to be more efficient in the afternoon, and insulin sensitivity is higher than at other times. It is also said that physical activity in the afternoon might line up with a natural dip in blood sugar levels that occurs late in the day or early evening.

Benefits of exercise:

- All forms of exercise—aerobic, resistance, or doing both (combined training)—were equally good at lowering HbA1c values in people with diabetes.
- Exercise helps control weight, lower blood pressure, lower harmful LDL cholesterol and triglycerides, raise healthy HDL cholesterol, strengthen muscles and bones, reduce anxiety, and improve your general well-being. There are added benefits for people with diabetes: exercise lowers blood glucose levels and boosts your body's sensitivity to insulin, countering insulin resistance.
- Insulin sensitivity is increased, so your muscle cells are better able to use any available insulin to take up glucose during and after activity.
- Whenever your muscles contract during activity, cells can take up glucose and use it for energy whether insulin is available or not.

This is how exercise can help lower blood glucose in the short term. And when active on a regular basis, it can also lower your A_1C.

Importance of 24-Hour Physical Behaviors for Type 2 Diabetes



	Glucose/ insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ Higher levels of improvement (physical function, quality of life) ↓ Lower levels of improvement (glucose/insulin, blood pressure, A1C, lipids, depression)
? No data available
↑ Green arrows = strong evidence ↑ Yellow arrows = medium-strength evidence ↑ Red arrows = limited evidence

Figure 6.1: Importance of 24 hours physical activities in T2DM management

Being physically active is one of the best ways to help manage type 2 diabetes. Not only does it help to control blood sugar levels, it can also lower the risk of health complications of diabetes, such as heart disease and nerve damage. It maintains mood regularity of life and hormone milieu of the body.

Being active can help to manage diabetes by keeping blood glucose levels (BGLs) within target range and helping to achieve and maintain a healthy weight.

Physical Activity Guidelines:

- Thinking of movement as an opportunity, not an inconvenience.
- To be active every day in as many ways as it can be.
- Engage in at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week. Same time of the day. No omission for 2 consecutive days.
- Muscle strengthening activities to be done on at least 2 days per week.
- Break up long periods of sitting as often as possible(never more tan 90 minutes sitting at a time),
- If possible, also enjoy some regular, vigorous activity for extra health and fitness.

Steps to get started with exercise

For best results in achieving a healthier lifestyle and reducing risk of developing a chronic disease, combine physical activity with healthy eating.

1. Builds up slowly. ...
2. Make time to exercise. ...
3. Choose activities that are right for you. ...
4. Build physical activity into your everyday life.
    - Buy yourself a pedometer — a wearable gadget that counts how many steps you take. Use this to motivate you to keep increasing your daily steps. 10,000 steps is a website dedicated to motivating people to build up to 10,000 steps a day.
    - Walk or cycle instead of using the car for short trips.
    - If you have to drive, park further away from your destination or get off the bus, train or tram one stop early.
    - Rather than spend 5 minutes circling a car park looking for that 'perfect space' near the entrance to the shops, park 5 minutes away and spend that time walking instead.
    - Walk on escalators - It’s quicker so you’ll actually save time. Or better still, use the stairs.
    - Work in the garden - Get into some energetic gardening activities like digging, shifting soil, and mowing the lawn to raise your heart rate.
    - Clean the house - Activities like vacuuming, cleaning windows and scrubbing floors that raise your heart rate are all good examples of moderate activity.

5. Make it fun Join a walking group.
   - Walking groups are an enjoyable way to get active and provide an opportunity to socialize and meet new people.
   - Catch up with friends by walking together rather than meeting for coffee or a meal
   - Join a gym with a friend.
   - Find a park run near you.
6. Get active with your family.
   - Play actively with your children — kick a footy around, skip, jump on the trampoline.
   - Go on a family bike ride.
   - Take your dog (or the neighbor's dog) for a walk.
   - If possible, walk to school with your children or park further from the school and walk part of the way.
   - Buy a fitness DVD and get the whole family to join in — a great way to have a laugh and be active.
7. Getting active at work
   - Park further away from work (or get off public transport a few stops early). If you walk for 10 minutes to and from work, you'll have done 20 minutes without even noticing.
   - Keep a pair of comfortable walking or running shoes at work and you will always be ready for a walk or run.
   - Go for a short walk during your lunch break.
   - Start a walking group with work colleagues or friends and stick to a routine of certain days or times to go out together.
   - If you work in an office, try to avoid long periods of sitting and get up as frequently as you can.
   - Walk the long way to the bathroom and kitchen/canteen.

Understand the intensity of exercise:

What is your preferred exercise intensity level?

- Moderate - intensity exercise – If you are "lightly puffing" and you can hold a short conversation – you're exercising at a moderate intensity. "Moderate" physical activity could be a brisk walk or dancing. The guidelines recommend you do between 150-300 minutes of moderate intensity exercise each week.
- Vigorous - intensity exercise – You would be short of breath but able to speak up to one sentence if you're doing vigorous intensity exercise. "vigorous" physical activity could be running or fast bicycling. The guidelines recommend you undertake between 75-150 minutes of vigorous intensity exercise each week, if you are able.

Exercise that is too light may not give you the recommended health benefits while exercise that is too hard can place you at risk of over-training and injury. Any type of physical activity is to be counted

High-intensity interval training (HIIT) :is a plan that involves aerobic training done between 65% and 90% VO2 peak or 75% and 95% heart rate peak for 10 s to 4 min with 12 s to 5 min of active or passive recovery. HIIT has gained attention as a potentially time-efficient modality that can elicit significant physiological and metabolic adaptations for individuals with type 1 and type 2 diabetes (3). Higher intensities of aerobic training are generally considered superior to low-intensity training. VO2 is measured in liters of oxygen consumed per minute and may be expressed in units of liters per minute (liters/minute). Your VO2 max is the maximum amount of oxygen your body can use.

A B

Figure 6.2 (A, B): Tai Chi

Suggestions

- Walking
- Swimming
- Cycling / exercise bike
- Dancing
- Gardening
- Golfing
- Weight training
- Tai Chi

07
CHAPTER

Glycemic targets

Glycemic Goals

An A1C goal for many nonpregnant adults of <7% (<53 mmol/mol) without significant hypoglycemia is appropriate. Setting a glycemic goal during consultations is likely to improve patient outcomes.

For all populations, the glycemic goals be woven into the overall person-centered strategy. For example, less stringent A1C goals are appropriate for individuals with limited life expectancy and/or significant functional and cognitive impairments. For glycemic goals in older adults, “Older Adults.” and” For glycemic goals during pregnancy, detail have been mentioned in the respective chapter. Glycemic targets: For all populations, it is critical that the glycemic goals be woven into the overall person-centered strategy

Glycemic targets for nonpregnant adults:

A_1C: <7% (53 mmol/L)

Pre-Prandial capillary plasma glucose: 80–130 mg/dL (4.4–7.2 mmol/L)

Peak postprandial capillary plasma glucose: <180 mg/dL (10.0 mmol/L)

TIR: CGM :70%(70-180mg/dl)

Target of control in pregnant DM: ADA

A_1C: <6.0%

Fasting glucose: 70–95 mg/dL (3.9–5.3 mmol/L) **

One-hour postprandial glucose: 110–140 mg/dL (6.1–7.8 mmol/L)

Two-hour postprandial glucose: 100–120 mg/dL (5.6–6.7 mmol/L)

*More or less stringent glycemic goals may be appropriate for individuals. Goals should be individualized. Postprandial glucose may be targeted if A1C goals are not met despite reaching pre-prandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

Frequency of Glucose test:

Glucometer

- On OHA; as and when needed
- On Insulin: Fasting, before sleeping any time in the day, as and as needed

Colorimeter: Once in a month (in the laboratory)

HbA1C: Well controlled twice in a year. Not controlled: every 3 months or when needed if the regimen changed

- **rtCGM:** 14th day: TIR 70%;Is CGM/FGM: any time

Intercurrent Illness & blood glucose:

Stressful events (e.g., illness, trauma, and surgery) increase the risk for both hyperglycemia and hypoglycemia among individuals with diabetes. In severe cases, they may precipitate diabetic ketoacidosis or a nonketotic hyperglycemic hyperosmolar state. Clinicians should be aware of medication interactions that may precipitate hypoglycemia. Notably, sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia.

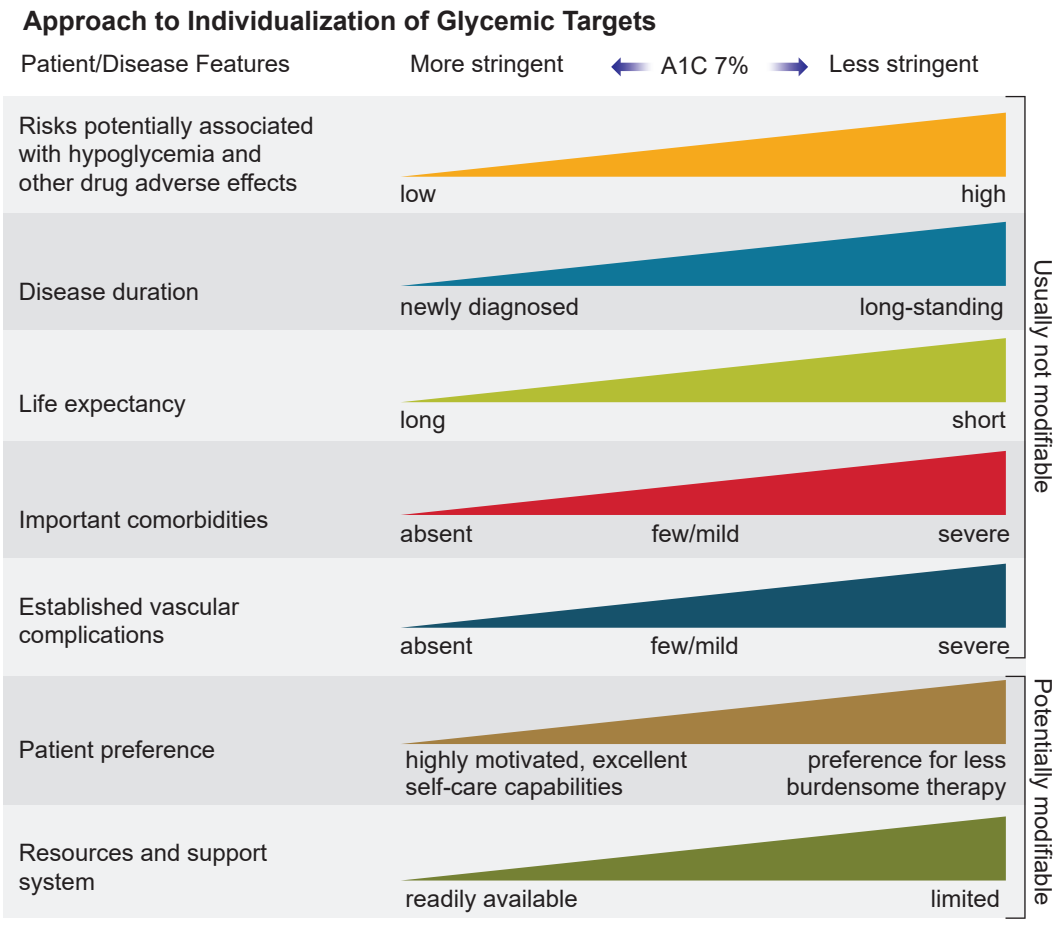


Figure 7.1: Individualization of glycemic goal

Person and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149

Assessment and treatment plan:

Microvascular outcomes:Glucose Lowering goals and Microvascular Complications:

The level of chronic hyperglycemia is the best-established concomitant risk factor associated with microvascular complications (i.e., diabetic retinopathy, nephropathy, and neuropathy). This is best understood by the fact that nerve, retinal, and kidney cells do not require insulin for intracellular glucose entry. Consequently, these cells, when exposed to elevated ambient glucose levels even in the presence of insulin deficiency (absolute or relative), will result in intracellular metabolic dysfunction and increased risk of microvascular complications.

The Diabetes Control and Complications Trial (DCCT), a prospective randomized controlled trial of intensive (mean A1C ~7% [53 mmol/mol]) versus conventional (mean A1C ~9% [75 mmol/mol]) glycemic control in people with type 1 diabetes, showed definitively that better glycemic status is associated with 50–76% reductions in rates of development and progression of microvascular complications (retinopathy, neuropathy, and diabetic kidney disease). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated persistence of these microvascular benefits over two decades even though the glycemic separation between the treatment groups diminished and disappeared during follow-up.

Among individuals with type 2 diabetes, three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes. Findings from these studies, including the concerning increase in mortality in the intensive treatment arm of ACCORD, suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes using medications with a high risk for hypoglycemia.

Macrovascular Outcomes :Glucose Lowering goals and chronic disease: Cardiovascular Disease

Cardiovascular disease (CVD) is a more common cause of death than microvascular complications in populations with diabetes. The modern multifaceted management of diabetes, with a focus on the treatment of hypertension and the use of statins, has reduced the prevalence of atherosclerotic CVD to around double compared with that of people without diabetes.

Meta-analysis of individual participant data from UKPDS, ACCORD, ADVANCE, and VADT demonstrated a significant reduction in myocardial infarctions and major CVD events but no

difference in stroke, heart failure, or mortality between intensive and less intensive glycemic control. The cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered.

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or a GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C goal.

Setting and Modifying Glycemic Goals:

Summary:

Glycemic goals and management should be individualized and not one size fits all. To prevent both microvascular and macrovascular complications of diabetes,

- There is a major call to overcome therapeutic inertia and treat to individualized goals Diabetes is a chronic disease that progresses over decades.
- A goal that might be appropriate for an individual early in the course of their diabetes may change over time.

Both DCCT/EDIC and UKPDS suggested that there is metabolic memory, or a legacy effect, in which a finite period of intensive glucose lowering yielded benefits that extended for decades after that period ended.

- Clinicians should continue to evaluate the balance of risks and benefits of diabetes medications for individuals who have achieved individualized glycemic goals, and they should deintensify (decrease the dose or stop) diabetes medications where their risks exceed their benefits.
- Hypoglycemia is the major risk to individuals treated with insulin, sulfonylureas, or meglitinides, and it is appropriate to deintensify these medications where there is a high risk for hypoglycemia (see hypoglycemia risk assessment, below).
- Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy. if needed to achieve individualized glycemic goals or
- where individuals have evidence-based indications for alternative medications (e.g., use of SGLT2 inhibitors in the setting of heart failure or diabetic kidney disease and use of GLP-1 receptor agonists in the setting of CVD or obesity
- Clinicians should also consider medication burdens other than hypoglycemia, including tolerability, difficulties of administration, impact on education or employment, and financial cost.).

Glucose Lowering goals and acute conditions: Hypoglycemia

Definition & Classification of Hypoglycemia: Glycemic criteria/description

Level 1 Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)

Level 2 Glucose <54 mg/dL (<3.0 mmol/L)

Level 3 A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level.

Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides is mandatory.

Clinical / biological risk factors:

Major risk factors

- Recent (within the past 3–6 months) level 2 or 3 hypoglycemia
- Intensive insulin therapy
- Impaired hypoglycemia awareness
- End-stage kidney disease

Other risk factors

- Multiple recent episodes of level 1 hypoglycemia
- Basal insulin therapy
- Age ≥ 75 years
- Female sex
- High glycemic variability
- Polypharmacy
- Cardiovascular disease
- Chronic kidney disease (eGFR <60 mL/min/1.73 m2 or albuminuria)
- Neuropathy
- Retinopathy
- Major depressive disorder

Social, cultural, and economic risk factors:

Major risk factors

- Food insecurity
- Low-income status
- Homelessness
- Fasting for religious or cultural reasons

Other risk factors

- Low health literacy
- Alcohol or substance use disorder

Hypoglycemia

Hypoglycemia and CV outcome

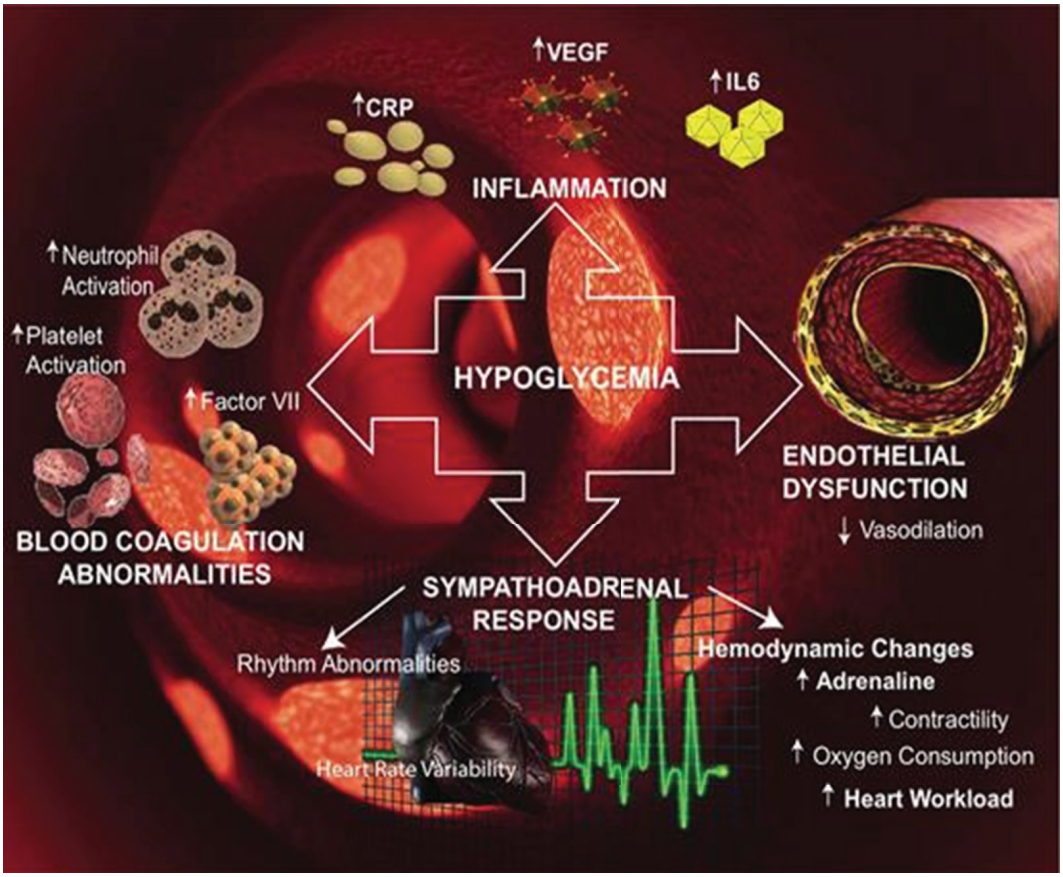


Figure 7.2: Hypoglycemia and CV outcome

- Hypoglycemia is associated with the activation of sympathetic nerves, inflammation, arrhythmia and increased coagulation, which may lead to increased risk of CV events and mortality

Hypoglycemia Assessment, Prevention, and Treatment

Assessment: History of hypoglycemia should be reviewed at every clinical encounter for all individuals at risk for hypoglycemia .Screen all individuals at risk for hypoglycemia for impaired hypoglycemia awareness. Consider an individual's risk for hypoglycemia when selecting diabetes medications and glycemic goals. Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia.

Treatment

a. Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may

be used. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. Added fat may slow and then prolong the acute glycemic response. Carbohydrate sources high in protein may increase insulin secretion and should not be used to treat hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery.

b. Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia.

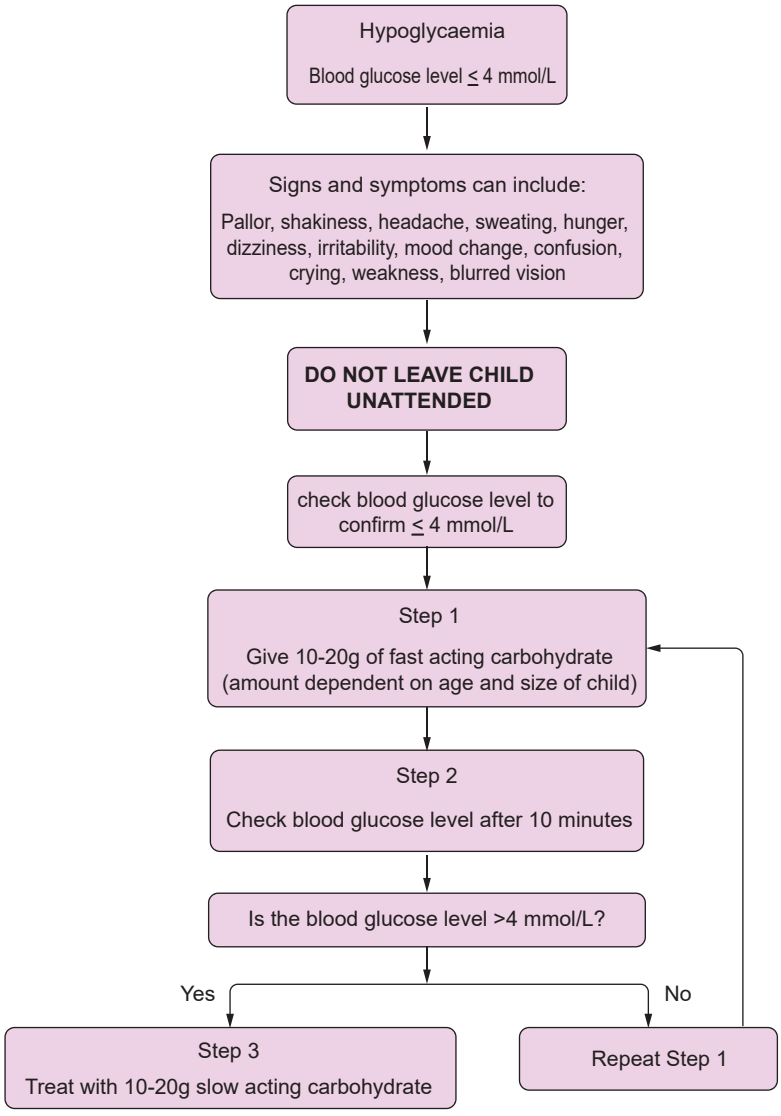


Figure 7.3: Suggested stepwise treatment of hospitalized children with hypoglycemia

Prevention

One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including deintensifying or switching diabetes medications if appropriate.

- Refer individuals with impaired hypoglycemia awareness to a trained health care professional to receive evidence-based intervention to help reestablish awareness of symptoms of hypoglycemia.
- All individuals taking insulin or at risk for hypoglycemia should receive structured education for hypoglycemia prevention and treatment. Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found.
- Clinicians should be aware of medication interactions that may precipitate hypoglycemia. Sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia. Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed.

Suggested citation: American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S111–S125

08 CHAPTER

Pharmacotherapy

Table 8.1 Glucose lowering agents

Comparison among glucose-lowering agents concerning glucose-lowering efficacy, risk of hypoglycemia, effect on weight, and beta cell protective effect.

	Glucose (HbA1c) lowering efficacy	Risk of hypoglycemia	Effect on weight	Beta cell protective effect
Metformin	Moderate to strong	Low	Neutral to loss	Yes
DPP-4 inhibitor	Moderate	Low	Neutral	Yes
GLP-1 receptor agonist	Strong	Low	Loss	Yes
SGLT2 inhibitor	Moderate	Low	Loss	Yes
α-glucosidase inhibitor	Modest	Low	Neutral	Yes
Thiazolidinedione	Moderate	Low	Gain	Yes
Insulin	Very strong	High	Gain	Yes
Sulfonylurea	Strong	High	Gain	No
Glinide	Modest to moderate	Low to moderate	Neutral	No

Table 8.2 Glucose lowering agents

General Class Compound/Brand Name	Generic Available	Dose Range	Cost
Glibenclamide	Yes	2.5mg qd to 10mg bid	Low
Glipizide	Yes	2.5mg qd to 20mg bid	Low
Glimepiride	Yes	0.5mg to 8mg qd	Low
Gliclazide	Yes	40mg qd to 160mg bid	Low
Meglitinides			
Repaglinide	Yes	0.5mg to 4 mg with meals. Max 16mg/day	Low
Nateglinide	Yes	60-120mg tid with meals	Low
Biguanide			
Metformin	Yes	500-2500mg qd or tid depending upon preparation	Low
Thiazolidinediones (TZDs)			
Pioglitazone	Yes	15-45mg qd	Low

(table continued)

Table 8.2 (cont'd)

General Class Compound/Brand Name	Generic Available	Dose Range	Cost
Alpha-glucosidase inhibitors			
Acarbose	Yes	25-100mg tid with meals	Low
Miglitol	Yes	25-100mg tid with meals	High
Voglibose	Yes	0.2mg tid with meals	
Dipeptidyl peptidase-IV (DPP-4) inhibitors			
Alogliptin	Yes	25mg qd	High
Linagliptin	No	5mg qd	High
Sitagliptin	No	25-100mg qd	High
Saxagliptin	No	2.5-5mg qd	High
Vildagliptin	No	50mg qd	
Bile Acid Sequestrant			
Colesevelam *	No	1875mg bid or 3.75-gram packet or bar qd	High
Dopamine Agonist			
Bromocriptine*	No	0.8 - 4.8mg qAM	High
Sodium-glucose co-transporter-2 (SGLT2) inhibitors			
Canagliflozin	No	100-300mg qd	High
Dapagliflozin	No	5-10mg qd	High
Empagliflozin	No	10-25mg qd	High
Ertugliflozin	No	5-15mg qd	High
Glucagon like peptide 1 (GLP-1) receptor agonists			
Semaglutide	No	7-14mg qd	High

- Not available in Bangladesh

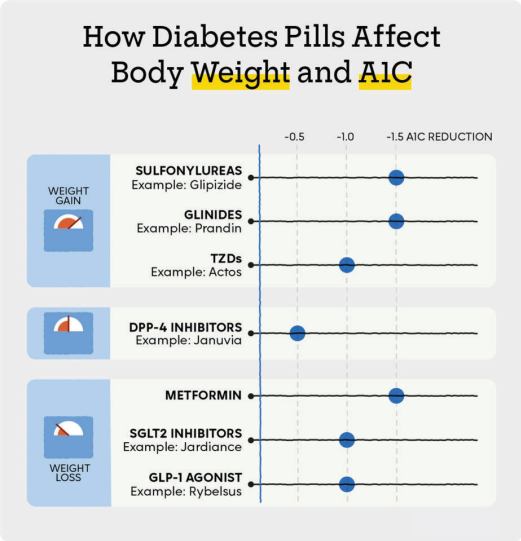


Figure 8.1: OHA effect on weight and HbA1C

Characteristics of hypoglycemic agents:

- Metformin, Sulfonylureas (SUs), Glitazones are low-cost high efficacy but DPP4 inhibitors are high-cost low to intermediate for glucose lowering, themselves do not cause hypoglycemia.
- SGLT2 inhibitors, GLP 1 RA, GIP high to very high potency drugs, do not have hypoglycemia, cause high to very high loss of weight and they are costly drugs. They have cardiovascular and renal benefits.
- Metformin, DPP4 inhibitors are weight neutral, Sulfonylurea and Glitazones cause weight gain.
- Metformin, Pioglitazone, Glimepiride, Gliclazide have cardiovascular (CV) benefits except in heart failure (HF) but no potential renal benefits.
- Insulin is highly effective high cost high potential hypoglycemic drug with no cardiorenal benefits.

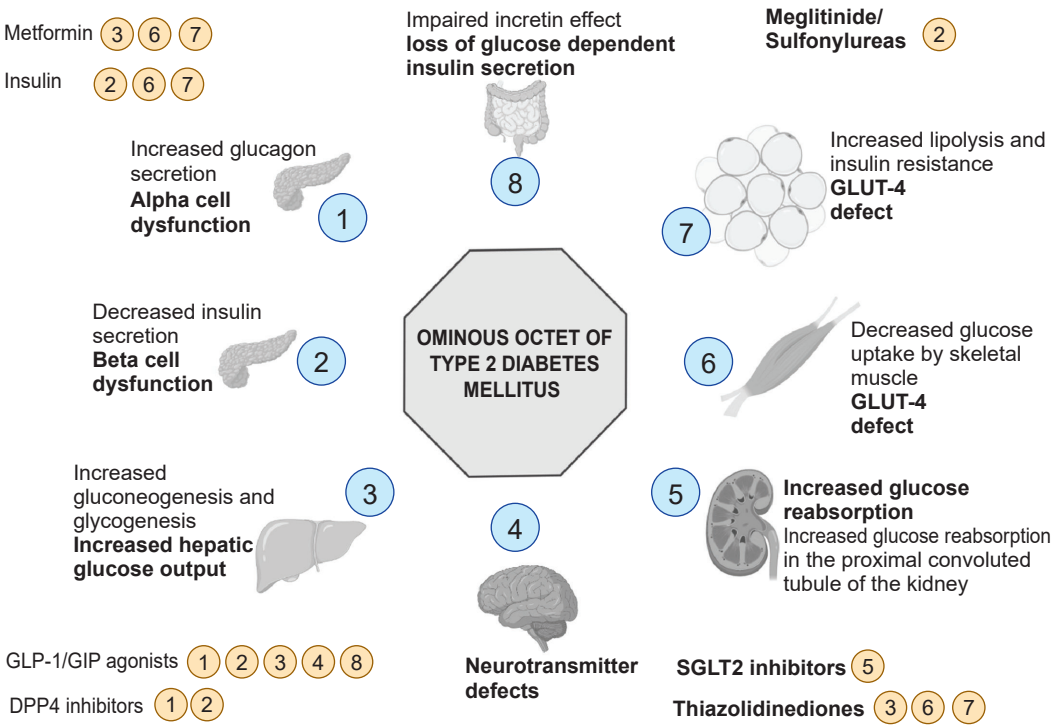


Figure 8.2: Multi factorial pathogenesis of Diabetes Mellitus: Ominous octet: Drugs targeting etiopathogenesis

Essentials:

1. Insulin resistance in muscles and liver and beat cell failure represent the core pathophysiologic defect in type 2 diabetes
2. The fat cells, GI tract, alpha cells, Kidneys and Brain all play important roles in developing glucose intolerance

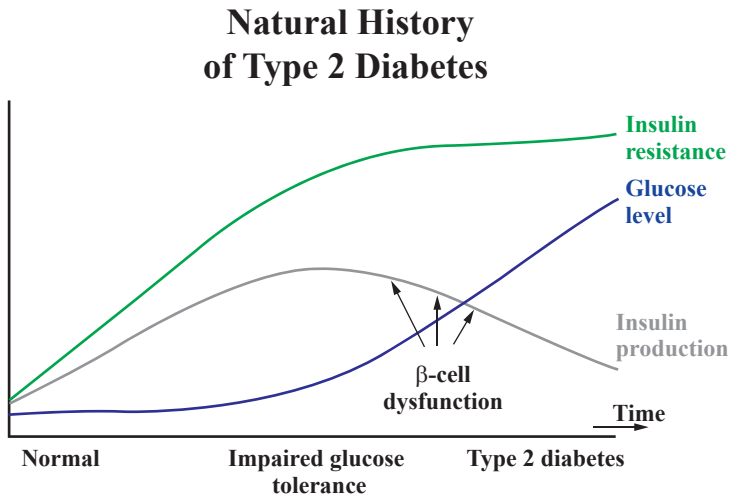


Figure 8.3: Natural history of T2 Diabetes mellitus

Worsening hyper- glycaemia in type 2 diabetes may result from a number of inter-related pathologies, including a decline in beta- cell function, insulin resistance, increased hepatic glucose production associated with inappropriately high levels of glucagon and reduced GLP-1 production. .

Type 2 Diabetes Mellitus: Etiology, Pathogenesis, and Natural History**:** *Christopher J. Hupfeld, C. Hamish Courtney and Jerrold M. Olefsky*

Published on 28/03/2015 by admin

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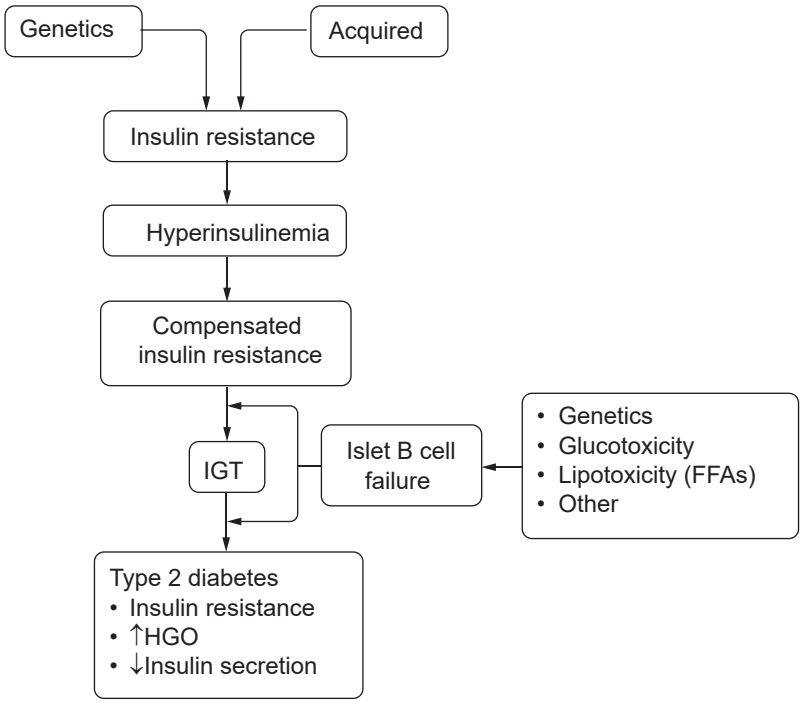


Figure 8.4: Interplay of etiopathogenic factors in Type 2 Diabetes mellitus

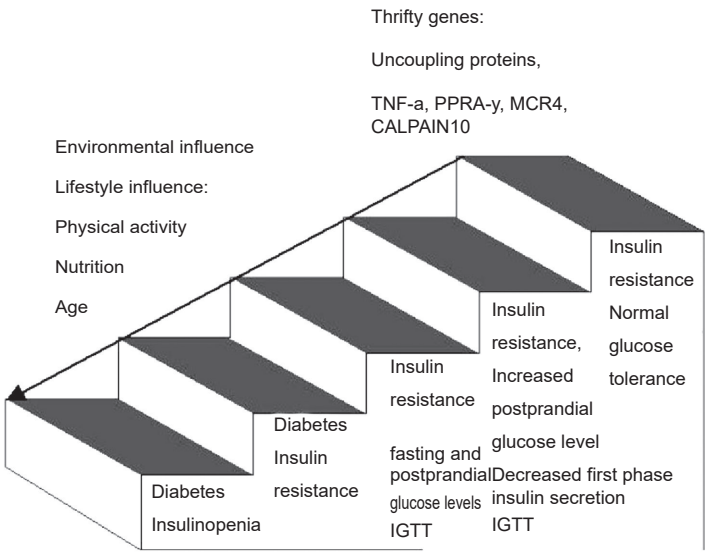


Figure 8.5: Stepwise progression of the pathogenesis of Diabetes

Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/ Natural-history-of-developing-diabetes-type-2.

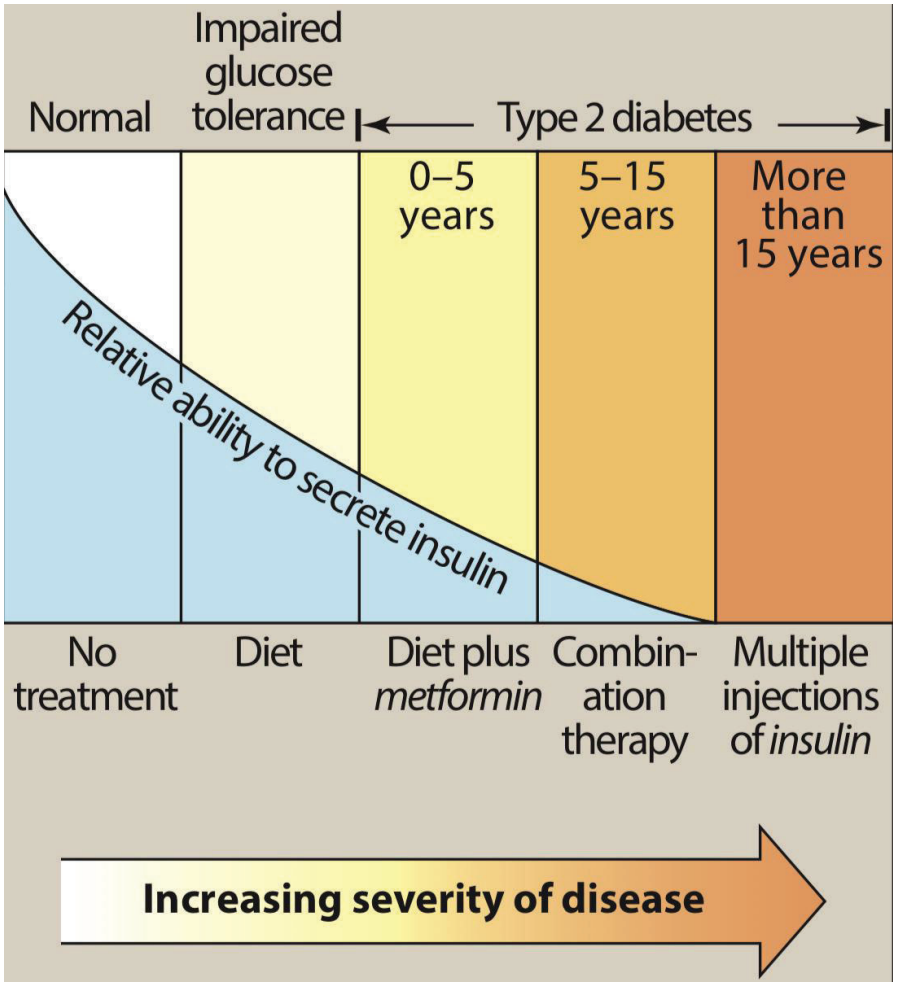


Figure 8.6: Stepwise addition of antidiabetic therapy complying with etiopathogenesis.

Background Type 2 diabetes is a progressive disease that requires stepwise additions of non-insulin and insulin therapies to meet recommended glycaemic goals. The final stage of intensification may require prandial insulin, adding complexity and increased risks of hypoglycaemia and weight gain.

Aim of treatments:

1. Glucose control
2. Avoidance of hypoglycemia
3. Restoration / Preservation of beta cell function

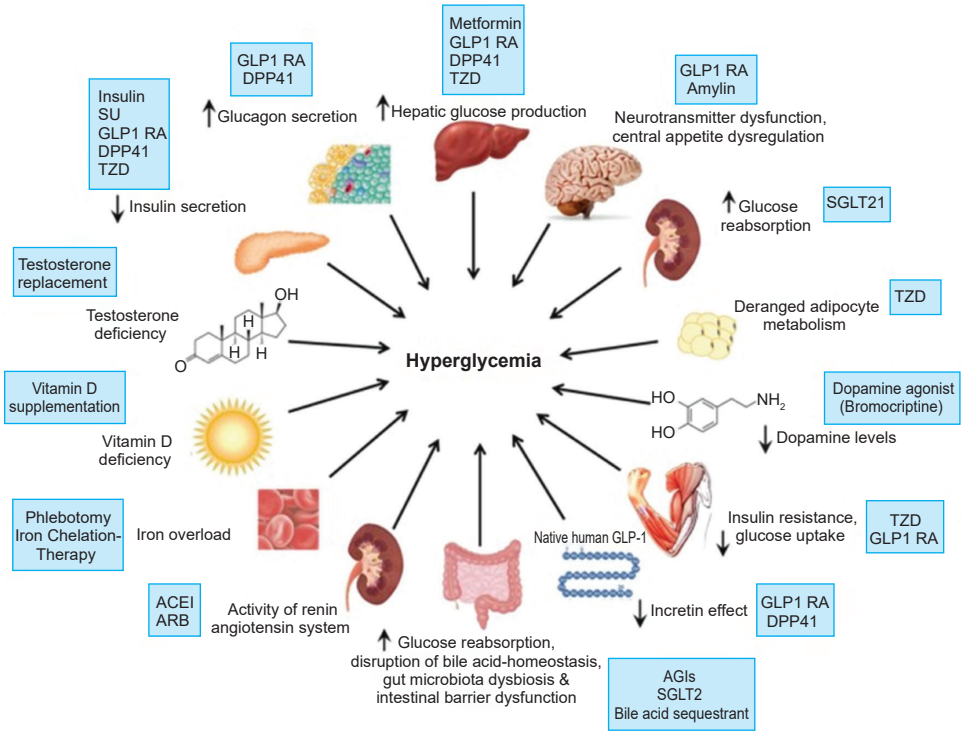


Figure 8.7: DIRTY DOZEN: Pathophysiology of Type 2 Diabetes & drugs with site of action

Challenges to face and overcome daily in managing diabetes mellitus

(1) ***O***ptimizing the use of currently available therapies to ensure adequate glycemic, blood pressure, and lipid control and to reduce complications

(2) ***E***ducating patients on diabetes self-management;

(3) ***i***mproving patient adherence to lifestyle and pharmacologic interventions;

(4) ***R***educing barriers to the early use of insulin; and

(5) ***I***mproving the delivery of health care to people with chronic conditions

Initiation of treatment policies

A.Single agent: LSA + OHA / Injection

***LSA**-Life style adjustment include dietary adjustment, weight management and physical activity

B.Dual combination (OHA-Oral hypoglycemic agents): When A_1C is ≥1.5% (12.5 mmol/mol) above the glycemic target many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their target A_1C level.

Insulin:

a. Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe.

b. If catabolic features (weight loss, hypertriglyceridemia, ketosis) are present.

c. It is common practice to initiate insulin therapy for people who present with blood glucose levels ≥300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss)

- **Normoglycemia and Rx**: As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible.
- **Sulfonylurea**: However, there is evidence that people with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea.
- Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals.

Evolution in therapeutic management of Diabetes mellitus:

- In the initial days of 500-5000 years before Egyptian and Indian physician could learn urine sugar was the symptom of diabetes .Herbs,chemical,starvation of their prescription.
- From the 15th to 19th centuries conception of exercise ,modification of diet specially carbohydrate was added to previous treatment modalities**.**
- Before 1921 diabetes was like cancer today. Anyone having diabetes was sure to die. After the discovery of insulin by Banting and Best the scenario has been changed.

Drugs used for Diabetes Mellitus: (Name with year of discovery)

Challenges of uses of drug:

A. The initial target was to reduce blood glucose and avoid hypo glycemia:

Insulin (Benting, Best 1921). NPH, Lente (1949s). First (SU) sulfonylurea (1955). Onward more SUs-Glipizide, Glibenclamide, Glimiperides (1960s). Metformin-outside USA (1957), USA (1995). Alpha Glucosidase Inhibitors (Acarbose, Voglibose, Miglitol) 1995 onwards. Glitazones (Pioglitazone) 1997 onwards. (2000 onwards) Insulin analogues. 2006 onwards: Incretins-DPP4 inhibitors (Vildagliptin, Sitagliptin, Linagliptin). 2010 onwards: Incretin GLP1 RA (Liraglutide, Dulaglutides, Semaglutude, Trizepatide). 2013 onwards - SGLT2 inhibitors (Empagliflozin, dapagliflozin. Globally overall CVD is 32.2% and one in three have CKD of T2 DM. FDA in 2008 conditioned that diabetic drug should have demonstrated cardiorenal benefit before being on the market.

B. The next challenge the use of antidiabetic drugs is to prove renal and cardiovascular safety and benefits.Since then so many cardiovascular outcome trials (CVOTs) were carried on. $SGLT_2$ inhibitors shows positive cardiorenal benefits and GLP1 receptor agonists (GLP1 RA) showed positive CV benefits and albuminuria benefits.

Glucose lowering medication:

How to initiate:

- Healthy lifestyle behaviors, diabetes self-management education, support and avoidance of therapeutic inertia are essential.
- Social determinants of health should be considered in the glucose lowering management of type 2 diabetes.
- A person-centered shared decision-making approach should guide the choice of pharmacotherapy.

How to choose a drug:

1. Consider the effects on cardiovascular and renal comorbidities and effectiveness; 2. Risks hypoglycaemia, 3. Impacts on weight, 4. Cost and availability, 5. Risk of adverse reaction & tolerability and 6. Individual preference.

- *Weight management goals for adults with type 2 diabetes should be in the centre.*
- *Regular evaluation and adjustment of therapy at 3-6 months would give a better outcome.*
- *Early combination at treatment initiation may have better a outcome (INITIAL, VERIFY).*

Adults without cardiovascular and/or kidney disease:

The pharmacological agent should include both individualised glycemic and weight goals. If cost considered sulfonylurea glitazones are better choice. These drugs increase weight. Sulfonylurea causes dangerous hypoglycaemia. DPP4 inhibitors are weight neutral. Reduces meal-related sugars so chance of hypoglycaemia is less.

Adults with established or high risk atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease:

SGLT2 inhibitor/and or GLP1 RA for comprehensive cardiovascular risk reduction and glycemic management.

Adults with T2 diabetes with HF:

(either HFrEF or HFpEF) an SGLT 2 inhibitors are recommended for glycemic management and prevention of HF hospitalization.

Adult with T2 Diabetes with CKD:

eGFR 20-60 and/or albuminuria. SGLT2 inhibitors should be used. It would minimize the progression of CKD and albuminuria, reduce cardiovascular events and reduce hospitalisation for HF. However, glycemic benefits are reduced at GFR <45ml/min/1.73 m2.

Adults with T2DM and advanced CKD:

For patients with eGFR <30-a GLP RA is preferred for glycemic management due to lower risk of hypoglycaemia and for cardiovascular event reduction.

GLP 1 receptor agonists (GLP 1 RA) and glucose-dependent insulinotropic agents in **(GIP):** In T2DM GLP1RA or dual GLP 1RA GIP is preferred to insulin. Combination therapy has greater glycemic, weight and hypoglycemia benefits as well as cardiorenal benefits. Insulin dosing to be reassessed when in combination

Decision-making on pharmacologic treatment for the management of glycemia in type 2 diabetes. (2009.2015.2019 EASD, ADA)

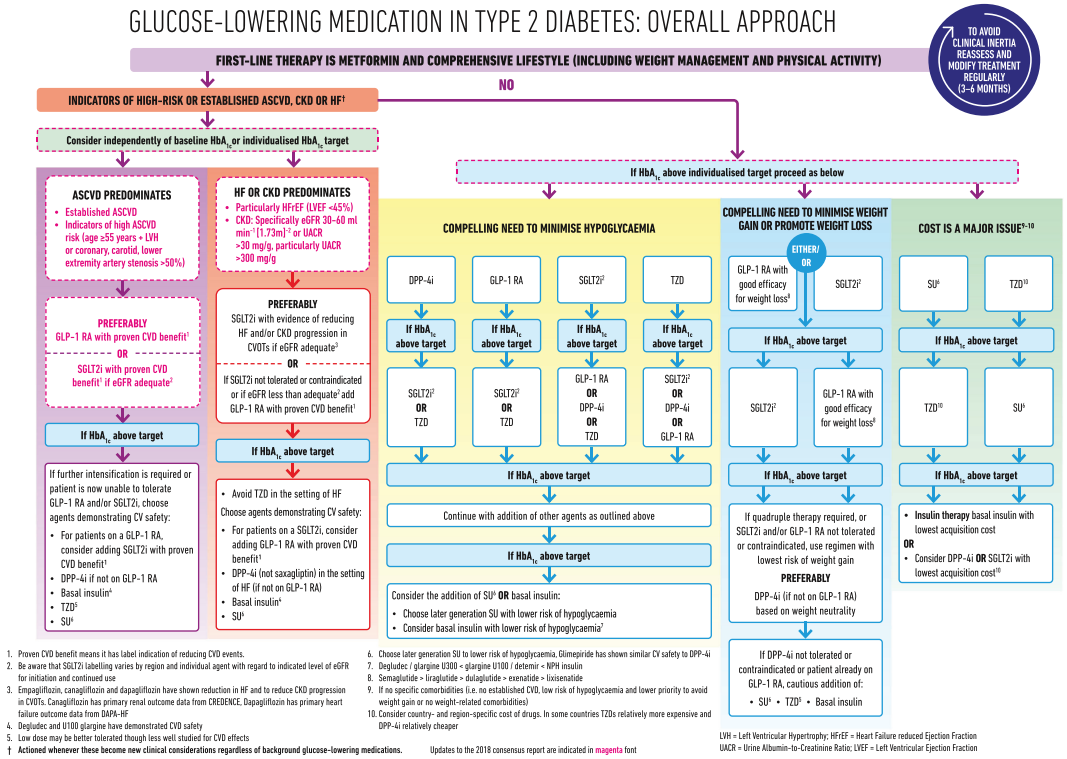


Figure 8.8: Use of glucose-lowering medications in the management of type 2 diabetes.

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, *thiazolidinedione. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786*

Suggested citation: American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S158–S178

ADA+EASD: Pharmacotherapy in treating T2DM: Focusing on the risk of diabetic complications to set treatment options.

1st or initial agent - pharmacotherapy:

Every agent have the potential to reduce but evidences advocate preferential choices.

Start with Metformin (M) lifestyle alteration (LSA) (ADA+EASD). Metformin is effective, safe, inexpensive and widely available. If may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, is weight neutral and does not cause hypoglycemia.

2nd agent - Pharmacotherapy:

Before adding 2nd agent consideration should be given

a. where cardiorenal protection concerns: If there are concerns about cardiorenal protection
b. cardiorenal protection not concerns -ADA+EASD: If there are no concerns....

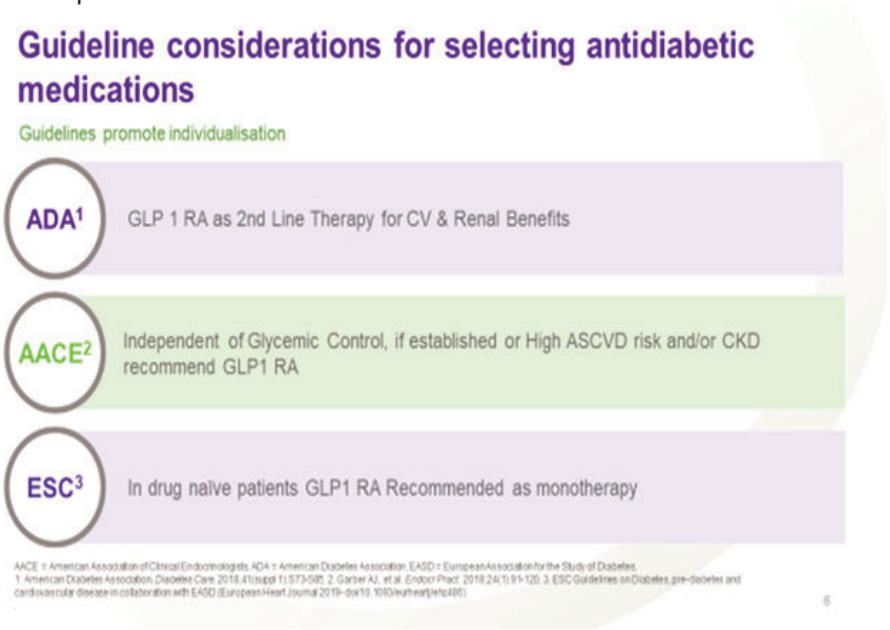


Figure 8.9: Guideline controversies

Assessing risk of diabetes complications

- ASCVD and heart failure, Heart failure with reduced ejection fraction (HFrEF), HFpEF
- ASCVD risk factors HTN, Dyslipidemia CAD and (Framingham 10-year ASCVD risk assessment - (Use ASCVD Risk Calculator **Google)
- Staging of chronic kidney disease (G1, G2, G3a,3b, G4, G5): A1, A2, A3 (**page-)
- Hypoglycemia risk (level 1, Level 2 and severe (**page-)
- Assessment for retinopathy (microsneurysm, non-proliferative, proliferative)
- Assessment for neuropathy: Clinical examination

Drugs with specific effects

- ASCVD/ASCVD risks: LSA+M+GLP1 agonists SGLT2 inhibitors
- ASCVD with HF: SGLT2 inhibitor (if eGFR ≥20)
- Nephropathy: (albuminuria): GLP1 agonists
- Nephropathy: albuminuria + CKD (if eGFR ≥20) and ASCVD: SGLT2 inhibitor
- Albuminuria + CKD (eGFR ≥30) + ASCVD: Finerenon+SGLT2i+GLP1 A

Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should incorporate that support weight management goals

2nd agent: **Pharmacotherapy (if there are no cardiorenal protection) (ADA+EASD)**

- Compelling need to minimise hypoglycemia: SGLT2i, TZD, GLP-1RA
- Compelling need to minimise weight gain or promote weight loss: SGLT2i, GLP1RA.
- SU, TZD

Choice of Pharmacological agents in T2 DM management:

- In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and Semaglutide, the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA Tirzepatide, insulin, combination oral therapy, and combination injectable therapy.
- Weight management is a distinct treatment goal, along with glycemic management, in individuals with type 2 diabetes, as it has multifaceted benefits, including improved glycemic management, reduction in hepatic steatosis, and improvement in cardiovascular risk factors. The glucose-lowering treatment plan should therefore consider approaches that support weight management goals, with Semaglutide and Tirzepatide currently having the highest weight loss efficacy among agents approved for glycemic management. Additional weight management approaches, alone or in combination, should be used if needed to achieve individual goals (i.e., intensive behavioral management programs, weight loss pharmacotherapies, or metabolic surgery.

Special consideration in choosing pharmacotherapy: There is evidence that people with poorly managed hyperglycemia due to type 2 diabetes can also be effectively treated with a sulfonylurea, GLP-1 RA, or dual GIP and GLP-1 RA.

GLP-1 RAs and Tirzepatide have after additional benefits compared to insulin and sulfonylureas, parcularly reducing risk of hypoglycemia (both) and promoting weight (both). They also provide cardiovascular and kidney protective effect.

Essential: One should consider financial obstacles while prescribing. Therefore prescribing sulfonylureas, metformin, thiazolidindions and Human insulin may be advisable.

Metformin: When appropriate metformin is currently the drug of choice in treating patients with type 2 diabetes mellitus (T2DM).

Mechanism of action: Its mechanisms are still elusive. Nevertheless, it lowers blood glucose through multiple mechanisms. First, it inhibits intestinal absorption of glucose. Second, it suppresses glucose production by the liver. Third, it facilitates glucose uptake into tissues, thus reducing blood glucose levels and enabling better health for pancreatic beta-cells. Finally, it improves insulin sensitivity and inflammation. The most accepted action of metformin in T2DM is inhibition of gluconeogenesis and reduction in hepatic glucose output (HGO).

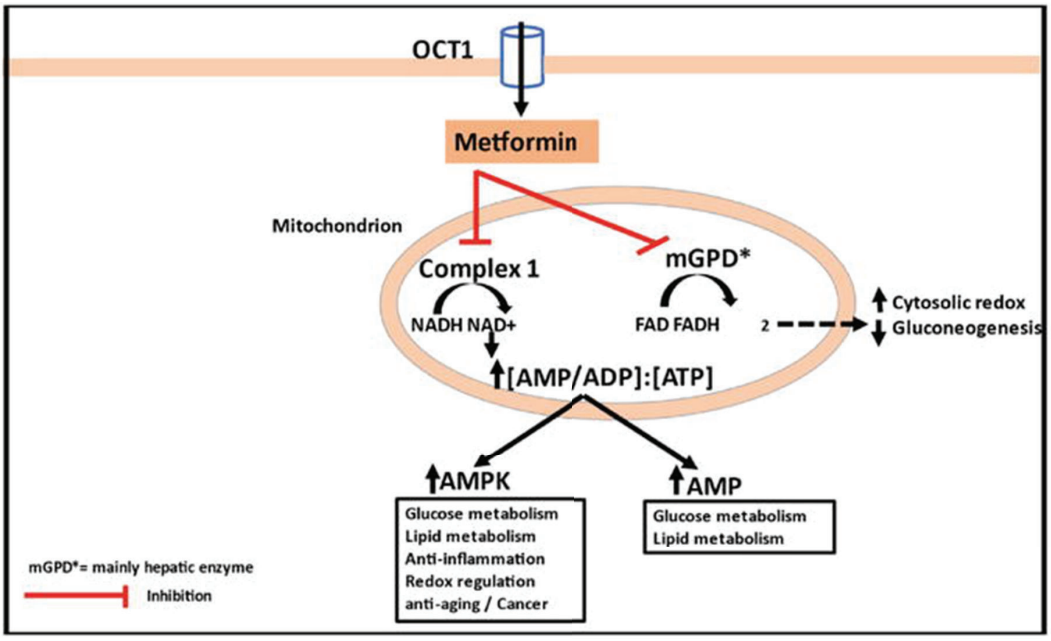


Figure 8.10: Primary molecular mechanism of metformin action

Hawley SA, Ross FA, Chevtzoff C, Green KA, Evans A, Fogarty S, et al. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. Cell Metab 2010; 11:554-565

Side effect of metformin:

- GI effect: The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose *titration*.
- B_{12} & Metformin: A randomized trial confirmed previous observations that metformin use is associated with vitamin B_{12} deficiency and worsening of symptoms of neuropathy suggesting periodic testing of vitamin $B_{12.}$

Metformin and kidney disease: FDA

The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare. The revised FDA guidance states that:

1. Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2,
2. eGFR should be monitored while taking metformin,
3. The benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2
4. Metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m^2, and
5. Metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m^2.

Sulfonylurea:

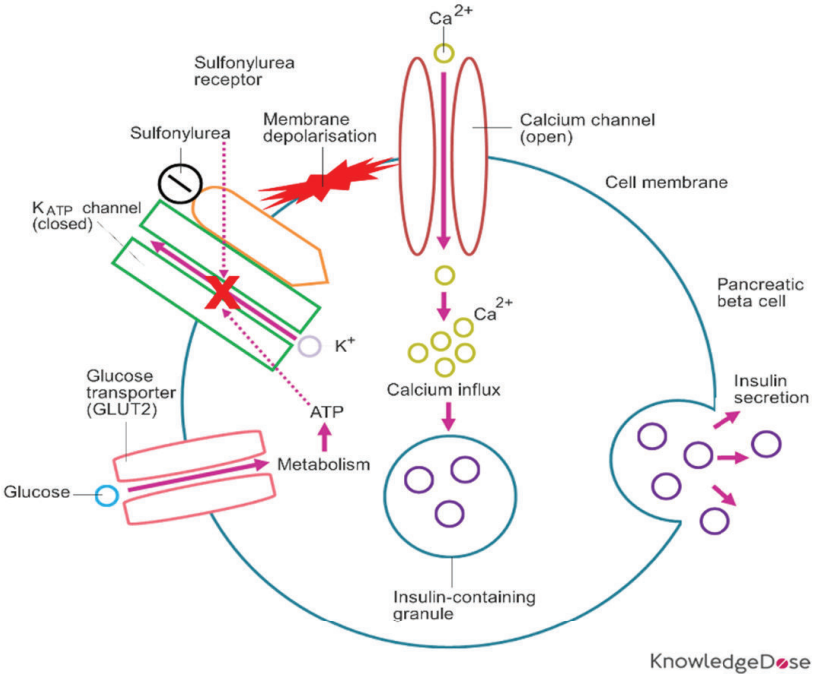


Figure 8.11: Schematic representation of sulfonylureas and their site of action

1) A sulfonylurea binds to the sulfonylurea receptor.
2) The closing of the KATP channels inhibits the efflux of potassium ions through the KATP channels resulting in membrane depolarisation.
3) Membrane depolarisation opens the calcium channels in the cell membrane of the pancreatic beta cell allowing the influx of calcium ions through the calcium channels.
4) The calcium concentration inside the pancreatic beta cell increases, leading to the exocytosis of insulin-containing granules

09
CHAPTER

Insulin

Insulin Therapy of Diabetes Mellitus:

Summary:

1. Insulin and injectable form of GLP-A, GIP: Insulin more effective than other agents and should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features such as weight loss, hypertriglyceridemia, ketosis are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels ≥300 mg/dL (≥16.7 mmol/L) or A1C >10% (>86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) .
2. As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is often possible.It is irrespective of disease stage or ongoing medication
3. Ongoing glucose lowering agents may be continued with insulin unless contraindicated or not tolerated.
4. To minimise hypoglycemia risk reassessment of the need for or dose of glucose lowering agents should be done (sulfonylurea, meglitinides having higher hypoglycemia risks)
5. Signs of over-basalization to be monitored (over-basalization).
   i. Basal dose exceeding 0.5 units/kg/day
   ii. Significant bedtime to morning or postprandial to preprandial glucose differential
   iii. Occurences of hypoglycemia
   iv. Huge glycemic variability

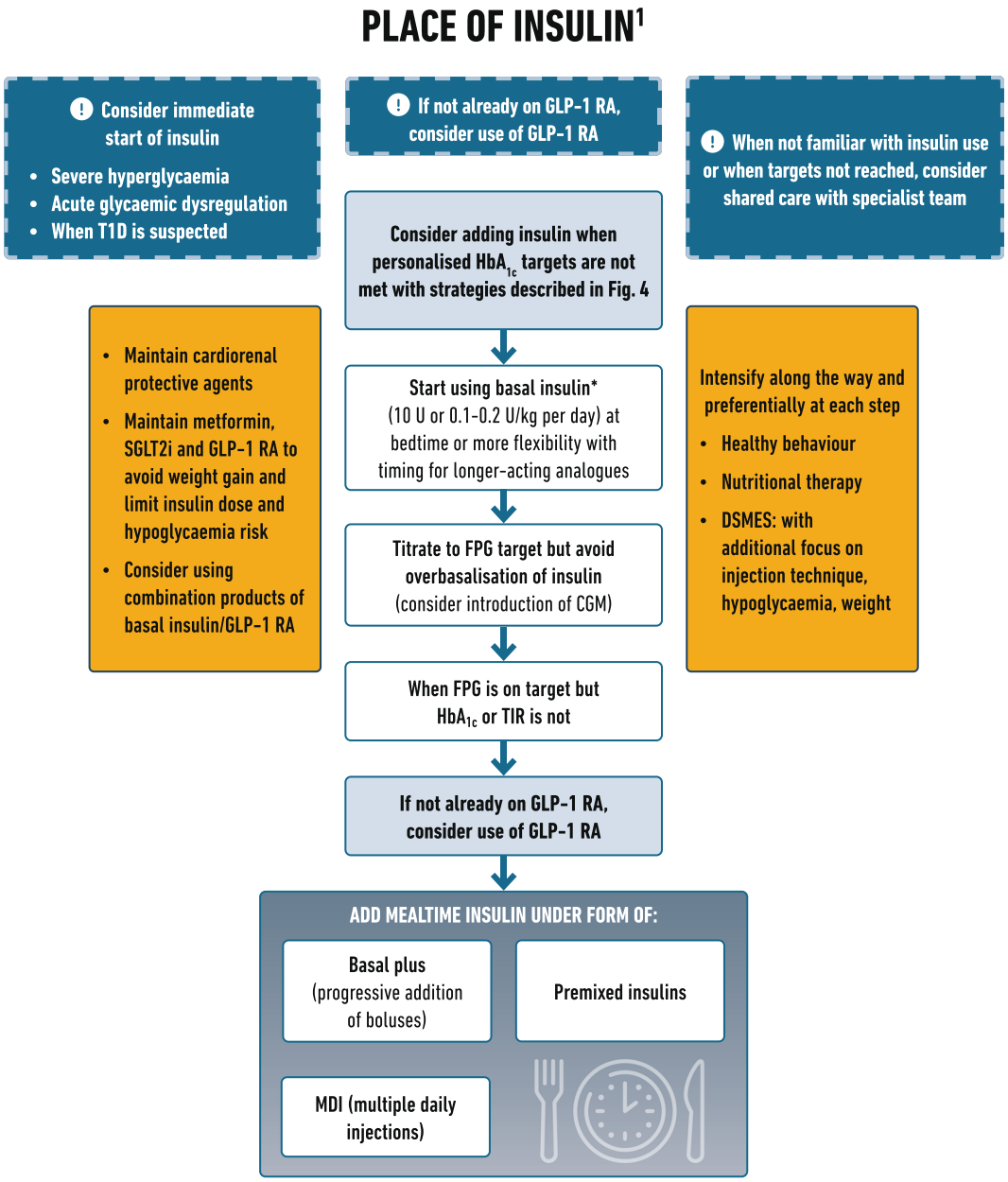


Figure 9.1: Insulin in diabetes management

Insulin in diabetes management:

Figure 9.2: INSULIN : HISTORY

Summary:

Insulin is at the center (heart) of diabetes management. Many adults with type 2 diabetes eventually require and benefit from insulin therapy. May be used as single agent or dual agent. May be subcutaneous, intramuscular and intravenous. May have an effect long-term, short-term used emergency uses. May be used in combination of any other anti-diabetic agents except sulphonylurea and DPP4 inhibitors. Insulin can reduce any level of blood glucose. There is no particular regimen or protocol for insulin use. Injection phobia, weight gain and hypoglycemia are main obstacles of insulin use. When needed, can be use at drug one unit/kg which is considered as a physiological approach to arrange hyperglycaemic

Basal insulin

Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals. Attainment of fasting glucose goals can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 Glargine or Detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin. Longer-acting basal analogs (U-300 Glargine or Degludec) convey a lower nocturnal hypoglycemia risk compared with U-100 Glargine.

Overbasalization:
Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ~ 0.5 units/kg, high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy.

Prandial insulin

For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin plan can then be intensified based on individual needs. Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia. Titration can be based on home self-monitored blood glucose or CGM. When significant additions to the prandial insulin dose are made, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia. If an individual is not already being treated with a GLP-1 RA or dual GIP and GLP-1 RA, a GLP-1 RA (either as an individual product or in a fixed-ratio combination with a basal insulin product) or dual GIP and GLP-1 RA should be considered prior to prandial insulin to further address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above goal, consider advancing to combination injectable therapy. This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin.

Intensification of insulin treatment can be done by adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and

effective, and it can be advanced to a plan with multiple prandial doses if necessary. Alternatively, for an individual on basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meal(s) is not feasible, the medication plan can be converted to two doses of a premixed insulin.

When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RA (or dual GIP and GLP-1 RA) should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued

Combination Therapy (OHA+Injection)

Traditional recommendations have been to use stepwise addition of medications to metformin to maintain goal A_1C. However, there are data to support initial combination therapy for more rapid attainment of glycemic goals and later combination therapy for longer durability of glycemic effect

- The initial combination therapy the metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor is superior to sequential addition of medications for preventing primary and secondary failure . Initial combination therapy should be considered in people presenting with A_1C levels 1.5–2.0% above target goal.
- Incorporating high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (*e.g.,* GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may allow for weaning of the current medication plan, particularly of agents that may increase the risk of hypoglycemia and weight gain.

Thus, treatment intensification may affect a tailoring of the medication plan in alignment with person-centered treatment and the pursuit of multifaceted health objectives.

- The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes.
- The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent medication plans is a well-established approach that is effective for many individuals.
- Utility of GLP-1 RAs in people not attaining their glycemic goals. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available).

Treatment intensification, deintensification, or modification—as appropriate should not be delayed. Shared decision-making is important in discussions regarding treatment change.

Important clinical characteristics include the presence of overweight or obesity, established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, hypoglycemia, and risk for specific adverse drug effects, as well as safety, tolerability, accessibility, usability, and cost.

Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents added to initial therapy with metformin generally lowers A_1C approximately 0.7–1.0% (8–11 mmol/mol); if a GLP-1 RA or the dual GIP and GLP-1 RA is added, a 1 to ≥2% lowering in A1C is expected.

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-300 glargine and U-200 Degludec are three and two times as concentrated as their U-100 formulations, respectively. U-They have similar onset but a delayed, blunted, and prolonged peak effect and longer duration of action compared with U-100 regular insulin; thus, it has characteristics more like a premixed intermediate-acting (NPH) and regular insulin product and can be used as two or three daily injections and allow higher doses of basal insulin administration per volume used. These concentrated preparations may be more convenient (fewer injections to achieve target dose) and comfortable (less volume to inject target dose and/or less injection effort) for individuals and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin.

Table 9.1 Currently Available Injectable Hypoglycemic Drugs Other than Insulin to Treat Type 2 Diabetes

General Class Compound/Brand Name	Generic Available	Dose Range	Cost
GLP-1 Receptor Agonist			
Exenatide/ Byetta**	No	5-10mcg bid	High
Exenatide/ Bydureon**	No	2mg once weekly	High
Liraglutide/ Victoza**	No	0.6-1.8mg qd**	High
Albiglutide/ Tanzeum*	No	30-50mg once weekly	High
Dulaglutide/ Trulicity	No	0.75-4.5mg once weekly	High
Lixisenatide/ Adlyxin **	No	10-20mcg qd	High
Semaglutide/ Ozempic/other	No	0.25-2.0mg once weekly	High
Dual GLP-1 Receptor/GIP Receptor Agonists			
Tirzepatide/ Mounjaro/other	No	5mg-15mg once weekly	High

** Not available in the market

Table 9.2 Insulin options

Insulin type	How it is Delivered	Expiration date	Onset	Peak	Duration
Rapid Acting					
Admelog	Pens and vials	28 days	15-30 min	30 min-2 ½ hrs	4-5 hours
Afrezza inhaled powder	4, 8 and 12 unit Cartridges	3 days	3-7 min	12-15 min	1%-3 hours
Apidra	Vials and pens	28 days	10-20 min	30 min-1 ½ hrs	2-4 hours
Flasp	Vials and pens	28 days	15-20 min	14-2 hours	5 hours
Humalog, U-100 and U-200	Vials, pens and cartridges refills	28 days	10-20 min	30 min-1/12 hrs	3-5 hours
Novolog	Vials, pens and cartridges refills	28 days	10-20 min	1-3 hours	3-5 hours
Short Acting **					
Regular	Vials and pens (varies by brand)	31-42 days	15-30 min	2 ½ hrs	4-12 hrs
U-500 (5x the concentration)	Vials and pens (varies by brand)	28 days	30 min	4-8 hours	18-24 hrs
Intermediate Acting					
NPH (created in 1946)	Vials and pens	31-42 days	1-2 hours	4-12 hours	14-24 hrs
Long Acting					
Basaglar	Vials and pens	28 days	3-4 hours	No peak+	11-24 hrs
Lantus	Vials and pens	28 days	3-4 hours	No peak+	11-24 hrs
Levemir	Vials and pens	42 days	3-4 hours	No peak+	6-23 hrs
Toujeo, U-300	Pen only	42 days	6 hours	No peak	24-36 hrs
Tresiba, U-100 and U-200	Pen only	56 days	1 hour	9 hours	36-42 hrs
Combination					
NPH/Regular 70/30	Vials and pens	31-42 day vial 10 day pen	30 min	50 min-2 hrs 6-10 hrs	18-24 hrs
Rapid acting 70/30	Vials and pens	28 day vial 14 d pen	15-30 min	1-4 hours	18-24 hrs
Rapid acting 75/25	Vials and pens	28 d vial 10 d pen	15-30 min	1-6% hours	12-24 hrs
Rapid acting 50/50	Vials and pens	28 d vial 10 d pen	15-30 min		

**Both short- and intermediate-acting insulin can be purchased without a prescription at most pharmacies. This is a good option in an emergency; be sure to ask your healthcare provider what option is best. + May affect blood glucose the most ~8-10 hours after being taken.

Evolution of Insulin

A. Devices of delivery
B. Molecular modification

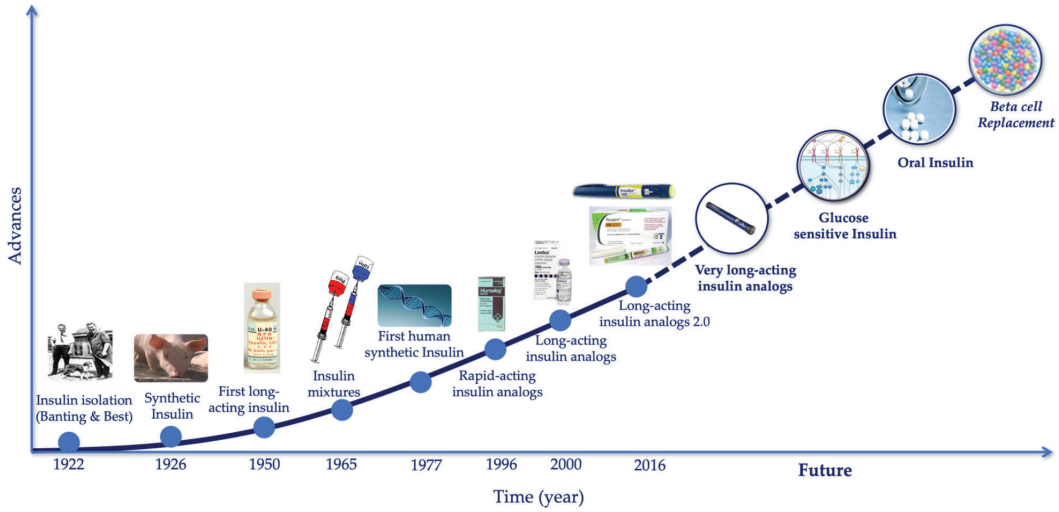


Figure 9.3: Evolution of insulin -summary

Suggested citation: American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S158–S178

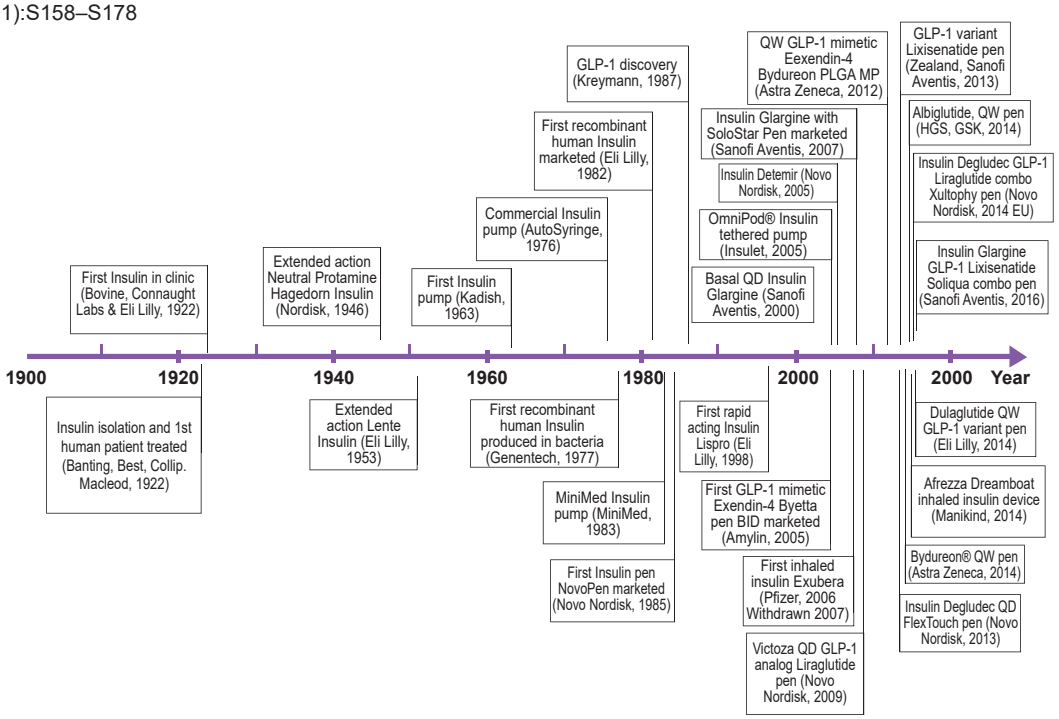


Figure 9.4: Molecular evlution of insulin

Insulin Delivery

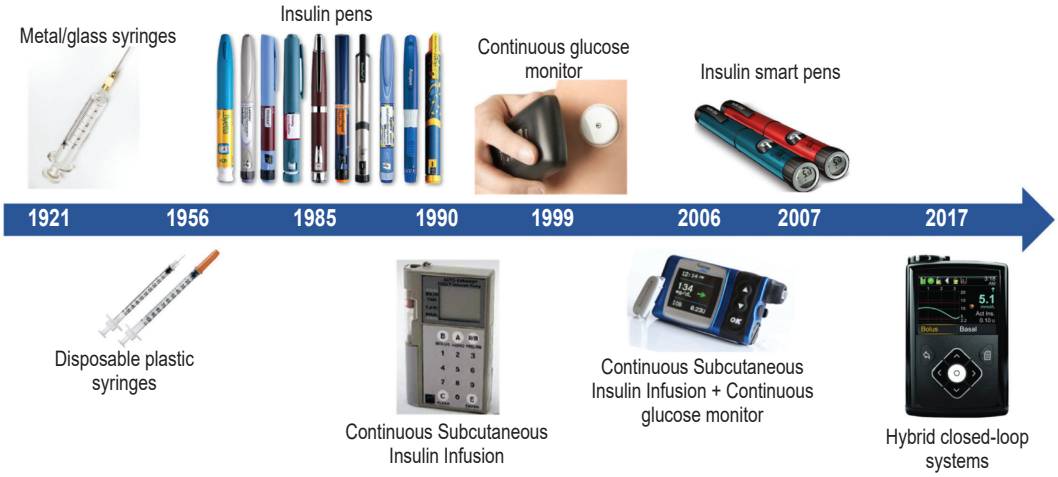
Summary

- Syringe,vials:Many people on MDI still comfortably use it and prefer it.Cost benefit is the main reason.Insulin injection aids dexterity issues for vision impairment
- Pen/devices: For people with insulin-requiring diabetes on MDI, insulin pens are preferred .Comfort of injection and easy carrying may be the choice. Administration devices provide some additional benefit.
- Connected insulin pens: Connected insulin pens can be helpful for diabetes management and may be used in people with diabetes taking subcutaneous insulin.
- Pump: use insulin pumps or AID devices: Insulin pumps have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage glucose levels.
- Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach(insulin patch) directly to the skin without tubing.
- Smart insulin patch(glucose responsive insulin): An adhesive patch loaded with insulin can help control glucose levels.
- iLet bionic artificial pancreas: a single device sense, calculate and deliver, insulin.It uses AI apps.Just putting the single data of weight one can get all the action.
- Artificial pancreas supplying both insulin and glucagon; hence there should not be any hypoglycemia
- Inhaled insulin can be useful in people who have an aversion to injection.
- Oral insulin:Oral insulin as tablet or chocolate may be used for human testing in 2025.
- *Individual preferences, cost, insulin type, dosing therapy, and self-management capabilities should be considered when choosing among delivery systems.*
- Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach(insulin patch) directly to the skin without tubing.
- Dose calculators: FDA-approved insulin dose calculators/decision support systems may be helpful for calculating insulin doses

Syringes: The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units, respectively, of U-100 insulin. Some 0.3-mL syringes have half-unit markings, whereas other syringes have 1- to 2-unit increment markings., and U-500 syringes are available for the use of U-500 insulin

Pen: Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, ranging from half-unit doses to 2-unit dose increments, with the latter available in U-200 insulin pens. U-500 pens come in 5-unit dose increments.

Needles: Needle thickness (gauge) and length are lequid considerations. Needle gauges range from 22 to 34, with a higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting that shorter needles (4–5 mm) lower the risk of intramuscular injection with erratic absorption and possibly the development of lipohypertrophy. When reused, (better not to use mor than 3 days), needles may be duller, making injections become more painful.



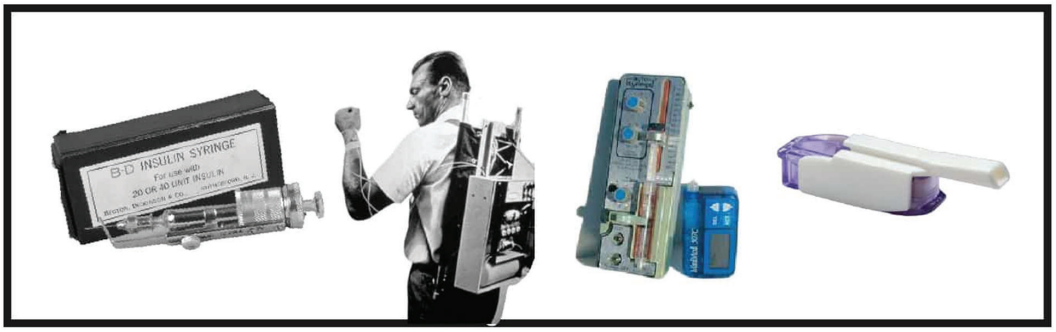


Figure 9.5: Evolution of insulin delivery system

https://americanhistory.si.edu/collections/search/object/nmah_730844

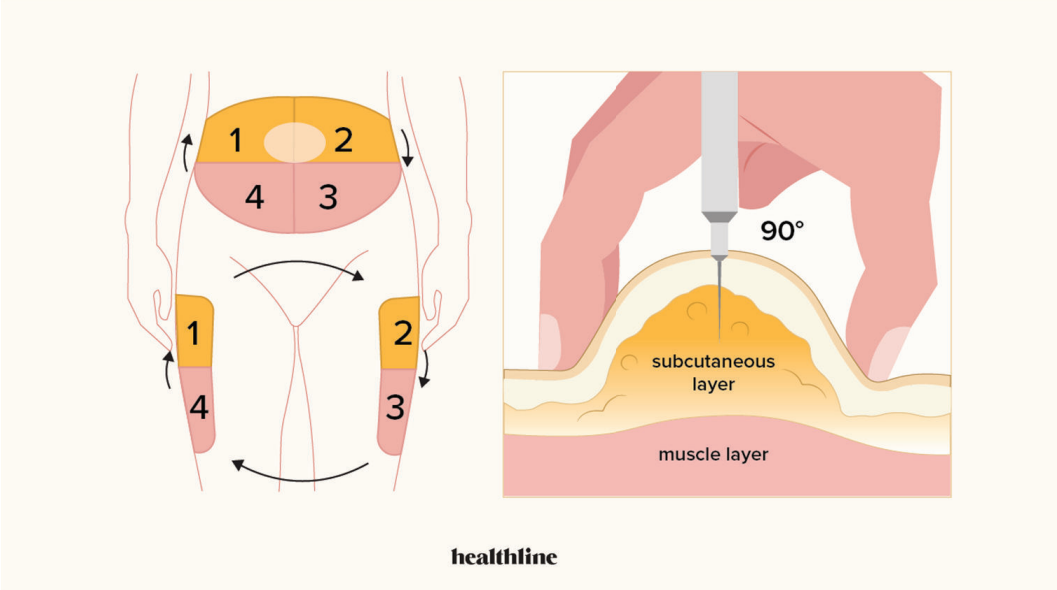


Figure 9.6: Steps of insulin injection

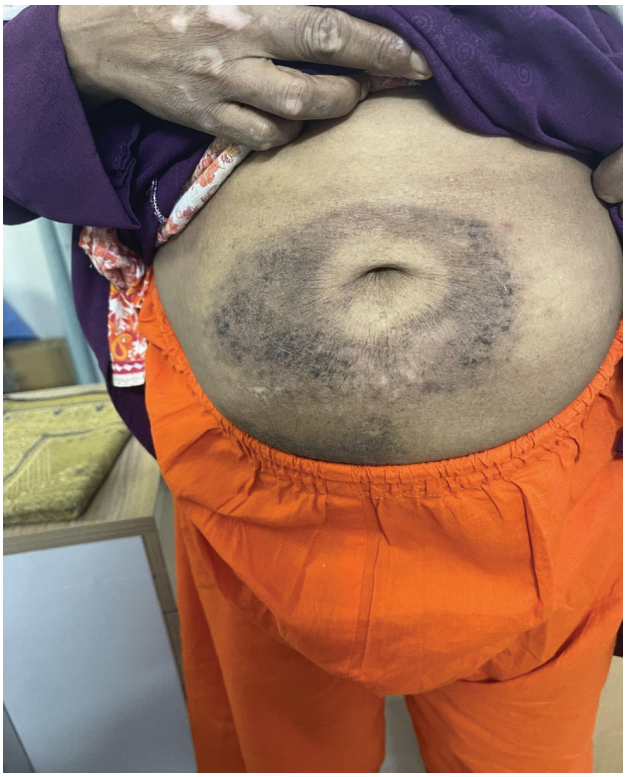


Figure 9.7: Faulty technique of insulin injection

Insulin dose:≤ one unit/Kg :physiological dose ie if 74 units is pushed,effect of 74 units will be obtained..>one unit/Kg pathological dose;ie if 74 unit is pushed obtained effect may be 70 unit or like that.

When some body is taking very high dose but blood glucose is not optimum faulty technique like picture need to be explored

Storage and transport of insulin is another faulty aspect;insulin should be transported in cool chain

Use of 40u/ml syringe for 100 u/ml insulin or 100u/ml injection syringe for 40u/ml insulin.

- A low C-peptide value should not be .....before stopping the insulin pump individuals with type 2 diabetes.
- Individuals with diabetes who have been using CSII should have continued access education, training and intermittent use of SMBG

Quest of physiological insulin delivery

Insulin Pumps

a.Sensor-Augmented Pumps

Sensor-augmented pumps (or partial closed-loop systems) consist of three components: an insulin pump, a CGM system, and an algorithm

1. Sensor- augmented pumps automates insulin suspension :Sensor-Augmented Pumps automates insulin suspension when glucose is low.

2. Sensor-Augmented Pumps automates insulin suspension when glucose is predicted to go low glucose is predicted to go low within the next 30 min.

Both these systems have been approved by the FDA.

These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia.

Thus it acts physiological insulin in body circulation when glucose is low with insulin or less insulin which sugar of insulin when blood glucose levels are high.

Clinical pearls

- Pump therapy can be successfully started at the time of diagnosis
- The safety of insulin pumps in youth has been established for over 15 years.Insulin pumps may be considered in all children and adolescents with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age
- Systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C levels (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults.

Inconveniences of pumps:

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden.

Complications of the pump can be caused by issues with infusion sets (dislodgement and occlusion), which place individuals at risk for ketosis and DKA and thus must be recognized and managed early.

Other pump skin issues include lipohypertrophy or, less frequently, lipoatrophy and pump site infection

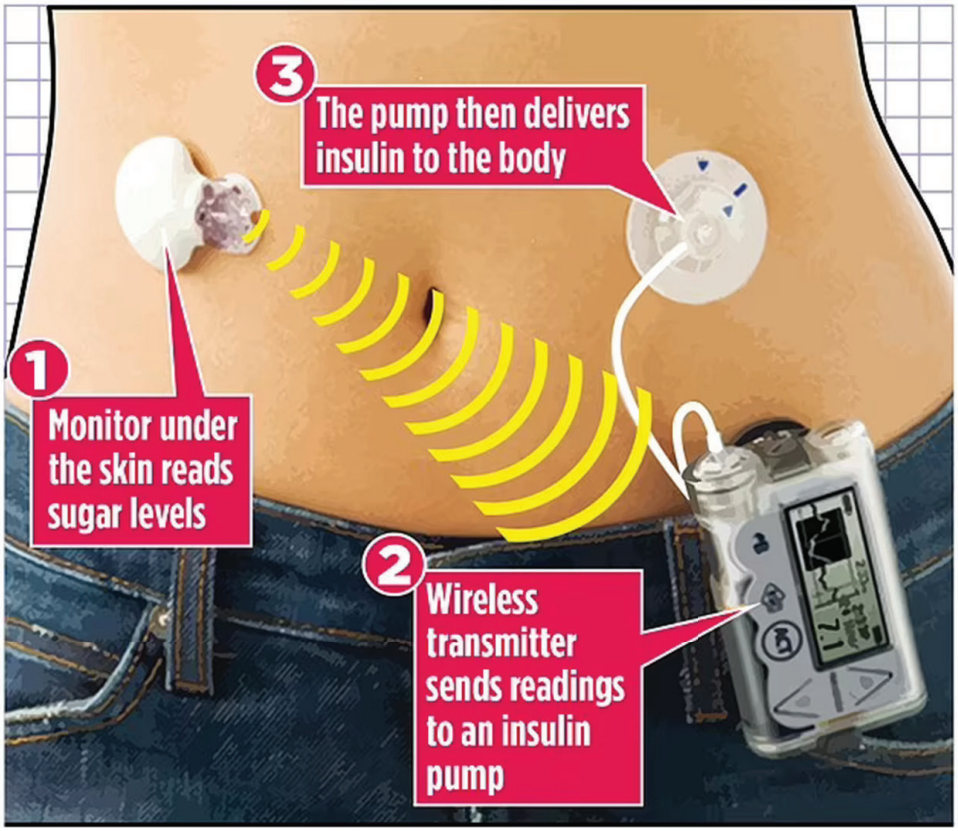


Figure 9.8: Insulin pump with tubing

Artificial pancreas: how does it work?

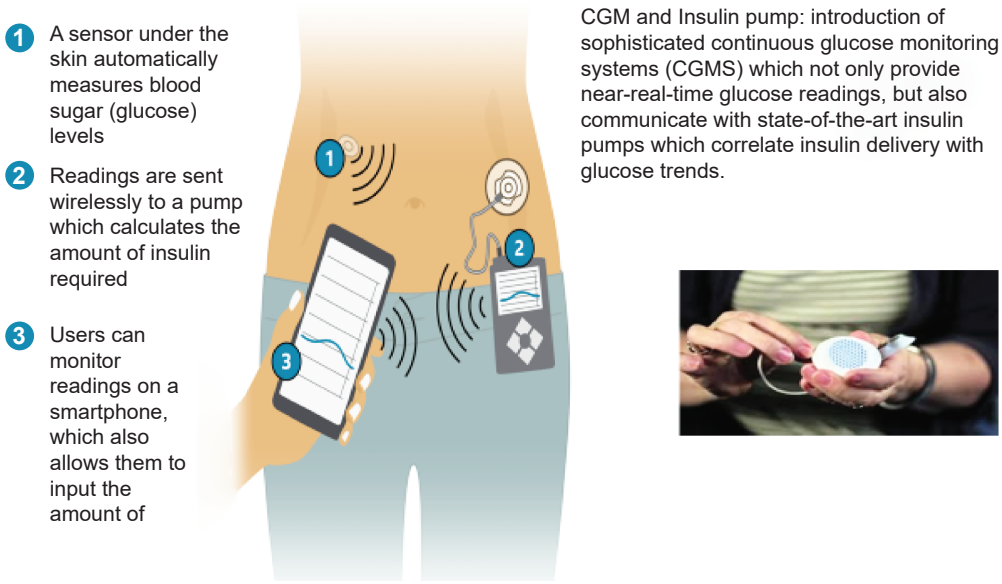


Figure 9.9: CSII (schematic)

Insulin pump (CSII-Continuous Subcutaneous Insulin Infusion): Those devices include continuous insulin pumps (programmable basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin.

Automated Insulin Delivery Systems (Closed loop pump)

AID systems are made up of a CGM, an insulin pump, and a smart algorithm that links the two devices together, allowing them to “talk” to each other. The CGM tracks your sugar levels every few minutes through a small sensor inserted under the skin.

AID systems increase and decrease insulin delivery based on sensor-derived glucose levels to mimic physiologic insulin delivery.

AID systems, which can adjust insulin delivery rates based on sensor glucose values and set algorithm are preferred over nonautomated pumps and MDI in people with type 1 diabetes.

The Omnipod 5 Automated Insulin Delivery System an Artificial Pancreas? Omnipod 5 is a hybrid closed-loop system, which automatically adjusts basal insulin with the user manually delivering bolus insulin to cover meals.

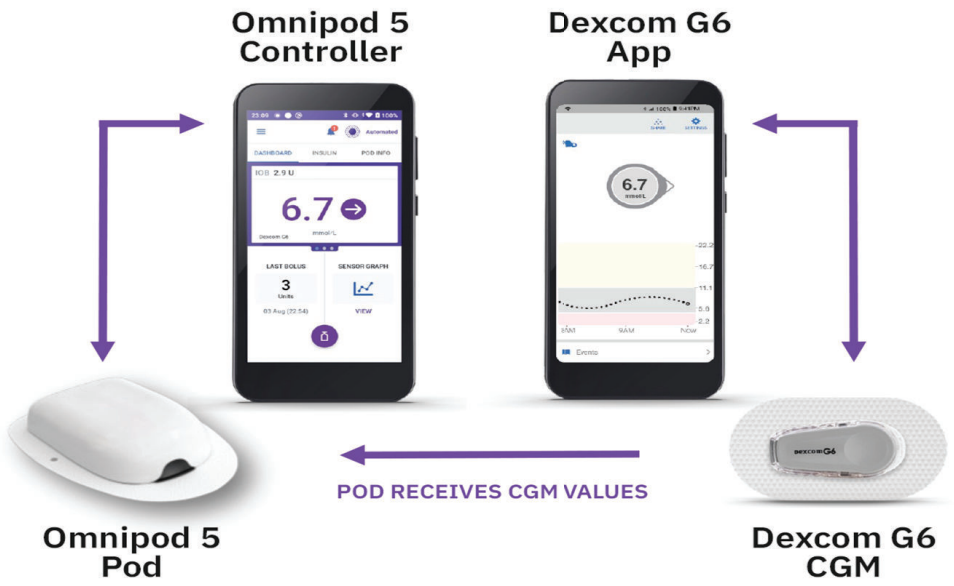


Figure 9.10: An automated insulin delivery (AID) (closed loop pump, non tube)

All AID systems on the market today adjust basal delivery in real time, and some deliver correction doses automatically.

While insulin delivery in closed-loop systems eventually may be truly automated, currently used AID systems require the manual entry(hybrid) of carbohydrates consumed or qualitative meal estimation announcements to calculate prandial doses, and adjustments for physical activity must be announced in most systems

The use of AID systems in diabetes and pregnancy presents particular challenges, as none of the current FDA-approved systems have glucose goals that are pregnancy specific or algorithms designed to achieve pregnancy-specific glucose goals.

Figure 9.11: AID system (Automated insulin delivery system & smart sensor)

Figure 9.12: InPen™ smart insulin pan

GuardianTM connect CGM
i-Port Advance™ injection port

Insulin smartpen: A smart insulin pen is a reusable injector pen with an intuitive smartphone app that can help people with diabetes better manage insulin delivery. This smart system calculates and tracks doses and provides helpful reminders, alerts, and reports. They can come in the form of an add-on to your current insulin pen or a reusable form which uses prefilled cartridges instead of vials or disposable pens. The first insulin pen devices were introduced in the late 1980s as an alternative to vials and syringes. They allowed for more accurate dosing, better adherence, and less injection site pain. As these devices evolved, they gained digital displays and memory of the most recent insulin doses. Eventually, data tracking “caps” or attachments were developed to help disposable insulin pens keep better track of doses. Glucose sensing, continuous glucose monitoring, dosage timing, reminders, and other advancements followed. The first Food and Drug Administration (FDA)–cleared reusable smart insulin pen was launched in 2017.

A smart insulin pen can: Calculate each dose based on current blood glucose level, carbohydrate amounts, meal size, active insulin, and settings prescribed by your doctor.

- Deliver accurate half-unit doses.
- Help prevent skipped or missed doses.

- Do the math for you when figuring out how to dose for a meal or correct a high blood glucose reading.
- Keep track of the time and amount of each dose, and remind you when it's time for the next one.
- This can avoid insulin "stacking"—
- Notify you when your insulin has expired or exceeded its temperature range, so you can replace the cartridge.
- Send diabetes data to your health care team whenever needed.
- Work with your smartphone or watch and popular diabetes data tracking platforms.

Inhaled insulin: In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to RAA. Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with the RAA insulin lispro, as well as clinically meaningful A1C reductions and weight reductions compared with the RAA insulin aspart over 24 weeks. Use of inhaled insulin may result in a decline in lung function. Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in individuals who smoke

Smart insulin patch: described in Nature Biomedical Engineering in 2020 Combination therapy;

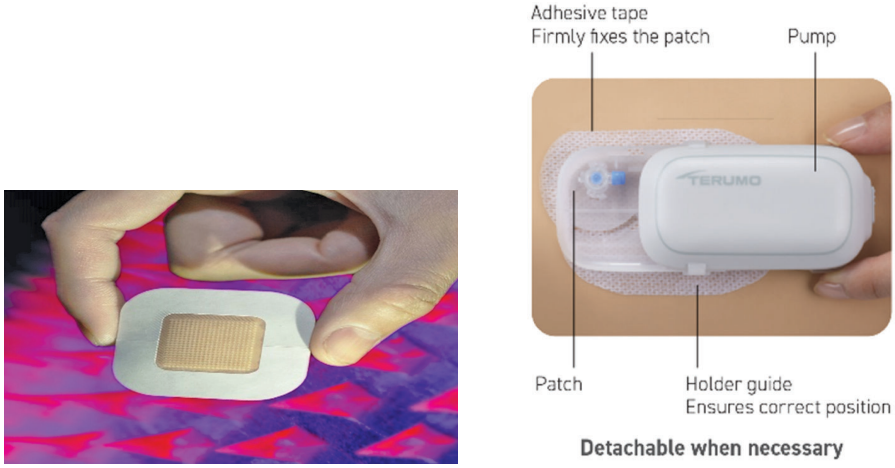


Figure 9.13: Smart Insulin Patch Automatically Manages Glucose Levels

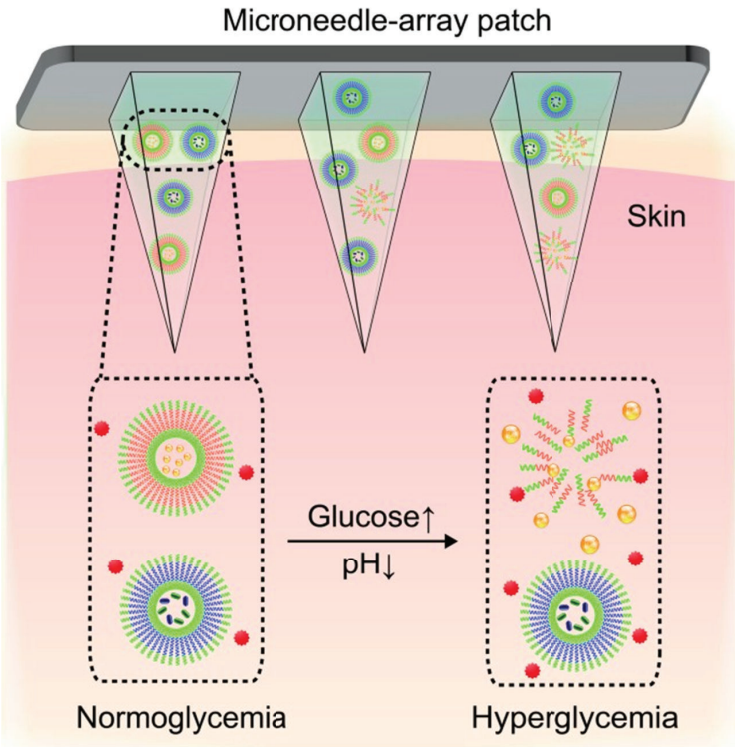


Figure 9.14: Microneedle of patch

Image: An adhesive Patch loaded with insulin can help control glucose levels. (Photo courtesy of Zhen Gu/ UNC)

A single use, removable transdermal patch bearing microneedles loaded with insulin can help monitor and manage glucose levels in diabetics, according to a new study.
the adhesive patch is made of glucose-responsive polymeric matrix, fabricated using photo-polymerization, which incorporates tiny microneedles (less than one mm long) that are pre-loaded with insulin. Once applied, the microneedles penetrate about one-half millimeter below the skin, enough to sense blood sugar levels. In studies to test blood glucose regulation in insulin-deficient diabetic mice and mini-pigs, a one quarter-sized patch successfully controlled glucose levels for about 20 hours. The patch works due to multiple phenylboronic acid units within the polymeric matrix that reversibly form glucose–boronate complexes that due to their increased negative charge, induce the swelling of the polymeric matrix and weakening the electrostatic interactions between the negatively charged insulin and polymers, thus promoting the rapid release of insulin. If the matrix senses glucose levels going up, the polymer is triggered to release insulin; when blood sugar eventually returns to normal, the patch's insulin delivery also slows down. The study was published on February 3, 2020, in Nature Biomedical Engineering.

10
CHAPTER

Blood Glucose Monitoring

Glycemic status is assessed by self blood glucose monitoring (SMBG) with capillary (finger-stick) blood glucose measurement by glucometer, A1C measurement, and continuous glucose monitoring (CGM) using time in range (TIR) with real time CGM(rt CGM)or Intermittant /Flash (IsCGM) glucose.

SMBG: People with diabetes should be provided with blood glucose monitoring (SMBG) devices as indicated by their circumstances, preferences, and treatment. People using CGM devices must also have access to BGM at all times. People who are taking insulin and using BGM should be encouraged to check their blood glucose levels when appropriate based on their insulin therapy.

Healthcare professionals and meter users should be aware of the differences in accuracy among blood glucose meters. Only meters approved by the U.S. Food and Drug Administration (FDA) (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired test strips purchased from a pharmacy or licensed distributor and properly stored.

Although SMBG in people on noninsulin therapies has not consistently shown clinically significant reductions in A1C levels, it may be helpful when altering meal plans, physical activity plans, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program.

Healthcare professionals should be aware of medications and other factors that can interfere with glucose meter accuracy and provide clinical management as indicated.

SMBG is thus an integral component of effective therapy for individuals using insulin. In recent years, CGM has emerged as a method for the assessment of glucose levels (discussed below). The specific needs and goals of the person with diabetes should dictate SMBG frequency and timing or the consideration of CGM use.

Glycemic Assessment by A_1C

A_1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether glycemic goals have been reached and maintained. Adults with type 1 diabetes or type 2 diabetes with stable glycemia within goal may do well with A1C testing or other glucose assessment only twice per year.

A_1C does not provide a measure of glycemic variability or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic status is best evaluated by the combination of results from SMBG or CGM and A_1C.

Conditions that affect red blood cell turnover (hemolytic anemia and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) can interfere with the accuracy of A_1C (6) A_1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (8).

Serum Glycated Protein Assays as Alternatives to A1C

Fructosamine and glycated albumin are alternative measures of glycemia that are approved for clinical use for monitoring glycemic status in people with diabetes. Fructosamine reflects total glycated serum proteins (mostly albumin). Glycated albumin assays reflect the proportion of total albumin that is glycated. Due to the turnover rate of serum protein, fructosamine and glycated albumin reflect glycemia over the past 2–4 weeks, a shorter-term time frame than that of A_1C.

Colorimeter

Glucometer

CGM /FGM

Figure 10.1: Blood glucose monitoring meter

Figure 10.2: CGM smartwatch,wearable transmitter

Having to prick finger several times a day to check glucose level is one of the painful experiences diabetics have to endure every day. The advent of wearable technology is inspiring medtech firms to develop various Continuous Glucose Monitoring (CGM) systems. FDA recently approved the first automated insulin system for Type 1 diabetics. Now, French biomedical company PKvitality has come up with a different solution; they've invented a CGM smartwatch.

Correlation Between A_1C and Blood Glucose Monitoring and Continuous Glucose Monitoring:

Table 10.1 Equivalent A1C levels and estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG.*These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92. *Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478*

Glycemic Assessment by Blood Glucose Monitoring (BGM)

Glycemic Assessment by Continuous Glucose Monitoring CGM: CGM measures interstitial glucose (which correlates well with plasma glucose, although at times, it can lag if glucose levels are rising or falling rapidly). Key points included in a standard ambulatory glucose profile (AGP) report.

Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625 .

Standardized, single-page glucose reports from CGM devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices.

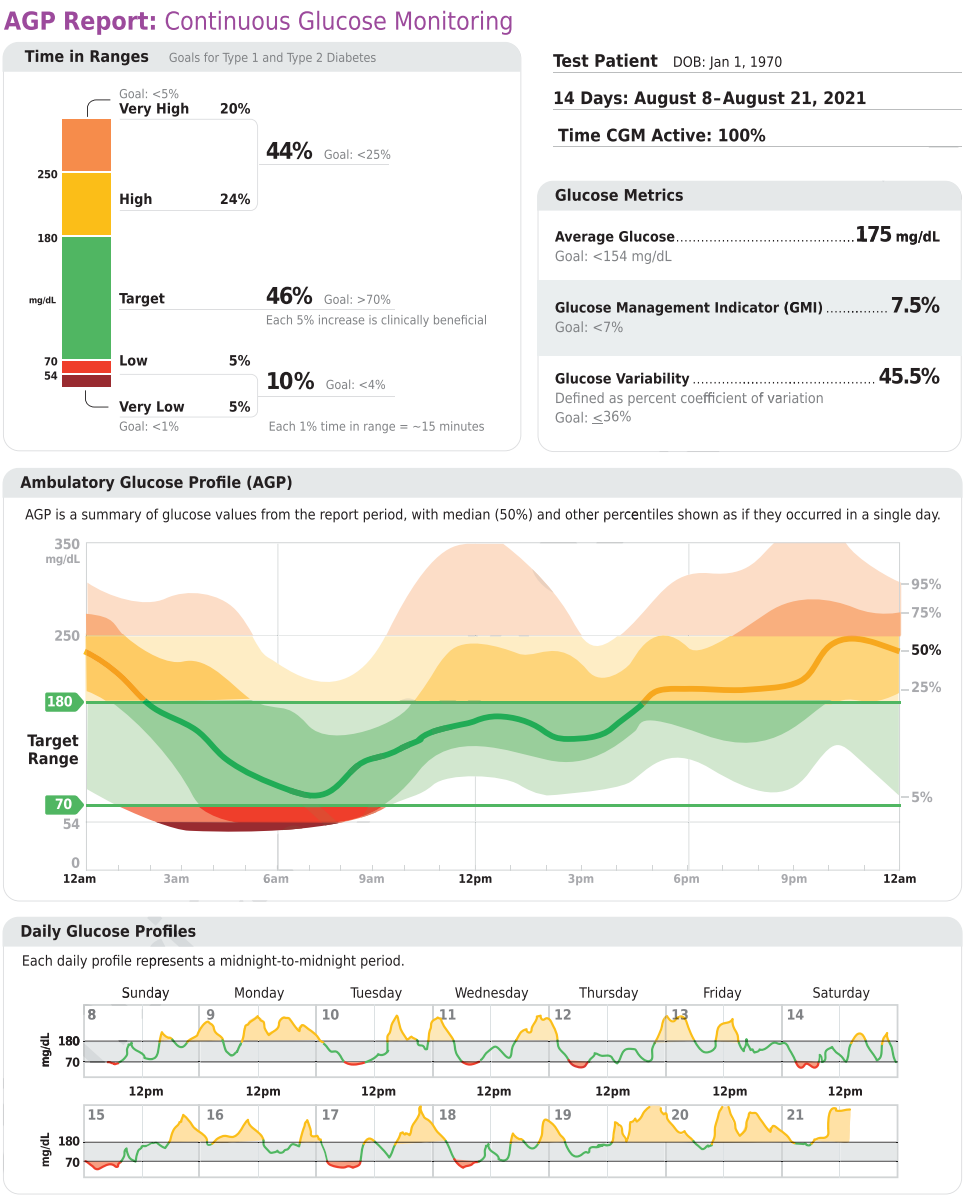


Figure 10.3: ambulatory glucose profile (AGP) report.

Time in range (TIR) can be used for assessment of glycemic status. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan. A 10- to 14-day CGM assessment of TIR, with CGM wear of 70% or higher, can be used to assess glycemic status and is useful in clinical management. TIR, especially mean CGM glucose, correlates with A_1C. Time below range (<70 and <54 mg/dL [<3.9 and <3.0 mmol/L]) and time above range (>180 mg/dL [>10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

Key points included in a standard ambulatory glucose profile (AGP) report. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625 Holt et al.

Table 10.2 Standardized CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
1. Number of days CGM device is worn		14-day wear for pattern management
2. Percentage of time CGM device is active		70% of data from 14 days
3. Mean glucose	Simple average of glucose values	*
4. Glucose management indicator	Calculated value approximating A1C (not always equivalent)	*
5. Glycemic variability (%CV) target	Spread of glucose values	≤36%‡
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia	<5% (most adults); <10% (older adults)
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia	<25% (most adults) ; <50% (older adults)‡
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range	>70% (most adults) ; >50% (older adults)
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia	<4% (most adults) ; <1% (older adults)§
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range Goals is for level 1 and level 2 hyperglycemia combined. § Goals are for level 1 and level 2 hypoglycemia combined. *Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603*

CGM systems have evolved rapidly in both accuracy and affordability. Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR.

General Device Principles

- Initiation of continuous glucose monitoring (CGM) should be offered to people with type 1 diabetes early in the disease, even at the time of diagnosis.
- The type(s) and selection of devices should be individualized using CGM, , CSII, connected insulin pens, and AID

  Initiation of CSII and/or AID early, even at diagnosis, in the treatment of diabetes can be beneficial depending on a person's or caregiver's needs and preferences.

Technology is rapidly changing, but there is no one-size-fits-all approach to technology use in people with diabetes. In such situations, training is vital and should include a discussion about realistic expectations for the ability of the initiated system to achieve glucose goals, the system's features and limitations, and the best way to utilize the new system to maximize the benefits it can offer

Blood glucose monitoring

People with diabetes should be provided with blood glucose monitoring (SMBG) devices as indicated by their circumstances, preferences, and treatment. People using CGM devices must also have access to SMBG at all times.

Glucometer-SMBG:This may include checking when fasting, before to meals and snacks, after meals, at bedtime, in the middle of the night, before to, during, and after exercise, when hypoglycemia is suspected, after treating low blood glucose levels until they are normoglycemic, when hyperglycemia is suspected, and before to and while performing critical tasks such as driving.

CGM: People with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, when there is a disruption in CGM transmission, for calibration (if needed) or if a warning message appears when CGM supplies are delayed, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose values.

Only meters approved by the U.S. Food and Drug Administration (FDA) (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired test strips purchased from a pharmacy or licensed distributor and properly stored

Meter Standards

ISO by FDA are two key organizations treat set standers for the accuracy of blood glucose meters. ISO has established standards such as ISO 15197;2013, while the FDA has several current standards treat also ensure the reliability of blood glucose meters device. International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA are two organizations to set standards for accuracy of blood glucose meters,. In Europe, currently, marketed meters must meet current ISO standards. People with diabetes assume their glucose meter is accurate because it is FDA- cleared, but that may not be the case.

Counterfeit Strips

People with diabetes should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure BGM accuracy.

Optimizing Blood Glucose Monitoring Device Use

In people with type 1 diabetes, there is a correlation between greater SMBG frequency and lower A1C levels

Among those who check their blood glucose at least once daily, many report taking no action when results are high or low . The ongoing need for and frequency of BGM should be reevaluated at each routine visit to ensure its effective use.

People With Diabetes on Intensive Insulin Therapies

Most individuals on intensive insulin therapies (multiple daily injections [MDI] or insulin pump therapy) should be encouraged to assess glucose levels using SMBG (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to, during, and after physical activity, when they suspect hypoglycemia or hyperglycemia, after treating hypoglycemia until they are normoglycemic, and prior to and while performing critical tasks such as driving.

People With Diabetes Using Basal Insulin and/or Oral Agents and Noninsulin Injectables

The evidence is insufficient regarding when to prescribe SMBG and how often monitoring is needed for insulin-treated people with diabetes who do not use intensive insulin therapy, such as those with type 2 diabetes taking basal insulin with or without oral agents and/or noninsulin injectables.

Those taking basal insulin: assessing fasting glucose with SMBG to inform dose adjustments to achieve blood glucose targets results in lower A1C levels

Those not taking insulin: In people with type 2 diabetes, not taking insulin routine glucose monitoring may be of limited additional clinical benefit.

However, for some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. It may be useful when coupled with a treatment adjustment program.

Clinical pearl: Performing SMBG alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management treatment plans.

Glucose Meter Inaccuracy

- A meter reading that seems discordant with the clinical picture needs to be retested or tested in a laboratory.
- Health care professionals in intensive care unit settings need to be particularly aware of the potential for incorrect meter readings during critical illness, and laboratory-based values should be used if there is any doubt.
- Some meters give error messages if meter readings are likely to be false.

Oxygen.

Currently available glucose monitors use an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase.

Glucose oxidase monitors: are sensitive to the oxygen available and should only be used with capillary blood in people with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low-glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to falsely elevated glucose readings.

Glucose dehydrogenase–based :monitors are generally not sensitive to oxygen.

Temperature.

Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range.

Interfering Substances.

There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems

Table 10.3 Interfering substances for glucose meter readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA
Ascorbic acid
Glucose dehydrogenase monitors using pyrroloquinolinequinone cofactor (GDH/PQQ)
Icodextrin (used in peritoneal dialysis

Continuous Glucose Monitoring Devices

Table 10.4 Continuous glucose monitoring devices:

Type of CGM	Description
rtCGM	CGM systems that measure and display glucose levels continuously
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for visualization and storage of glucose values
Professional CGM	CGM devices that are placed on the person with diabetes in the health care professional's office and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. Unlike rtCGM and is CGM devices, these devices are clinic-based and not owned by the person with diabetes.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

Summary:

- MDI, CSII: Real-time CGM (rtCGM) or intermittently scanned CGM (isCGM) should be offered for diabetes management in adults with diabetes on multiple daily injections (MDI) or CSII who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.
- Type 1 & Type 2 DM:rtCGM or isCGM should be offered for diabetes management in youth with type 1 ,Type 2 diabetes on MDI or CSII who are capable of using the devices safely (either by themselves or with a caregiver).
- Frequency of views: In people with diabetes on MDI or CSII, rtCGM devices should be used as close to daily as possible for maximal benefit. isCGM devices should be scanned frequently, at a minimum once every 8 h to avoid gaps in data.
- Adjunct SMBG: When used as an adjunct to preprandial and postprandial BGM, CGM can help to achieve A1C targets in diabetes and pregnancy.
- Potentialhazards: Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in the successful use of devices.
- Knowledge & education:People who wear CGM devices should be educated on potential interfering substances and other factors that may affect accuracy.

User Profile of CGM:

Owner use: The first type includes those that are owned by the user, unblinded, and intended for frequent or continuous use, including real-time CGM (rtCGM) and intermittently scanned CGM (isCGM).

Prpfessional use: The second type is professional CGM devices that are owned by practices and applied in the clinic, which provide data that are blinded or unblinded for a discrete period of time. The types of sensors currently available are either disposable (rtCGM and isCGM) or implantable (rtCGM)..

Adjunctive: Some CGM systems are called adjunctive, meaning the user should perform BGM for making treatment decisions such as dosing insulin or treating hypoglycemia.

Nonadjunctive: Devices that do not have this requirement outside of certain clinical situations (see BLOOD GLUCOSE MONITORING, above) are called nonadjunctive.

Availability of isCGM device: One specific isCGM device (Freestyle Libre 2 [no generic form available])

Availability Mv rtCGM Devices: Three specific rtCGM devices (Dexcom G6 [no generic form available], Dexcom G7 [no generic form available], and FreeStyle Libre 3 [no generic form available]) have been designated integrated CGM (iCGM) devices.

This is a higher standard set by the FDA so that these devices can be integrated with other digitally connected devices.

AID:Dexcom G6 rtCGM, Dexcom G7 rtCGM, and a modified version of Libre 2 and Libre 3 are FDA-approved for use with AID systems. At this time, Dexcom G6 is integrated with

four AID systems (t: slim ×2 with control IQ, Omnipod 5, iLet, and Mobi). Similarly, the Medtronic Guardian 3 rtCGM (no generic available) and the Medtronic Guardian 4 rtCGM are FDA-approved for use with the 670/770G and 780G AID systems, respectively.

Benefits of Continuous Glucose Monitoring

Rt CGM: Multiple randomized controlled trials (RCTs) have been performed using rtCGM devices, and the results have largely been positive in terms of reducing A1C levels and/or episodes of hypoglycemia, as long as participants regularly wore the devices.

RCT data for isCGM are fewer but increasing.

isCGM: isCGM has been widely available in many countries for people with diabetes, and this allows for the collection of large amounts of data across groups of people with diabetes.

In adults with diabetes, these data include results from observational studies, retrospective studies, and analyses of registry and population data).

In individuals with type 1 diabetes wearing isCGM devices, most, but not all, studies have shown improvement in A1C levels. Reductions in acute diabetes complications, such as diabetic ketoacidosis (DKA), episodes of severe hypoglycemia or diabetes-related coma, and hospitalizations for hypoglycemia and hyperglycemia, have been observed, with persistent effects observed even after 2 years of CGM initiation.

Some retrospective/observational data have shown an improvement in A1C levels for adults with type 2 diabetes on MDI, basal insulin, and basal insulin or noninsulin therapies.

Table 10.5 Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6, Dexcom G7	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre 14 day, Free Style Libre 2, FreeStyle Libre 3	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Dexcom G7, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose
Sorbitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose

There are limited RCT data for many of these interventions, and long-term follow-up is lacking..

Inpatient Care

- In people with diabetes using personal CGM, the use of CGM should be continued when clinically appropriate during hospitalization, with confirmatory point-of-care glucose measurements for insulin dosing and hypoglycemia assessment and treatment under an institutional protocol.
- People with diabetes who are competent to safely use diabetes devices such as insulin pumps and CGM systems should be supported to continue using them in an inpatient setting or during outpatient procedures, whenever possible, and when proper supervision is available. Data are emerging on the inpatient use of AID systems and their challenges."

Suggested citation: American Diabetes Association Professional Practice Committee. 7. Diabetes technology: *Standards of Care in Diabetes-2024*. Diabetes Care 2024;47(Suppl. 1): S126–S144.

11
CHAPTER

Digital Health Technology

- Systems that combine technology and online coaching can be beneficial in managing prediabetes and diabetes for some individuals. Increasingly, people are turning to the internet for advice, coaching, connection, and health care.

Telemedicine and telehealth:

Remote monitoring allows the patient to communicate real-time blood glucose data to their physician to support diabetes self-management and recognize problems early. Telemedicine provides an opportunity to improve patient-centered approaches in diabetes care.

Figure 11.1: Telemedicine

https://www.sciencedirect.com/science/article/pii/S0002934320303399

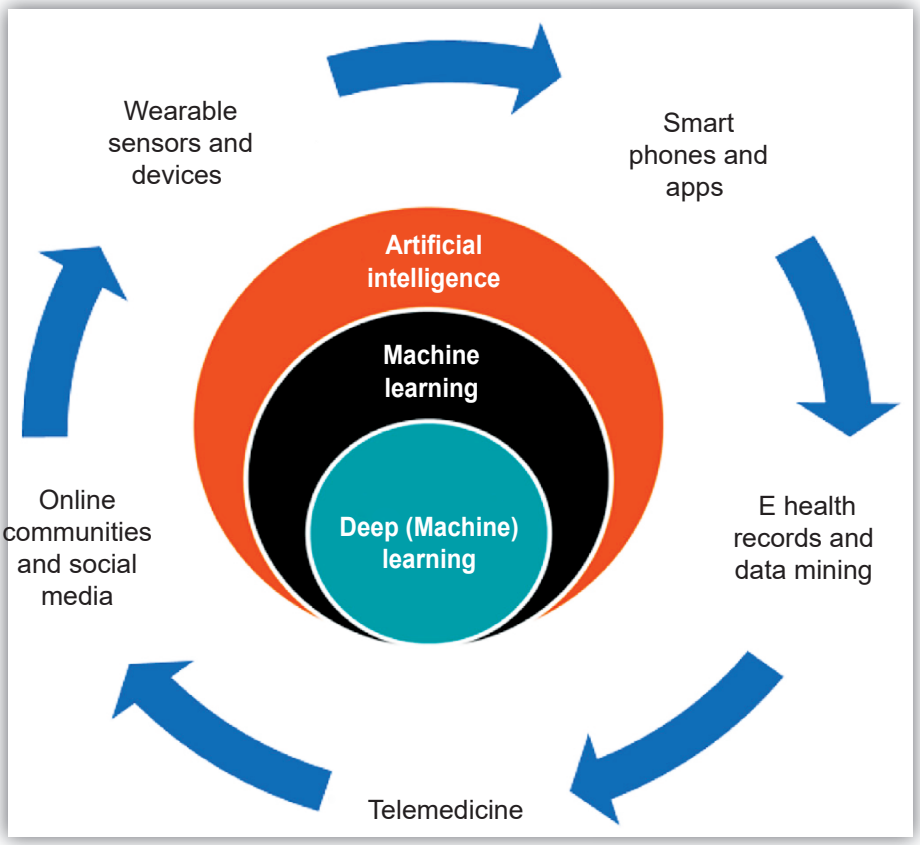


Figure 11.2: Artificial intelligence

Artificial intelligence (AI):Using AI in diabetes management involves several practical steps and tools that can enhance care for individuals with diabetes. Here's how AI can be integrated into diabetes management:

1. Utilize Continuous Glucose Monitors (CGMs): Employ AI-powered CGMs that analyze glucose levels in real-time. These devices can predict glucose trends and provide alerts to help prevent dangerous fluctuations.
2. Leverage Diabetes Management Apps: Use AI-driven apps that offer personalized insights based on glucose data, dietary intake, exercise, and other factors. These apps can recommend adjustments to insulin doses, meal plans, and lifestyle changes.
3. Implement Predictive Analytics: Adopt AI tools that analyze historical data to forecast potential complications or identify patterns that may indicate worsening conditions. This helps in proactive management and early intervention.
4. Integrate Data Sources: Use AI systems that combine data from CGMs, blood glucose meters, fitness trackers, and electronic health records to create a comprehensive view of a patient's health and improve decision-making.

5. Adopt Decision Support Systems: Utilize AI-powered decision support tools in clinical settings to assist healthcare providers in optimizing treatment plans based on the latest evidence and patient-specific data.
6. Engage with AI Chatbots: Employ AI chatbots or virtual health assistants to provide real-time support, answer patient questions, and offer educational resources, enhancing patient engagement and adherence.
7. Monitor and Adjust Treatments: Use AI tools to continuously monitor and analyze treatment efficacy, allowing for timely adjustments to medication and lifestyle interventions.

By incorporating these AI technologies and tools, individuals with diabetes and their healthcare providers can achieve more personalized, efficient, and effective management of the condition.

Precision medicine:

Paradigm shift in diabetes treatment.

A form of medicine that uses information about a person's genes, proteins, environment, and lifestyle to prevent, diagnose, or treat disease also variously known as individualized medicine, personalized medicine or genomic medicine.

Precision medicine is the intersection between people, their environment, changes in their markers of health and illness and social and behavioral factors over time.

Precision diabetes medicine aims to exploit the growing volume of clinical and molecular data available to clinicians to optimize patient diagnosis and prognostication, disease prevention, and treatment selection. Patient-tailored prevention and care are being increasingly enabled by an improved understanding of the genetic and environmental contributors to disease risk and progression; emerging highly efficacious therapies. Tailoring health care to each person's unique genetic makeup – that's the promising idea behind precision medicine. Digital technologies aid better appreciation of the importance of patient-centered outcomes and quality of life.

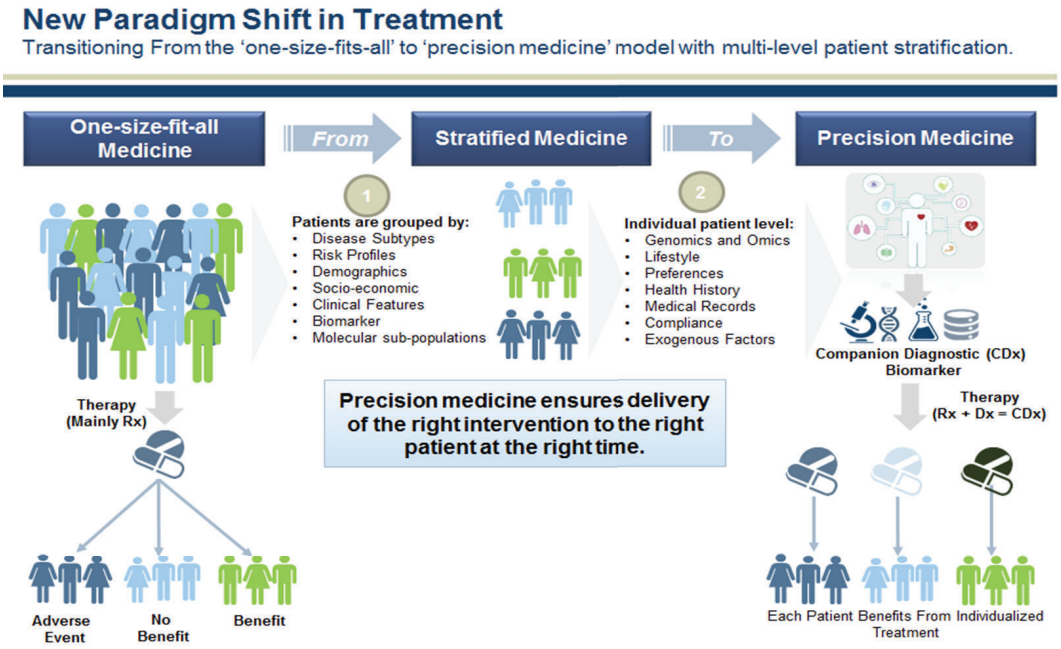


Figure 11.3: Precision medicine

Last frontier:Transplant therapy

Pancreas/Islet Transplants

Human Embryonic Stem Cells (**hESCs**)

Human induced Pluripotent Stem Cells (**hiPSCs**)

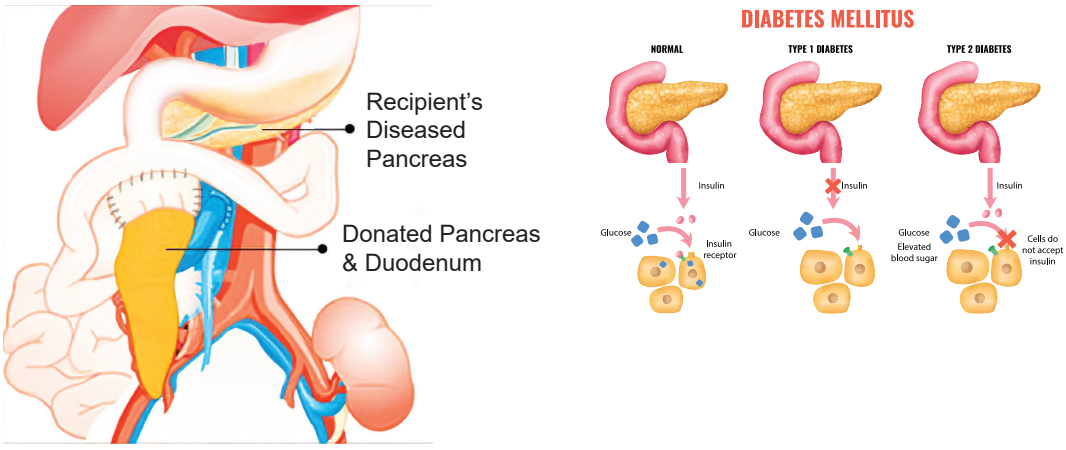


Figure 11.4: Pancreas-transplantation.
https://www.medindia.net/patients/patientinfo

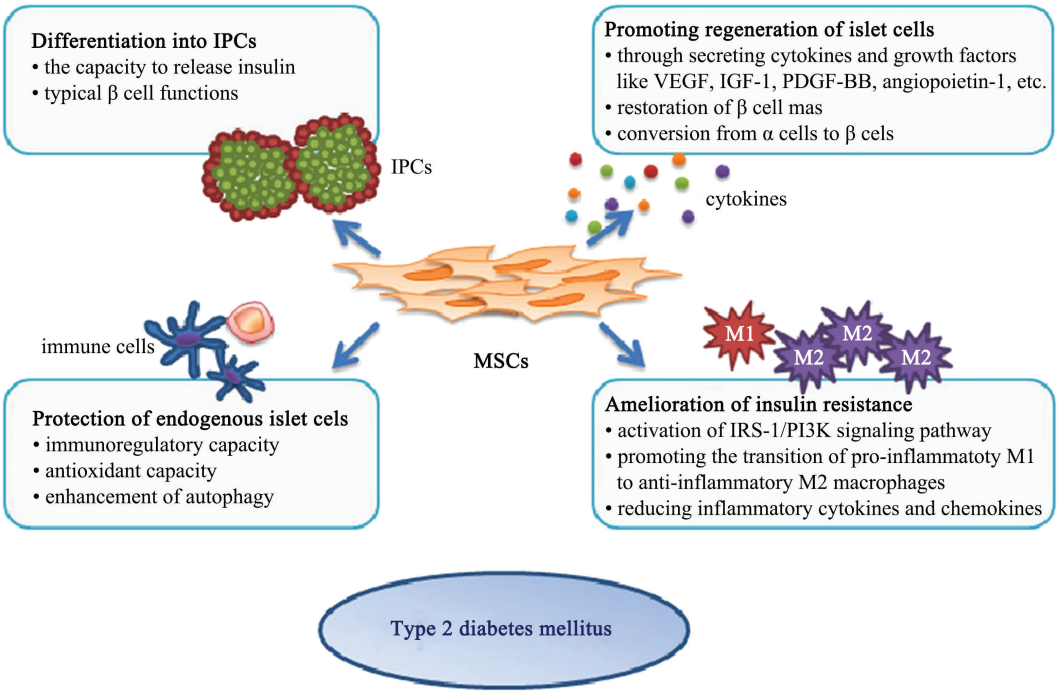


Figure 11.5: Stem cell therapy

Prevention of diabetes:

If prevention is not possible delaying the development of overt DM is achievable.Trials demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation).

Summary:

- Type 2 DM: In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify based on individual risk assessment.
- Type 1 DM: In people with preclinical type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and a 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify the frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics.

Table 11.1 Staging of type 1 diabetes(3 distinct stages)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials *. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 2017;66:241–255*

Lifestyle Behavior Change for Diabetes Prevention

Clinical pearls:

- As seen in the Diabetes Prevention Program (DPP)-Adults with overweight or obesity at high risk of type 2 diabetes, , an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity.
- A variety of eating patterns can be considered to prevent type 2 diabetes in individuals with prediabetes.
- .Diabetes prevention programs should be offered.
- Certified technology-assisted diabetes prevention programs may be effective

The Diabetes Prevention Program (DPP)

A. Lifestyle alteration

1. Lifestyle alteration & T2 DM

(DPP) trial: The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial: These trial could help reduce the risk of incident type 2 diabetes by 58% over 3 years.

Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403

Da Qing study: There is a 39% reduction at 30 years in the Da Qing study.
Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019;7:452–461

Finnish DPS: There is a 43% reduction at 7 years: *Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673–1679 the*

U.S. Diabetes Prevention Program Outcomes Study (DPPOS): There is a 34% reduction at 10 years and 27% reduction at 15 years. *Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015;3:866–875*

2. Lifestyle and Type 1 Diabetes Progression

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand-including less physical activity, a higher dietary glycemic index, and increase total sugar intake are associated with a progression to clinical diabetes.

B. Pharmacological Intervention and Prevention of Diabetes

Summary:

- Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus.
- Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy
- Delay Symptomatic Type 1 Diabetes: Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be considered in selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel.

Suggested citation: American Diabetes Association Professional Practice Committee. 3. Prevention or delay of diabetes and associated comorbidities: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S43–S51

Diabetes remission: Concept of DM Remission 2000s

Remission should be defined as a return of HbA1c to < 6.5% (< 48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy

1. **Intensive Lifestyle:** DiRECTrial;
2. **Bariatic Surgery:** Roux-en-Y gastric bypass (RYGB) with greater remission than sleeve gastrectomy.
3. **Trizeptide (GLP1 +GIP):** SURPASS-1 trial.

Cure of Diabetes

Cure of diabetes: There's no cure for type 2 diabetes, studies show some people can reverse it. Through diet changes and weight loss, you may be able to reach and hold normal blood sugar levels without medication. This doesn't mean you're completely cured. Type 2 diabetes is an ongoing disease

By meeting type 2 diabetes treatment goals, life expectancy can increased by 3 years, or for some, as much as 10 years.

The FLAME OF HOPE:
Keeps a hope and aspiration for CURE OF DIABETES one day

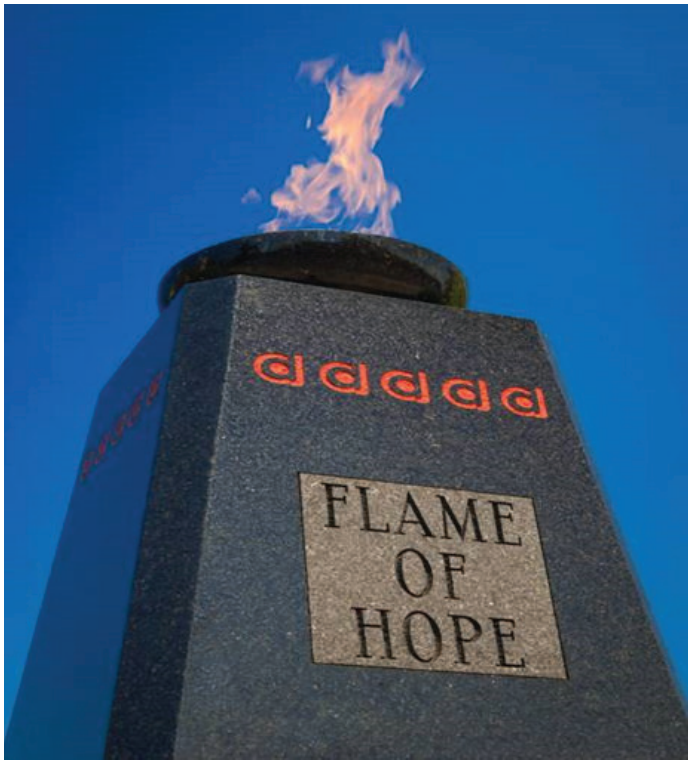


Figure 11.6: Diabetes Flame of Hope At Dr Banting's House Now A Museum To Insulin In London Ontario Canada

Figure 11.7: Flame of hope

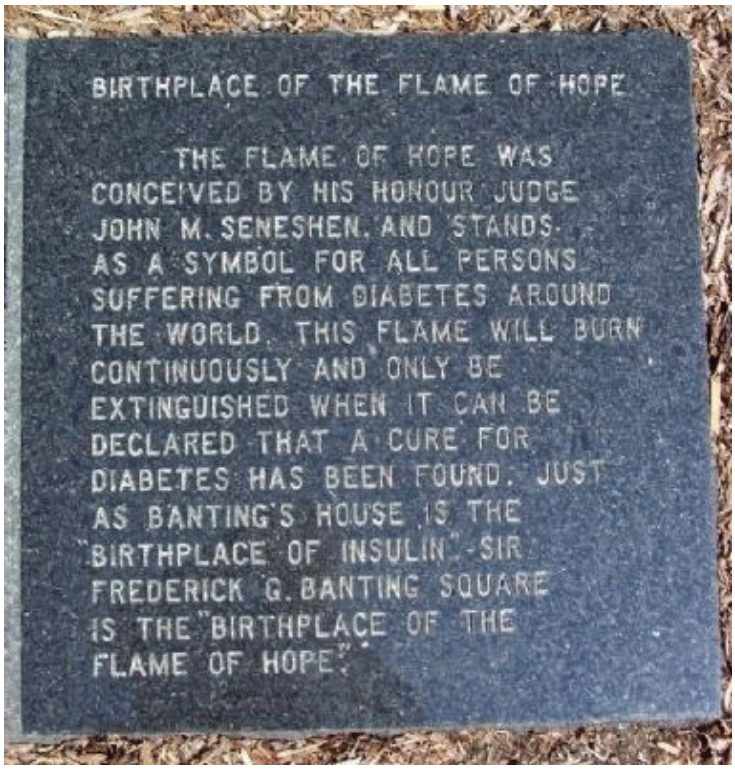


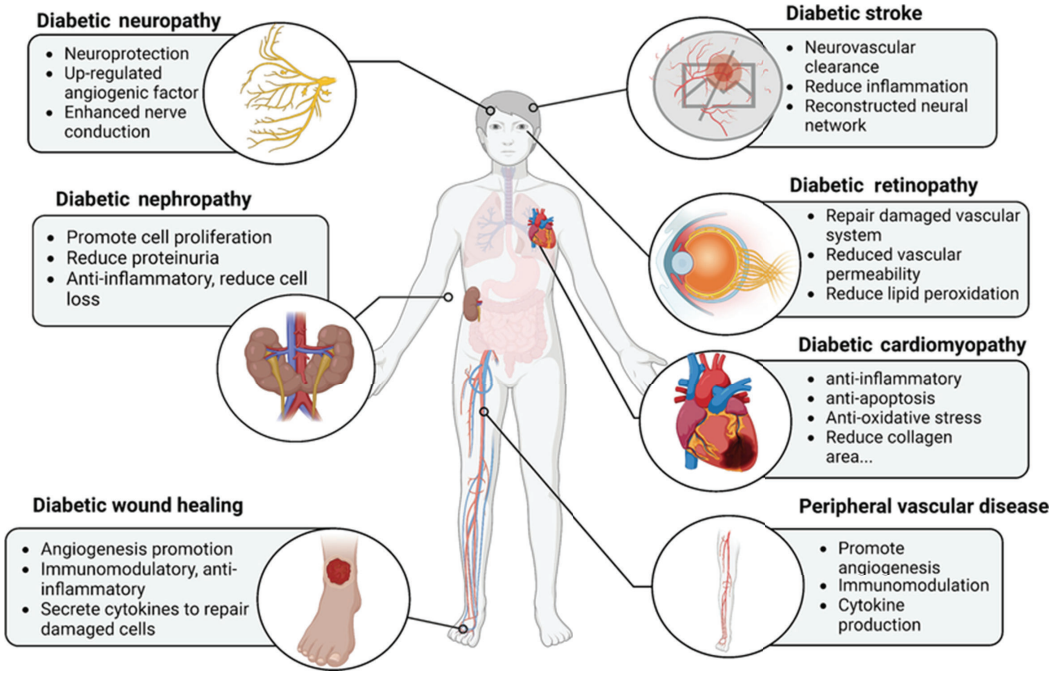
Figure 11.8: Flame of hope

References:

1. Singh N, Stewart RAH, Benatar JR. Intensity and duration of lifestyle interventions for long-term weight loss and association with mortality: a meta-analysis of randomised trials. BMJ Open 2019;9:e029966
2. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551
3. Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol 2017;16:37
4. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
5. Anenbaum ML, Zaharieva DP, Addala A, et al. "I was ready for it at the beginning": parent experiences with early introduction of continuous glucose monitoring following their child's type 1 diabetes diagnosis. Diabet Med 2021;38:e14567

Research gate

Cell therapy for diabetic complications.



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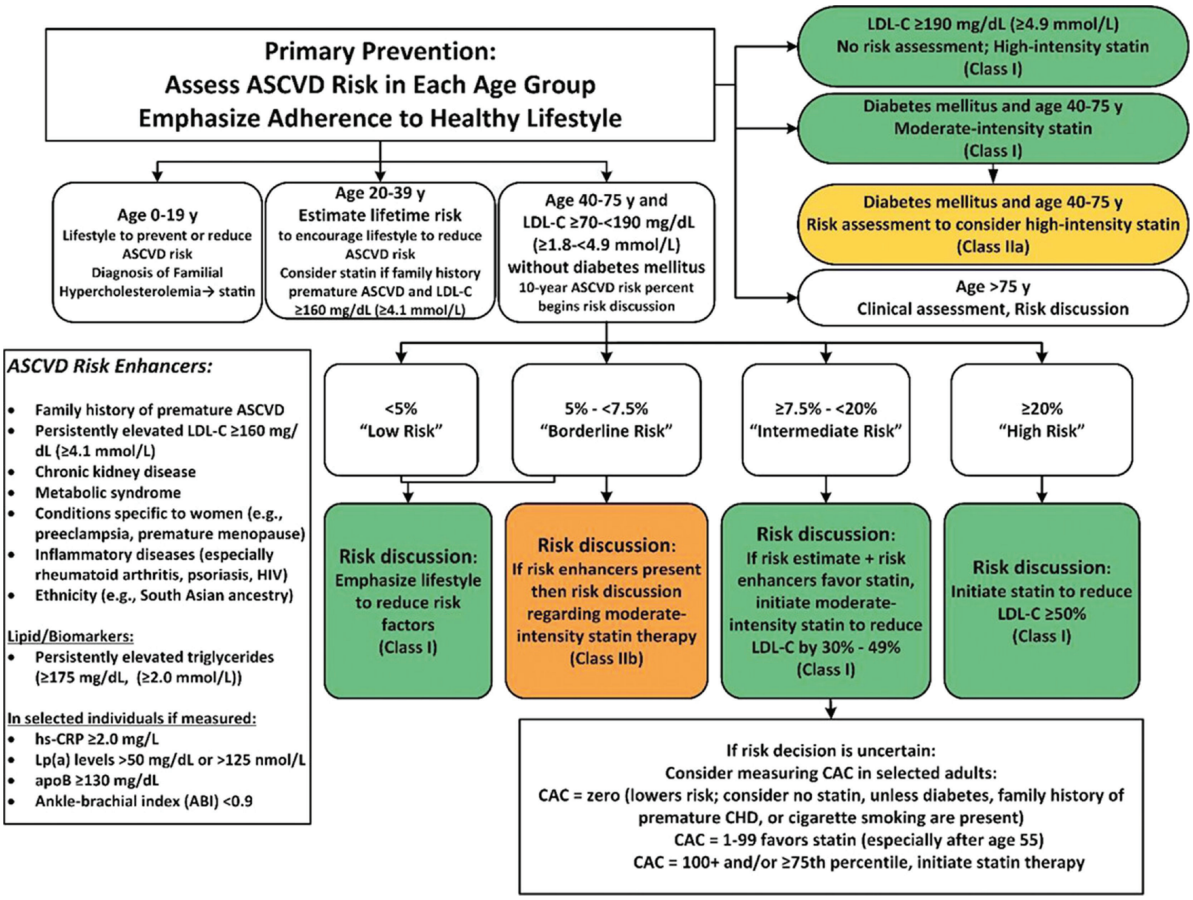
Diabetes in Daily Life

PART - 2
SPECIALIZED MANAGEMENT OF DIABETES MELLITUS

Dr. Khwaja Nazim Uddin
MBBS FCPS FRCP FACP
Professor of Medicine
Internist and Diabetologist

Lipid management in diabetes



Diabetes with Comorbidity

12
CHAPTER

Essential of Diabetes

Diabetes comorbidities: Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes.

Bone Health:

Diabetes-specific risk factors for fracture

- Lumbar spine or hip T-score ≤−2.0
- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylurea
- A1C >8%
- Peripheral and autonomic neuropathy
- Retinopathy and nephropathy

Age-specific fracture risk is significantly increased in people with type 1 or type 2 diabetes in both sexes, with a 34% increase in fracture risk compared with those without diabetes. In people with type 2 diabetes, hip fracture risk is increased by 1.79 times, and risk throughout life is 40–70% higher than in it is in individuals without diabetes. A meta-analysis revealed an 8% increased fracture risk per 1% rise in A1C level fracture incidences in women using thiazolidinediones (TZD), the risk doubling with 1–2 years of TZD use. Furthermore, individuals with type 2 diabetes on insulin (RR 1.49 [95% CI 1.29–1.73]) or sulfonylurea (RR 1.30 [95% CI 1.18–1.43]) treatment exhibit a heightened fracture risk.

Screening: People with type 2 diabetes have 5–10% higher BMD than people without diabetes. A T-score adjustment of −0.5 has been proposed to improve fracture prediction by dual-energy X-ray absorptiometry (DXA). In people with type 2 diabetes, in the absence of other comorbidities, DXA scan should be performed at least 5 years after the diagnosis of diabetes, and reassessment is recommended every 2–3 years. DXA should be performed every two years in subjects undergoing bariatric-metabolic surgery.

Management

Maintaining glucose control and minimizing hypoglycemic episodes are crucial for bone health in people with diabetes.

Exercise: Moderate regular physical activity to enhance muscle health, gait coordination, and balance as part of fracture preventive strategies. Aerobic and weight-bearing exercise should be recommended.

Diet and supplements: adequate daily intake of proteins, calcium, and vitamin D, stop smoking,

Vit-D and Calcium: The optimal level of 25-hydroxyvitamin D is a matter of controversy (1), although serum levels ≥20 ng/mL are generally thought to be sufficient. Because diabetes is a risk factor for fractures, other guidelines suggest a goal >30 ng/mL. The safe upper limit is also a matter of debate

Daily allowances: The U.S., the recommended daily allowance of vitamin D is 600 IU for people aged 51–70 years and 800 IU for people aged >70 years. In clinical practice, this dose of supplement is often not enough to reach recommended goals, and higher doses of D2 or D3 may be needed.

Pharmacological treatment: Antiosteoporosis medications a) reduce bone resorption (bisphosphonates, selective estrogen receptor modulators, and denosumab), b) stimulate bone formation (teriparatide and abaloparatide), or c) have dual actions by stimulating bone formation and reducing bone resorption (romosozumab).

Primary Prevention of Fragility Fractures in People with Diabetes

In the general population, a T-score ≤−2.5 is the threshold to consider pharmacological treatment for osteoporosis. In type 2 diabetes, since T-score underestimates fracture risk (as discussed above), a T-score ≤−2.0 may be more appropriate for considering initiation of a first-line drug, including bisphosphonates (alendronate, risedronate, and zoledronate) or denosumab

Secondary Prevention of Fragility Fractures

The risk of subsequent fracture in individuals with hip or vertebral fracture is significantly high, especially in the first 1–2 years after a fracture. Antiosteoporosis treatment reduces the risk of fracture in older individuals with prior hip or vertebral fracture.

As in the general population, people with diabetes who experience fragility fracture should 1) be given the diagnosis of osteoporosis regardless of DXA data and 2) receive therapy to prevent future fractures. It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation, if needed, as early as possible.

Glucose-Lowering Medications and Bone Health

Medications other than TZD are advisable for postmenopausal women or elderly men with type 2 diabetes due to their safer bone health profiles. Tirzepatide may play a positive effect through glucose-dependent insulinotropic polypeptide (GIP) receptor agonism, preventing bone loss associated with weight loss.

Use of sodium–glucose cotransporter 2 inhibitors have raised some concerns. Although few data are available, use of empagliflozin, ertugliflozin, or dapagliflozin has not been associated with negative effects on bone health (2)

Use of insulin and SU has been shown to double the risk of hip fractures, likely because of higher risk of hypoglycemia, longer duration of the disease, and comorbidities.

In conclusion, glucose-lowering medications with good bone safety profiles should be preferred, especially in the elderly, in people with longer duration of disease, or in people with complications. Aggressive therapeutic approaches should be avoided in the frail and in the elderly to prevent hypoglycemic events and falls.

Cognitive Impairment/Dementia and mental health in diabetes:

In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. A meta-analysis of prospective observational studies found that individuals with diabetes had a 43% higher risk of all types of dementia, a 43% higher risk of Alzheimer dementia, and a 91% higher risk of vascular dementia compared with individuals without diabetes.

Cognitive Capacity/Impairment

Cognitive capacity is generally defined as attention, memory, logic and reasoning, and auditory and visual processing, all of which are involved in diabetes self-management behavior. Having diabetes (type 1 or type 2) over decades has been shown to be associated with cognitive decline. A host of factors have been linked with cognitive impairment in people with type 1 diabetes, including diabetes-specific (e.g., younger age at diagnosis, longer disease duration, more time in glycemic extremes, recurrent diabetic ketoacidosis, higher A1C, and presence of microvascular complications), other medical (e.g., dyslipidemia, intestinal flora, and poorer sleep quality), and sociodemographic (e.g., female gender and lower educational level) factors. Monitoring of cognitive capacity and skills among individuals with or at risk for diabetes is recommended, particularly regarding their ability to self-monitor and to make judgments about their symptoms, physical status, and need of alterations to their self-management behaviors, all of which are mediated by executive function. Cognitive decline is more severe in older adults with type 2 diabetes. Longitudinal epidemiological studies have documented that chronic hyperglycemia, older age, less education, retinopathy, and nephropathy are associated with diabetes-related cognitive dysfunction. Importantly, the risk of cognitive decline can be reduced through improved A1C. Exercise may be a potential nonpharmacological treatment pathway for cognitive impairment in older adults with type 2 diabetes.

Low Testosterone in Men

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder.

In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity or erectile dysfunction,

Screening: In men with diabetes who have symptoms or signs of hypogonadism consider screening with a morning serum testosterone level. In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations. Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the individual.

Testosterone replacement in men with symptomatic hypogonadism may have benefits, including improved sexual function, well-being, muscle mass and strength, and bone density.

Erectile Dysfunction

Erectile dysfunction (ED) affects approximately 34% to 45% of men with diabetes and has been demonstrated to negatively impact quality of life among those affected across all age strata Among men with diabetes, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen-deficiency states and cardiovascular disease (CVD side effect of many drugs commonly prescribed to men with diabetes, such as certain antihypertensives and antidepressants. Obstructive sleep apnea (OSA) is commonly associated with ED and, like diabetes, is an independent risk factor for the presence of ED. Organic causes of ED include microvascular and CV disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED.

Treatment: Based on these conflicting data, a prudent clinician should encourage optimal glycemic control as a potential factor in maintaining erectile function.

Treatment of Dyslipidemia and hypertension benefit from statin treatment on erectile function. A small study of losartan in combination with tadalafil in men with type 2 diabetes showed an improved ED response rate compared to tadalafil monotherapy.

PDE5 inhibitors: The current mainstay of treatment for ED in men with diabetes is therapy with PDE5 inhibitors. should be offered as first-line therapy to men with diabetes wishing treatment for ED .

Testosterone: In treatment of nonresponders to PDE5 inhibitors with testosterone replacement is successful in roughly 50% of individuals.

Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates. Interestingly, men with diabetes appear to have lower rates of side effects with PDE5 inhibitors than the general population. This is believed to be a result of altered vasomotor tone or other factors.

Second-line therapies (e.g., vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], or intraurethral therapy using PGE1 or third-line therapy (penile prosthesis) may be considered for these men.

Obstructive Sleep Apnea and sleep health for Diabetics

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity. The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58%. Individuals with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, and witnessed apnea) should be considered for screening (4).

Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. The evidence for a treatment effect on glycemic control is mixed.

Sleep Health

Counsel people with diabetes to practice sleep-promoting routines and habits (e.g., maintaining consistent sleep schedule and limiting caffeine in the afternoon).

The associations between sleep problems and diabetes are complex: In type 1 diabetes, estimates of poor sleep range from 30% to 50%, and estimates of moderate to severe obstructive sleep apnea are >50%. In type 2 diabetes, 24–86% of people are estimated to have obstructive sleep apnea, 39% to have insomnia, and 8–45% to have restless leg syndrome (i.e., an uncontrollable urge to move legs. Further, people with type 2 diabetes and restless leg syndrome are more likely to experience microvascular and macrovascular complications. Health care professionals should consider a comprehensive evaluation of the daily lifestyles of people with diabetes to decrease risk factors, including low sleep duration, shift work, and days off, given their associations with hyperglycemia, hypertension, dyslipidemia, and weight gain.

As for the general population, there are evidence-based strategies to improve sleep for people with diabetes. CBT shows benefits for sleep in people with diabetes, including CBT for insomnia, which demonstrates improvements in sleep outcomes and possible small improvements in A_1C and fasting glucose. There is also evidence that sleep extension and pharmacological treatments for sleep can improve sleep outcomes and possibly insulin resistance. Lastly, sleep education, or sleep hygiene, improves sleep quality, reduces A1C, and decreases insulin resistance in adults with type 2 diabetes. Thus, diabetes care professionals are encouraged to counsel people with diabetes to use sleep-promoting routines and practices, such as establishing a regular bedtime and rise time, creating a dark, quiet area for sleep with temperature and humidity control, establishing a pre-sleep routine, putting electronic devices (except diabetes management devices) in silent/off mode, exercising Obstructive Sleep Apnea and sleep health for Diabetics.

Pancreatitis

Diabetes is linked to diseases of the exocrine pancreas, such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of individuals with diabetes may have some degree of impaired exocrine pancreas function. People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis. Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of individuals after an episode of acute pancreatitis; thus, the relationship is likely bidirectional. Post pancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes. Studies of individuals treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial.

Special Sensory Impairment: hearing, smell, taste

Hearing impairment: Both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people. Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress to cochlear microangiopathy and auditory neuropathy.

Impairment in smell: but not taste has also been reported in individuals with diabetes.

Statins

Systematic reviews of observational studies and randomized trials have found no adverse effects of statins on cognition (5). The FDA post marketing surveillance databases have also revealed a low reporting rate for cognitive function–related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications. Therefore, fear of cognitive decline should not be a barrier to statin use in people with diabetes when indicated.

Psychosocial influences in Diabetes management: Smoking Cessation: Tobacco, E-cigarettes, and Cannabis. Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and multiple health risks that can have a profound impact on morbidity and mortality for people with diabetes. As a routine component of diabetes care and education, ask people with diabetes about the use of cigarettes or other tobacco products.

Behavioral support: Behavioral strategies should be used to support diabetes self-management and engagement in health behaviors (e.g., taking medications, using diabetes technologies, and engaging in physical activity and healthy eating, monitoring 24 hours daily life) to promote optimal diabetes health outcomes.

Psychological care: When indicated, refer to behavioral health professionals or other trained health care professionals, ideally those with experience in diabetes, for further assessment and treatment for symptoms of diabetes distress, depression, suicidality, anxiety, treatment-related fear of hypoglycemia, disordered eating, and/or cognitive capacities

Diabetes Distress: Diabetes distress is very common. While it shares some features with depression, Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic condition such as diabetes. The prevalence of diabetes distress is reported to be 18–45%, with an incidence of 38–48% over 18 months in people with type 2 diabetes. Diabetes distress is also associated with

symptoms of anxiety, depression, and reduced health-related quality of life. Diabetes distress should be routinely monitored.

Anxiety: Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes. The Behavioral Risk Factor Surveillance System estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes. May be experiencing symptoms of obsessive-compulsive disorder. General anxiety is a predictor of injection-related anxiety and is associated with fear of hypoglycemia. Specialized behavioral intervention from a qualified professional is needed to treat hypoglycemia-related anxiety.

Depression: Conduct at least annual screening of depressive symptoms in all people with diabetes Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes. Elevated depressive symptoms and depressive disorders are affecting approximately one in four people with type 1 or type 2 diabetes, and among parents of youth with diabetes also with gestational diabetes mellitus, and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men. As with DSMES, person-centered collaborative care approaches have been shown to improve both depression and medical outcomes. It is important to note that the medical treatment plan should also be monitored in response to reduction in depressive symptoms.

13
CHAPTER

Fatty Liver

Nonalcoholic fatty liver disease (NAFLD) includes a broad spectrum of disease, ranging from macrovesicular hepatic steatosis (with or without mild inflammation) to nonalcoholic steatohepatitis (NASH) to cirrhosis. This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding evaluation) or other secondary causes of hepatic steatosis.

NAFLD: Recent studies in adults in the U.S. estimated that NAFLD is prevalent in >70% of people with type 2 diabetes (3). This is consistent with studies from other countries. NASH is defined histologically as having ≥5% hepatic steatosis and is associated with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis. Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with NAFLD to NASH.

Diabetes is a major risk factor for developing NASH, disease progression, and worse liver outcomes . and appears to be a driver for the development of fibrosis. NASH is a leading cause of hepatocellular carcinoma.

Fibrosis: Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis.

MASLD: Metabolic dysfunction–associated steatotic liver disease has been proposed to replace the term nonalcoholic fatty liver disease (NAFLD) to identify steatosis liver disease in the presence of at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of steatosis.

MetALD: Separate category outside of MASLD, named metabolic dysfunction and alcoholic liver disease was created for circumstances in which alcohol intake is greater than that allowed for NAFLD but less than that attributed to alcoholic liver disease.

Screening: The goal of screening for NAFLD is to identify people at risk for adverse health outcomes associated with NASH, such as cirrhosis, HCC, and death from liver disease. This risk is higher in people who have central obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for >6 months)

A recent meta-analysis reported a prevalence of NAFLD of 22% in people with type 1 diabetes . This risk may be linked to the fact that about one-third of people with type 1 diabetes in the U.S. have obesity.

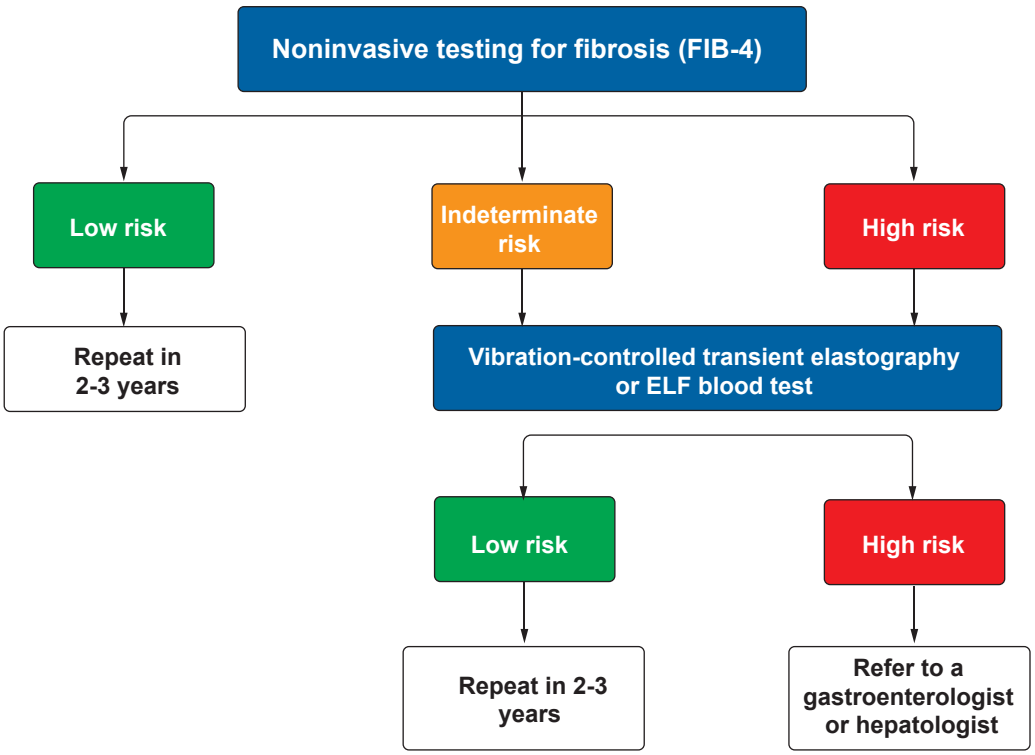


Figure 13.1: A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index. Elastography is fiboscan. *Adapted from Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. Diabetes Care 2021;44:2162–2172*

Fibrosis-4 index (FIB-4): There is consensus that the fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or with type 2 diabetes in primary care and diabetes clinical settings. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). Low risk of having advanced fibrosis (F3–F4): A value of <1.3 is considered low risk of having advanced fibrosis (F3–F4): and for developing adverse liver outcomes, while Advanced fibrosis (F3–F4): >2.67 is considered as having a high probability of advanced fibrosis (F3–F4) and increased risk of adverse liver outcomes.

Indeterminate" (or intermediate) risk group for advanced fibrosis and adverse liver outcomes: when FIB-4 is between 1.3 and 2.67; people with diabetes often fall in the intermediate group. However, its low cost, simplicity, and good specificity make it the initial test of choice. Performance is better in a population with higher prevalence of significant fibrosis (i.e., hepatology clinics) compared with primary care settings. FIB-4 has not been well validated in pediatric populations and does not perform as well in those aged <35 years. In people with diabetes ≥65 years of age, higher cutoffs for FIB-4 have been

recommended (1.9–2.0 rather than >1.3)

Fibroscan and other tests: In people with an indeterminate or high FIB-4, additional risk stratification is required with a liver stiffness measurement (LSM) by transient elastography (fibroscan) or, if unavailable, by commercial blood fibrosis biomarkers such as the enhanced liver fibrosis (ELF) test or others. Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in NAFLD. An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) and indicates low risk for clinically significant fibrosis.

ELF test is a good alternative to LSM. Individuals with ELF <7.7 are considered at low risk for adverse outcomes. If the LSM is >12 kPa, the risk for advanced fibrosis is high and people with diabetes should be referred to the hepatologist.

MRE: Magnet resonance elastography (MRE): having the best overall performance (particularly for early fibrosis stages). However, the accessibility and costs associated with MRE are barriers to its use.

Liver Biopsy: While liver biopsy remains the gold standard for the diagnosis of NASH, its indication is reserved to the discretion of the specialist.

The American Gastroenterological Association and ADA Consensus has emerged to start screening with FIB-4 followed by LSM or ELF and patented biomarkers as needed for the noninvasive fibrosis risk stratification of individuals with NAFLD in primary care and diabetes clinics.

Management of NASH

FDA approval and drug therapy for NASH: Obeticholic acid (OCA) is a first-in-class farnesoid X receptor agonist and antifibrotic agent in development for the treatment of pre-cirrhotic liver fibrosis due to non-alcoholic steatohepatitis (NASH). Obeticholic acid (OCA), a potent farnesoid X nuclear receptor activator, has shown promise for treating NASH-related fibrosis due to its anti-fibrotic effects. The US Food and Drug Administration (FDA) has rejected Intercept Pharmaceutical's second bid for approval of obeticholic acid (OCA) for treatment of nonalcoholic steatohepatitis (NASH) with stage 2 or 3 fibrosis.

Resmetirom, sold under the brand name Rezdiffra: In March 2024, the U.S. Food and Drug Administration (FDA) approved a pill called resmetirom, sold under the brand name Rezdiffra™, for NASH (nonalcoholic steatohepatitis).

Drugs for NASH: At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment for people with type 2 diabetes and NASH is centered on the dual purpose of treating hyperglycemia and obesity, especially if clinically significant fibrosis (≥ F2) is present. The rationale for the treatment of people with type 2 diabetes is based on their high prevalence of NASH with significant fibrosis (10–15% of people with type 2 diabetes), Therefore, early diagnosis and treatment of NAFLD offers the best opportunity for cirrhosis prevention. Pioglitazone and some glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been shown to be effective to treat steatohepatitis

GLP-1 RAs are effective at inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis. Glucagon-like peptide 1 (GLP-1) receptor agonist: demonstrated benefits in nonalcoholic steatohepatitis (NASH) as an adjunctive therapy to lifestyle interventions for weight loss.

Liraglutide: improved some features of NASH and delayed the progression of fibrosis., Semaglutide: once-daily subcutaneous semaglutide in 320 people with biopsy-proven NASH (62% having type 2 diabetes) reported resolution NASH at higher dose (equivalent to 2.4 mg/week semaglutide) semaglutide significantly slowed over 72 weeks the progression of liver fibrosis

Tirzepatide: sodium–glucose cotransporter inhibitors, and insulin reduce hepatic steatosis, but their effects on steatohepatitis remain unknown.

Pioglitazone: Pioglitazone or GLP-1 receptor agonists are the preferred agents for significant fibrosisi NASH In adults with type 2 diabetes and NAFLD Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes or type 2 diabetes and even without diabetes. Fibrosis also improved in some trials. Pioglitazone treatment results in resolution of NASH and may improve fibrosis. Pioglitazone may halt the accelerated pace of fibrosis progression observed in people with type 2 diabetes and is overall cost-effective for the treatment of NASH.

Saroglitazor: (pprgama 1 & 2 antagonist): Is approved in India (available in Bangladesh) by drug controller general for treatment of type 2 DM, Dyslidemia, NASH and NAFLD.

Vitamin E: Vit E may be beneficial for the treatment of NASH in people without diabetes. However, in people with type 2 diabetes, vitamin E monotherapy was found to be negative in a small RCT

Side effects of Pioglitazone: Pioglitazone causes dose-dependent weight gain (15 mg/day, mean of 1–2%; 45 mg/day, 3–5%), increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial.

Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, with nonalcoholic fatty liver disease (NAFLD) should be recommended lifestyle changes that promote weight loss. use of glucose-lowering therapies other than pioglitazone or GLP-1 receptor agonists may be continued as clinically indicated, but these therapies lack evidence of benefit in NASH. Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis.

Statin therapy: is safe in adults with type 2 diabetes and compensated cirrhosis from NAFLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. Overall, its use appears to be safe in adults with type 2 diabetes and NASH, including in the presence of compensated cirrhosis (Child-Pugh class A or B cirrhosis) from NAFLD.

Metabolic surgery: in appropriate candidates as an option to treat NASH in adults with type 2 diabetes and to improve cardiovascular outcomes. Metabolic surgery improves NASH and cardiometabolic health, altering the natural history of the disease. Meta-analyses report that

70–80% of people have improvement in hepatic steatosis, 50–75% in inflammation and hepatocyte ballooning (necrosis), and 30–40% in fibrosis. It may also reduce the risk of HCC.

Obesity and NASH

While steatohepatitis and cirrhosis occur in lean people with diabetes there is ample evidence to implicate excess visceral and overall adiposity in people with overweight and obesity in the pathogenesis of the disease. Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis. Therefore, clinicians should enact evidence-based interventions to promote healthy lifestyle change and weight loss for people with overweight or obesity and NAFLD. A minimum weight loss goal of 5%, preferably ≥10%, is needed to improve liver histology, with fibrosis requiring the larger weight reduction to promote change.

Dietary recommendations: same with those without NAFLD. The Mediterranean diet both aerobic and resistance training improve NAFLD in proportion to treatment engagement and intensity of the program.

Obesity pharmacotherapy may assist with weight loss

14
CHAPTER

Obesity and Weight Management

Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes:

Summary: Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation that presents a risk to health. Obesity is characterized by 20% excess of lean body mass.

It is a chronic, often relapsing disease with numerous metabolic, physical, and psychosocial complications, including a substantially increased risk for type 2 diabetes. Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and inflammatory state), and ultimately cardiovascular and kidney disease. There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes) and is highly beneficial in treating type 2 diabetes). Metabolic surgery, which induces on average >20% of body weight loss, strongly improves glycemia and often leads to remission of diabetes, improved quality of life.

Obesity: **If diabetes is epidemic obesity is pandemic**.

Figure 14.1: Obesity: Prevalence

Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016.The worldwide prevalence of obesity nearly tripled between 1975 and 2016.

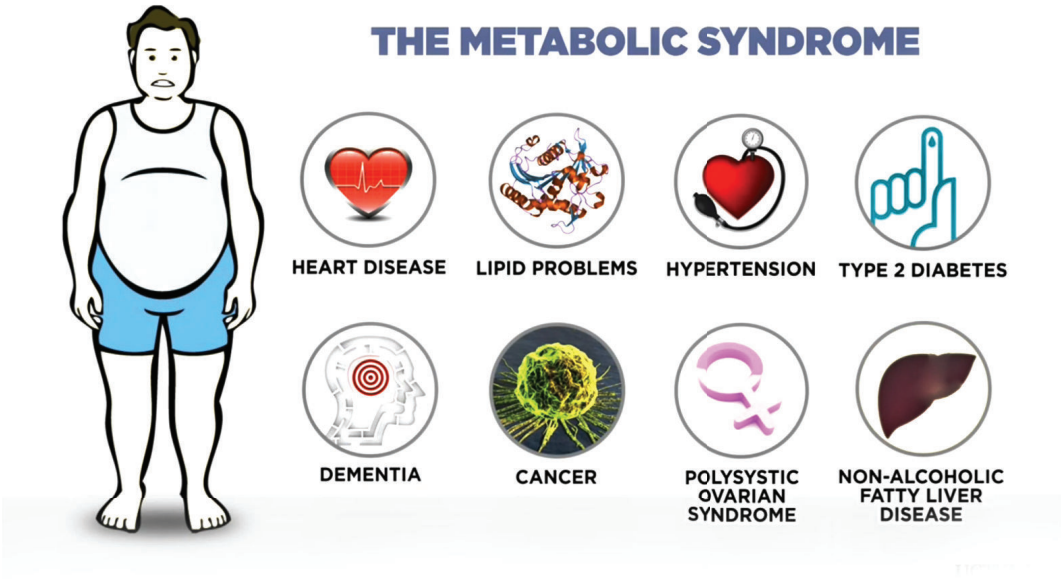


Figure 14.2: Obesity is part of metabolic syndrome and related to different synastrous conditions

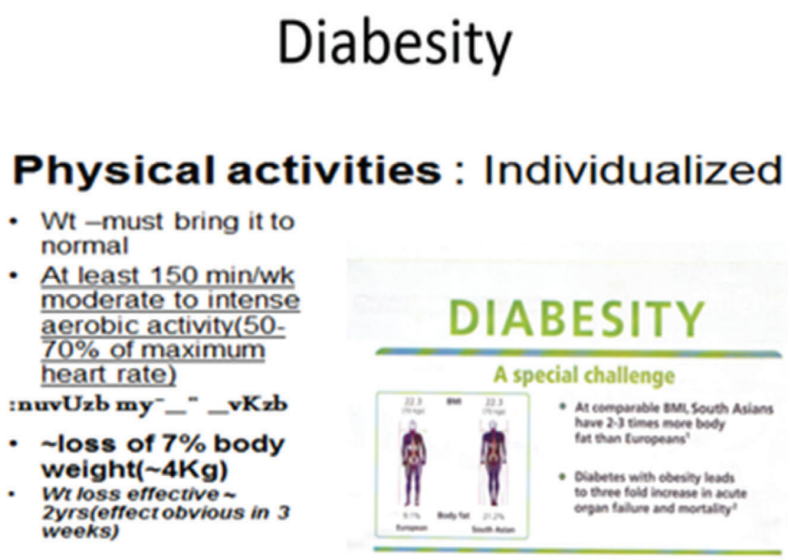


Figure 14.3: Diabesity, Diabesity is defined as co-existence of both diabetes and obesity. www.ncbi.nlm.nih.gov>pmc

Figure 14.4: Problems of obesity beyond metabolic syndromes

Clinical assessment:

Diagnosis: To support the diagnosis of obesity, measure height and weight to calculate BMI and perform additional measurements of body fat distribution, like waist circumference, waist-to-hip ratio, and/or waist-to-height ratio. BMI (calculated as weight in kilograms divided by the square of height in meters [kg/m2]) has been used widely to diagnose and stage obesity (overweight: BMI 25–29.9 kg/m2; obesity class I: BMI 30–34.9 kg/m2; obesity class II: BMI 35–39.9 kg/m2; obesity class III: BMI ≥40 kg/m2);

1. **Quantification of problem:** Waist circumference >102 cm in men,>85 cm in women (risk for CVS, metabolic complications)
2. **Exclude an underlying cause:** hypothyroid, cushing, syndrome drug, monogenic, syndromic causes.

3. Identify complications (other risk): BP with larger cuff, Fasting BG, Lipid profile, SGPT, TSH, overnight dexamethasone suppression test.

Etiopathogenesis:

Energy consumption > expenditure. Sedentary work> active work (Obesogenic environment)

Increased consumption: Increased portion size, increased snacking missing regular meals. Increased energy dense food (mainly fat), affluences.

Decreased energy expenditure: Car owner. Not walking to school/work. Increased automation. Decreased manual work. Avoid sports in school/college. Increased screen time. Increased central heating/cooling

Susceptibility to obesity

Is Polygenic (different gene <5%), single gene in childhood obesity-melanocortin 4 receptor mutation, mutation of leptin gene. Genetic diseases-prader willi syndrome, Laurence-Moon-Biedlsyndrome.

Potentially reversible causes:

Endocrine causes: hypothyroidism, cushing's syndrome, insulinoma. Hypothalamic disorders / injury.

Drugs: Sulphonylureas, corticosteroids, estrogen containing contraceptive pills, trycyclic antidepressant, Sodium valproate, beta blockers.

Table 14.1 Complications of obesity

Risk factors	Outcome
Metabolic syndrome Type 2 diabetes, Hypertension, hyperlipidemia	Coronary heart diseases, stroke, Diabetic complications
Liver fat accumulation	NAFLD, NASH, cirrhosis Liver
Retracted ventilation	Exertional dyspnea, sleep apnoea, respiratory failure- pickwickian syndrome
Mechanical effect of weight	Urinary incontinence, Osteoarthitis, Hernia, Vericose vein
Increased peripheral interconversion of steroid in adipose tissue	Cancer-Breast, uterus Polycystic ovary syndrome
Other	Psychosocial morbidity; Low self-esteem, depression, stigmatization, Socioeconomic disadvantage: low income, less likely to be promoted. Fungal infection-groin, submammary candidiasis. Hydroadenitis Gallstone, Colorectal cancer

Body fat distribution and clinical significance:

1. Cntral: abdalominal, visceral, android (apple shaped obesity in men)
2. Generalised: Subcuateneous, gynoid (Pearshaped obesity-women)

Type1 (intrabdominal fat)-closely associated with type 2 diabetes, metabolic syndrome and cardiovascular disease: Drain direct into portal vein to liver. Substances released from fat (FFA, adipokines, TNF, adiponectins, resistins, steroid hormones) induces insulin resistances hence type 2 DM and CVD.

Obesity in diabetes management: In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management. Individualize initial treatment approaches for obesity (i.e., lifestyle and nutritional therapy, physical activity and exercise, behavioral counseling, pharmacotherapy, medical devices, and metabolic surgery. Consider combining treatment approaches if appropriate.

Nutrition, Physical Activity, and Behavioral Therapy:

Interventions including high frequency of counseling (≥16 sessions in 6 months) with focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit have been shown to be beneficial for weight loss and should be considered when available.

For those who achieve weight loss goals, long-term (≥1 year) weight maintenance programs are recommended, when available. Effective programs provide monthly contact and support, recommend ongoing monitoring of body weight (weekly or more frequently) and other self-monitoring strategies, and encourage regular physical activity (200–300 min/week). Continuing adopted interventions to maintain goals long term. When short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) is considered, it should be prescribed to carefully selected individuals by trained practitioners in medical settings with close monitoring Nutritional supplements have not been shown to be effective for weight loss and are not recommended.

Table 14.2 Summary of obesity treatment

	BMI category (kg/m²)		
Treatment	25.0-26.9 (or 23.0-24.9*)	27.0-29.9 (or 25.0-27.4*)	≥30.0 (or ≥27.5*)
Nutrition, physical activity, and behavioral counseling	±	±	±
Pharmacotherapy		±	±
Metabolic surgery			±

Pharmacotherapy for obesity:

Whenever possible, minimize medications for comorbid conditions that are associated with weight gain.

Obesity pharmacotherapy should be considered for people with diabetes and overweight or obesity along with lifestyle changes. In people with diabetes and overweight or obesity, the preferred pharmacotherapy should be a glucagon-like peptide 1 receptor agonist or dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist with greater weight loss efficacy (*i.e.,* Semaglutide or Tirzepatide), especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic).

To reach goals, reevaluate weight management therapies and intensify treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs).

Glucose-Lowering Therapy:

Agents associated with clinically meaningful weight loss include glucagon-like peptide 1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist (Tirzepatide), sodium–glucose cotransporter 2 inhibitors, metformin, and amylin mimetics.

Dipeptidyl peptidase 4 inhibitors, centrally acting dopamine agonist (bromocriptine), α-glucosidase inhibitors, and bile acid sequestrants (colesevelam) are considered weight neutral.

In contrast, insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are often associated with weight gain.

Concomitant Medications:

Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), (fluoxetine, sibutramine does not increase weight) glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin and pregabalin), β-blockers, and possibly sedating antihistamines and anticholinergics

Obesity pharmacotherapy:

Medication name and typical adult maintenance dose:

- Short-term treatment (12 weeks): Sympathomimetic amine anorectic-Phentermine (8–37.5 mg q.d.)
- Long-term treatment (52 or 56 weeks): Lipase inhibitor -Orlistat (60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)
- Sympathomimetic amine anorectic/antiepileptic combination- Phentermine/topiramate (7.5 mg/46 mg q.d.)

- Opioid antagonist/antidepressant combination -Naltrexone/bupropion ER (16 mg/180 mg b.i.d).

Glucagon-like peptide 1 receptor agonist –

1. Liraglutide (3 mg q.d.)
2. Semaglutide (2.4 mg once weekly)

   Dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist

3. Tirzepatide (5 mg, 10 mg, or 15 mg once weekly)

Health care professionals should be knowledgeable about the benefits, dosing, and risks for each treatment option to balance the potential benefits of successful weight loss against the potential risks for each individual. Who achieve sufficient early weight loss upon starting a chronic obesity medication (typically defined as >5% weight loss after 3 months of use) should continue the medication long term.

Medical Devices for Weight Loss

Several minimally invasive medical devices have been approved by the FDA for short-term weight loss, including implanted gastric balloons, a vagus nerve stimulator, and gastric aspiration therapy. An oral hydrogel (cellulose and citric acid) has been approved for long-term use in those with BMI >25 kg/m2 to simulate the space-occupying effect of implantable gastric balloons all have uncertainty for their current use.

Metabolic surgery: Surgical procedures for obesity treatment—often referred to interchangeably as bariatric surgery, weight loss surgery, metabolic surgery, or metabolic/bariatric surgery—can promote significant and durable weight loss and improve type 2 diabetes.

Obesity

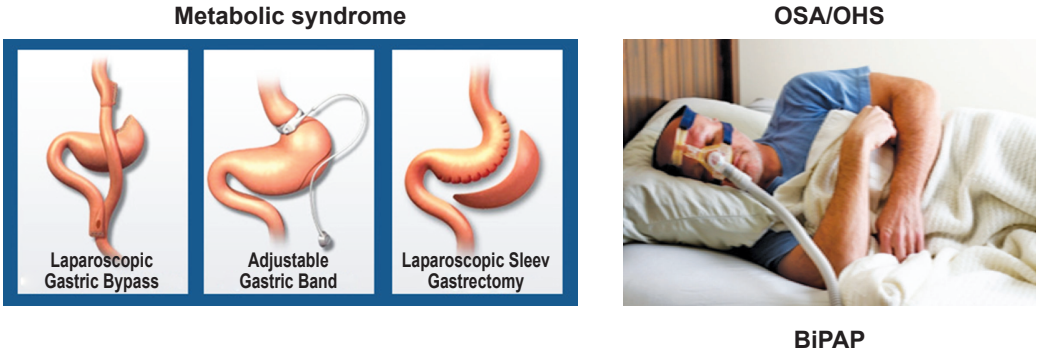


Figure 14.5: Metabolic Surgery

Bariatric surgery: Reduce size of stomach, most effective in long term, with low mortality. The overwhelming majority of procedures in the U.S. are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in enteroendocrine hormones. In VSG, ~80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch. RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum.

Disrupt release of ghrelin from stomach and other peptide from small bowel thereby enhances satiety signals to hypothalamus. Pursuit for motivated overwhelmingly indicated patient. Need Experienced specialists.

Cosmetic surgery like Apronectomy (-overhanging abdominal skin Liposuction) has no value in long term. Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI ≥40 kg/m2 (BMI ≥37.5 kg/m2 in Asian American individuals) and in adults with BMI 35.0–39.9 kg/m2 (32.5–37.4 kg/m2 in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods.

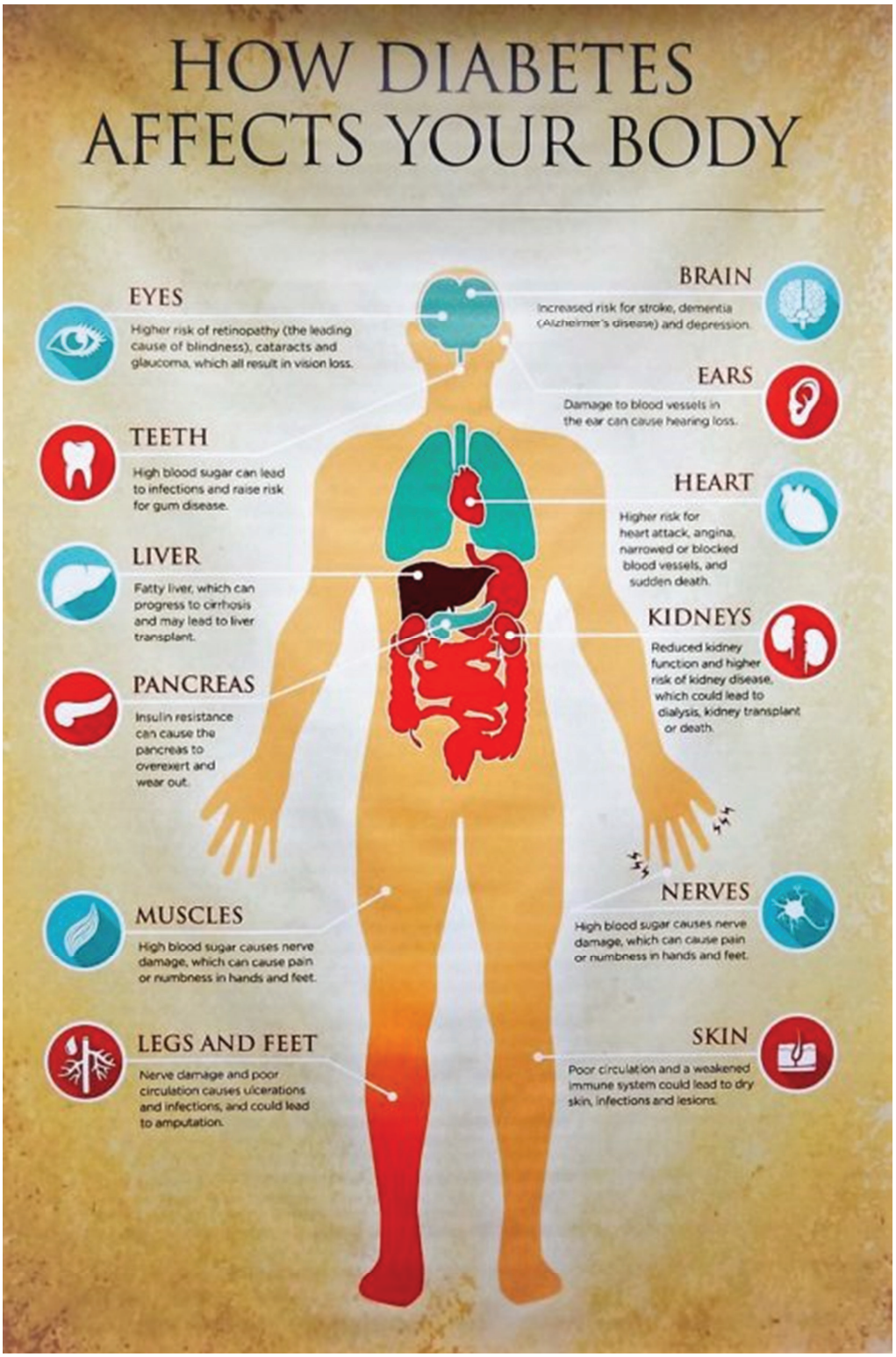
Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m2 (27.5–32.4 kg/m2 in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery. Studies have documented diabetes remission after 1–5 years in 30–63% of individuals with RYGB. and the majority of those who undergo surgery maintain substantial improvement of glycemia from baseline for at least 5–15 years.

Good predictor of success of metabolic surgery:

Younger age, shorter duration of diabetes (e.g., <8 years), and lesser severity of diabetes (better glycemic control, not using insulin) are associated with higher rates of diabetes remission. Greater baseline visceral fat area may also predict improved postoperative outcomes, especially among Asian American people with type 2 diabetes.

Suggested citation: *American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S52–S76*

Suggested citation: *American Diabetes Association Professional Practice Committee. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S145–S157*


HOW DIABETES AFFECTS YOUR BODY
EYES
Higher risk of retinopathy (the leading cause of blindness), cataracts and glaucoma, which all result in vision loss.
TEETH
High blood sugar can lead to infections and raise risk for gum disease.
LIVER
Fatty liver, which can progress to cirrhosis and may lead to liver transplant.
PANCREAS
Insulin resistance can cause the pancreas to overexert and wear out.
MUSCLES
High blood sugar causes nerve damage, which can cause pain or numbness in hands and feet.
LEGS AND FEET
Nerve damage and poor circulation causes ulcerations and infections, and could lead to amputation.
BRAIN
Increased risk for stroke, dementia (Alzheimer's disease) and depression.
EARS
Damage to blood vessels in the ear can cause hearing loss.
HEART
Higher risk for heart attack, angina, narrowed or blocked blood vessels, and sudden death.
KIDNEYS
Reduced kidney function and higher risk of kidney disease, which could lead to dialysis, kidney transplant or death.
NERVES
High blood sugar causes nerve damage, which can cause pain or numbness in hands and feet.
SKIN
Poor circulation and a weakened immune system could lead to dry skin, infections and lesions.

Diabetes with Complications

15
CHAPTER

Cardiovascular Diseases in Diabetes and Risks Managements

Summary:
Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral artery disease (PAD) presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes. Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes.

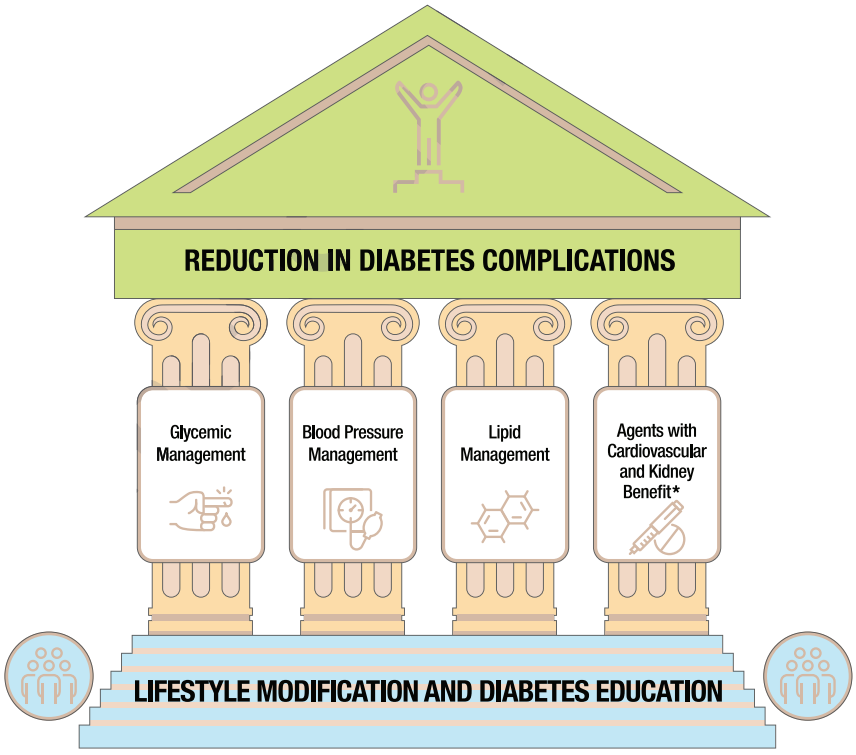


Figure 15.1: Multifactorial approach to reduction in risk of diabetes complications.
*Risk reduction interventions to be applied as individually appropriate.

Large benefits are seen when multiple cardiovascular risk factors (glycemic, blood pressure, and lipid control) are addressed simultaneously. There is evidence that measures of 10-year CHD risk among (ref:2013 ASCVD risk calculator, Google) in U.S. adults with diabetes have improved significantly over the past decade.

High Blood Pressure (hypertension) Control to reduce CVD risks

Summary: Numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications.

- Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (ACCA, AHA).
- Blood pressure should be measured at every routine clinical visit.
- When possible individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension.
- Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit.

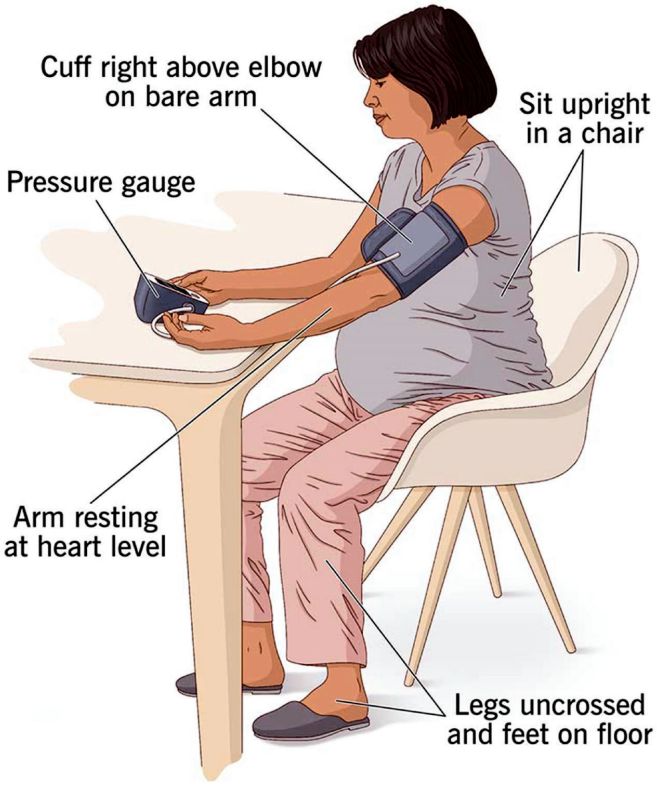


Figure 15.2: Method of BP measurement

Method of BP measurement: Measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference.

Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and “true” blood pressure. Home blood pressure monitoring may improve medication-taking behavior and thus help reduce cardiovascular risk .

Treatment Goals

1. For people with diabetes and hypertension: Blood pressure targets should be individualized. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. Treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Risk of adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury (AKI) needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

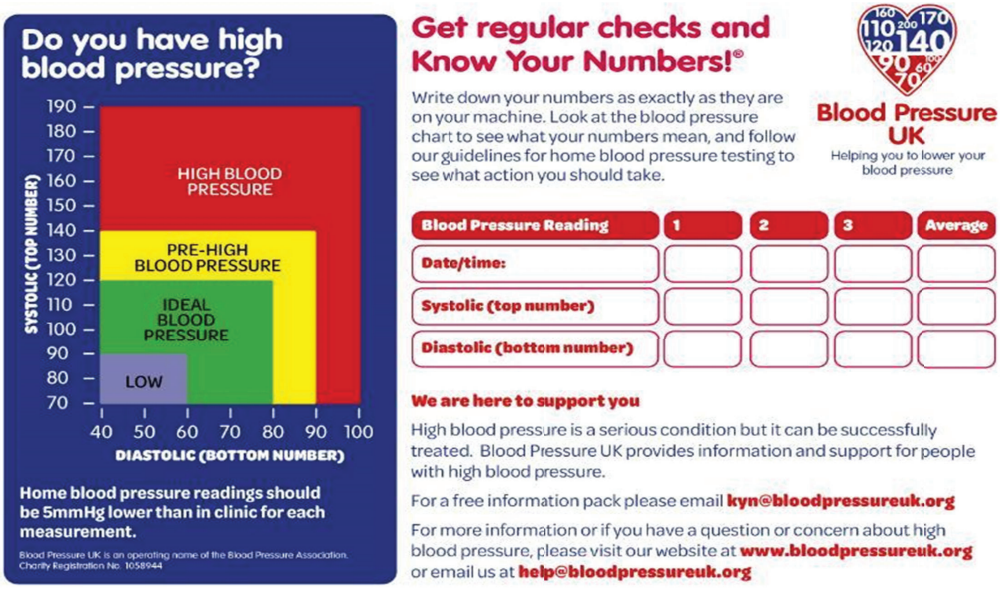


Figure 15.3: Individualization of Treatment Targets BP

Evidences: Recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association, the International Society of Hypertension, and the European Society of Cardiology. Based several meta-analyses of stratified clinical trials on antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg.

Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

2. Individualization of Treatment Targets

Absolute benefit from blood pressure reduction correlated with absolute baseline This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes. The presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

3. Pregnancy Hypertension and Antihypertensive Medications

Gestational hypertension (ACOG) definition:Blood pressure greater than or equal to 140 mmHg systolic or 9o mmHg diastolic on two occasions at least 6 hours apart without proteinuria after 20 weeks of pregnancy when previous blood pressure was normal.

Target of treatment: In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure <90/60 mmHg. Blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth.

Drugs in Pregnancy hypertension:

During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors, and spironolactone are contraindicated, as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy.

Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia. Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control.

Follow up of gestational HTN:

The American College of Obstetricians and Gynecologists (ACOG)also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and 7–10 days postpartum.

Long-term follow-up is recommended for these individuals, as they have increased lifetime cardiovascular risk.

Treatment strategies of hypertension in diabetes:

- Lifestyle Intervention: For people with blood pressure >120/80 mmHg:

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects.

Dietary Approaches to Stop Hypertension (DASH)–style eating pattern including reducing sodium and increasing potassium intake, increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women, smoking cessation and increasing activity levels.

Lifestyle therapy consists of reducing excess body weight through caloric restriction at least 150 min of moderate-intensity aerobic activity per week.

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (Fig.15.4).

A lifestyle therapy plan should be developed in collaboration with the person with diabetes and discussed as part of diabetes management.

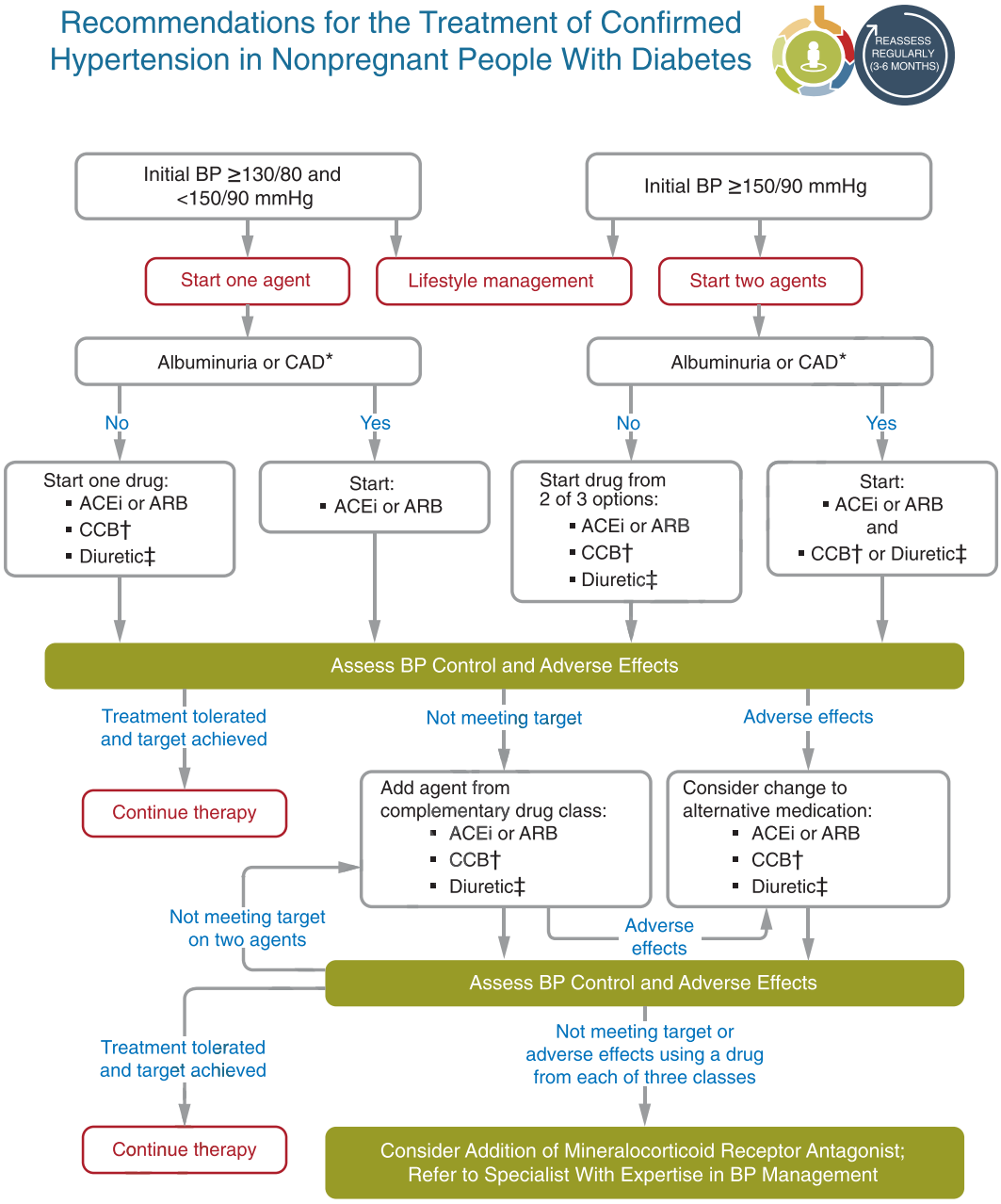


Figure 15.4: Individualization of Treatment Targets recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes.

*An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. †Dihydropyridine calcium channel blocker (CCB). Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. BP, blood pressure. *de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017; 40:1273–1284.*

Summary of pharmacologic Interventions

1. Individuals with confirmed office-based blood pressure ≥130/80 mmHg qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of <130/80 mmHg.

2. Individuals with confirmed office-based blood pressure ≥150/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes.

3. Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs/neprilysin inhibitors) with direct renin inhibitors should not be used.

4. An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine or 30–299 mg/g creatinine. If one class is not tolerated, the other should be substituted.

5. For adults treated with an ACE inhibitor, ARB, mineralocorticoid receptor antagonist (MRA), or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored within 7–14 days after initiation of therapy and as and when needed or annually.at least

Treatment pearls:

1. Initial Number of Antihypertensive Medications:

   Those with blood pressure between 130/80 mmHg and 150/90 mmHg may begin with a single drug. For individuals with blood pressure ≥150/90 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended). Single-pill antihypertensive combinations may improve medication taking in some individuals.

2. Classes of Antihypertensive Medications:

   a) treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors ARBs, thiazide-like diuretics, or dihydropyridine calcium channel blockers.

   b) In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension. For individuals with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB to reduce the risk of progressive kidney disease (Fig.15.4). In individuals receiving ACE inhibitor or

ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease. In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardio protection compared with thiazide-like diuretics or dihydropyridine calcium channel blockers.

c) β-Blockers are indicated in the setting of prior MI, active angina, or HFrEF but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions.

3. Multiple-Drug Therapy:

Multiple-drug therapy is often required to achieve blood pressure targets (Fig-15.4), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated. Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

4. Bedtime Dosing:

Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications, these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended.

5. Hyperkalemia and Acute Kidney Injury:

Treatment with ACE inhibitors/ARBs or mineralocorticoid receptor antagonists (MRAs) can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death. Therefore, serum creatinine and potassium should be monitored after initiation of treatment with an ACE inhibitor/ARB, MRA, or diuretic and monitored during treatment particularly among individuals with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI.

Resistant Hypertension

Definition: Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses:

Prior to diagnosing resistant hypertension, a number of other conditions should be excluded,

1. Including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension.

2. People with diabetes and confirmed resistant hypertension should be evaluated for secondary causes of hypertension, including primary hyperaldosteronism, renal artery stenosis, diabetic kidney disease, and obstructive sleep apnea.

Treatment of resistant HTN: MRAs, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker. In addition, MRAs reduce albuminuria in people with diabetic nephropathy. However, adding an MRA to a treatment plan that includes an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these individuals, and long-term outcome studies are needed to better evaluate the role of MRAs in blood pressure management.

Dyslipidemia in Diabetics & management to reduce CVD risks

Introduction: Thrombogenic dyslipidemia

Lipid profile in diabetics is usually thrombogenic characterized by:

1. High triglycerides, low HDL (good cholesterol), Normal or high LDL (low density lipoprotein-bad cholesterol), high 'small, dense' LDL (IDL intermediate dense lipoprotein).

Lipid measurement pearl:

Fasting lipid profile: measured after 12 hours fasting. It helps using friedewald equation to estimate lipid profile.

Friedewald Equation:

LDL(C) = TC-HDL(C) - (TG/2.2) mmol/L

Or

LDL(C) = TC-HDL(C) – (TG/5) mg/dl

TC- Total cholesterol
TG- Triglyceride
LDL- Low density lipoprotein
HDL- High density lipoprotein

The formula become unreliable if TG level exceed 4 mmol/L or 350 mg/dL.

Non fasting lipid measurement:

Non-HDL(C) = TC-HDL(C); normal nonHDL(C) = LDL(C) + 30mg/dl

In diabetes mellitus TG mostly high. Measurement Non-HDL(C) and Apo B may provide more accurate risk assessment.

Lipid Management in Diabetes mellitus

Summary (Four essentials)

1. Lifestyle Intervention -Diet &physical activity to attain ideal weight, behavior change.
    - Application of a Mediterranean or DASH eating pattern; reduction of saturated fat and trans-fat; increase of dietary n-3 fatty acids, viscous fiber (such as in oats, legumes, and citrus), and plant stanol/sterol intake (vegetable oil, nut, legumes, cereals, vegetables); and increased physical activity.

- Intensify lifestyle therapy and optimize glycemic control for people with diabetes with elevated triglyceride levels (≥150 mg/dL [≥1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women).
- Lifestyle intervention, including weight loss in people with overweight or obesity, increased physical activity, and medical nutrition therapy,

2. Glycemic control
3. Pharmacotherapy
4. Smoking cessation

Monitoring: Ongoing Therapy and Monitoring with Lipid Panel

Frequency of test:

A. In adults with prediabetes or diabetes not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diagnosis. Those who are taking statins or other lipid-lowering therapy at an-

- Initial medical evaluation,
- 4–12 weeks after initiation or
- At a change in dose, and
- Annually thereafter, or
- More frequently if indicated.

B. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable.

Clinical pearl:

In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood. Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses.

Statin Treatment

Primary Prevention

- For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy.
- For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy.
- For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L)

- For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple ASCVD risk factors and an LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy.
- In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment.
- In adults with diabetes aged >75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks.
- In people with diabetes intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan.
- Statin therapy is contraindicated in pregnancy.

Secondary Prevention

- For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy.
- For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy.
- For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, Bempedoic acid therapy, or PCSK9 inhibitor therapy with inclisiran siRNA should be considered as an alternative cholesterol-lowering therapy.

Initiating Statin Therapy Based on Risk

Important:

Meta-analyses including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years) demonstrated a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol. The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed.

Two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve an approximately ≥50% reduction in LDL cholesterol, and moderate-intensity statin plans achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that an individual can tolerate. For individuals who

do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

Table 15.1 High-intensity and moderate-intensity statin therapy:

High-intensity statin therapy	Moderate-intensity statin therapy
(Lowers LDL cholesterol by ≥ 50%)	(Lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

****As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing.*

Primary Prevention (People Without ASCVD) with diabetes:

For primary prevention,

A. Aged ≥40 years: moderate-dose statin therapy is recommended for those, although high-intensity therapy should be considered in the context of additional ASCVD risk factors. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to target an LDL cholesterol of <70 mg/dL (<1.8 mmol/L). It may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol target of <70 mg/dL (<1.8 mmol/L

B. Age <40 Years and/or Type 1 Diabetes.

Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age. Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Individuals <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high.

Secondary Prevention (People With ASCVD)

Because cardiovascular event rates are increased in people with diabetes and established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe. Data (IMPROVE-IT) showed a significant reduction of major adverse cardiovascular events.

Intolerance to Statin Therapy

Initial steps in people intolerant to statins may include 1. switching to a different high-intensity statin if a high-intensity statin is indicated, 2. switching to moderate-intensity or low-intensity statin, 3. lowering the statin dose, or 4. using nondaily dosing of statins. While considering these alternative treatment plans, 5.the addition of nonstatin treatment plans to maximum tolerated statin therapy should be considered, as these are frequently associated with improved adherence and target LDL cholesterol goal achievement.

Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia treatment:

- For individuals with fasting triglyceride levels ≥500 mg/dL (≥5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis.
- In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL [2.0–5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides.
- In individuals with ASCVD or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL [1.5–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk.
- Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol. Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see statin treatment).

Clinical pearl:

1. Low levels of HDL cholesterol: often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy. In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes.
2. Combination Therapy: Statin plus fibrate

   Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended.
3. Diabetes Risk with Statin Use

   An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes, even for individuals at highest risk for diabetes
4. Lipid-Lowering Agents and Cognitive Function

   Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement ,the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) published data do not reveal an adverse effect of statins on cognition Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD .

Cardiovascular diseases risk reduction:
Antiplatelet Agents

Summary

- Dosing: Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD.For individuals with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used.
- Duration: Dual antiplatelet: length of treatment with dual antiplatelet therapy using low-dose aspirin and a P2Y12 inhibitor in individuals with diabetes after an acute coronary syndrome or acute ischemic stroke/transient ischemic attack should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively.
- Combination with (anti thrombotic, aspirin): Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) and low bleeding risk to prevent major adverse limb and cardiovascular events.

The risks and benefits of dual antiplatelet (aspirin, ticagerol, prasugrel, clopidegrol) or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible individuals, and shared decision-making should be used to determine an individually appropriate treatment approach. However, a higher incidence of major bleeding, bleeding without a corresponding increase in the risks of mortality and ischemic events in TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial was ludent.

Aspirin dialogue

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk individuals with previous MI or stroke (secondary prevention) and is strongly recommended. The excess risk may be as high as 5 per 1,000 per year in real-world settings.

For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit.

Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended

Aspirin Use in People <50 Years of Age.

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors), as the low benefit is likely to be outweighed by the risk of bleeding.

use in individuals aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects. In the U.S., the most common low-dose tablet is 81 mg.

Cardiovascular Disease

Screening

- In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated.
- Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves).
- Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP

[NT-proBNP]) to facilitate prevention of stage C heart failure.

- In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure.
- In asymptomatic individuals with diabetes and age ≥50 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended to guide treatment for cardiovascular disease prevention and limb preservation. In individuals with diabetes duration ≥10 years, screening for PAD should be considered.

Treatment strategies of diabetic cardiovascular diseases:

Summary:

1. Among people with type 2 diabetes who have established ASCVD or multiple ASCVD risk factors or established kidney disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated cardiovascular disease benefit or their combination is recommended as part of the comprehensive cardiovascular risk and kidney events reduction and/or glucose-lowering treatment plans.
2. In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor (including SGLT1/2 inhibitor) with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death and also to improve symptoms, physical limitations, and quality of life.
4. For individuals with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of Finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. In individuals with type 2 diabetes and diabetic kidney disease, Finerenone is recommended to reduce the risk of hospitalization for heart failure.
5. In individuals with diabetes with established ASCVD or aged ≥55 years with additional cardiovascular risk factors, ACE inhibitor or ARB therapy is recommended to reduce the risk of cardiovascular events and mortality.
6. In individuals with diabetes and asymptomatic stage B heart failure, an interprofessional approach to optimize guideline-directed medical therapy, which should include a cardiovascular disease specialist, is recommended to reduce the risk for progression to symptomatic (stage C) heart failure.
7. In individuals with diabetes and asymptomatic stage B heart failure, ACE inhibitors/ARBs and β-blockers are recommended to reduce the risk for progression to symptomatic (stage C) heart failure.
8. In individuals with type 2 diabetes and asymptomatic stage B heart failure or with high risk of or established cardiovascular disease, treatment with an SGLT inhibitor

(including SGLT2 or SGLT1/2 inhibitors) is recommended to reduce the risk of hospitalization for heart failure.

10. In individuals with diabetes, guideline-directed medical therapy for myocardial infarction and symptomatic stage C heart failure is recommended with ACE inhibitors/ARBs, MRAs, angiotensin receptor/neprilysin inhibitor, β-blockers, and SGLT2 inhibitors, similar to guideline-directed medical therapy for people without diabetes.
11. In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m2 but should be avoided in unstable or hospitalized individuals with heart failure.
12. Individuals with type 1 diabetes and those with type 2 diabetes who are ketosis prone and/or those consuming ketogenic diets who are treated with SGLT inhibition should be educated on the risks and signs of ketoacidosis and methods of risk management and provided with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate).

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting electrocardiogram (ECG).

Exercise ECG testing without or with echocardiography may be used as the initial test.

Coronary artery calcium: In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population.

Nuclear imaging: Pharmacologic stress echocardiography or nuclear imaging should be considered in an individual with diabetes in whom-

a. resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities).

b. those are unable to exercise.

Clinical pearls:

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes. The ultimate balance of benefit, cost, and risk of such an approach in asymptomatic individuals remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Diabetes and heart failure

Screening for Asymptomatic Heart Failure in People with Diabetes

People with diabetes are at an increased risk for developing heart failure, as shown in multiple longitudinal, observational studies. *For a detailed review of screening, diagnosis, and treatment (ADA consensus report "Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association*").

Heart failure in people with diabetes is classified as:

a. Stage A heart failure: an increased risk for heart failure but without symptoms, structural heart disease, or biomarker evidence of myocardial strain.

b. Stage B heart failure: Similar to those with stage A heart failure, people with stage B heart failure are asymptomatic but have evidence of structural heart disease or functional cardiac abnormalities, including elevated biomarkers of myocardial strain or increased filling pressures. During these asymptomatic stages of heart failure, people with diabetes are at particularly high risk for progression to.

c. Symptomatic stage C and D heart failure.

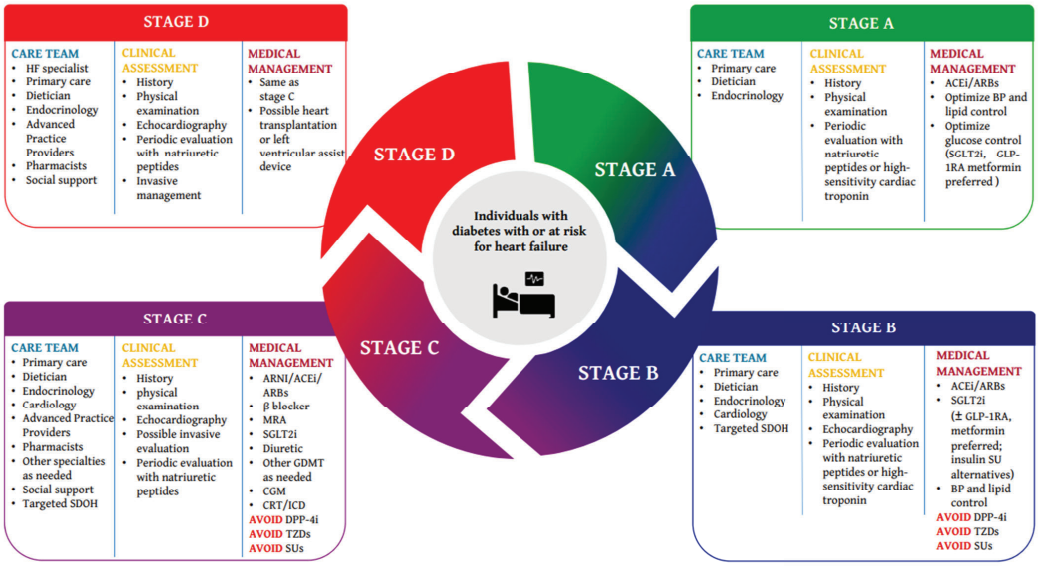


Figure 15.5: Stages of heart failure & treatment guideline

Natriuretic peptides:

In people with type 2 diabetes, measurement of natriuretic peptides, including B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), identifies people at risk (CANVAS, EXAMINE MESA trials,).

Results from several randomized controlled trials revealed that more intensive treatment of risk factors in people with increased levels of natriuretic peptides reduces the risk for symptomatic heart failure, heart failure hospitalization, and newly diagnosed left ventricular dysfunction. (PONTIAC, STOP-HF, Steno-2 trial).

BNP or NT-proBNP levels (**Biomarker for Heart Failure**): The biomarker threshold for abnormal values is a BNP level ≥50 pg/mL and NT-proBNP ≥125 pg/mL.

Falacies:

- Non cardiac causes of Increased levels of natriuretic peptide: including renal insufficiency, pulmonary disease including pulmonary hypertension and chronic obstructive lung disease, obstructive sleep apnea, ischemic and hemorrhagic stroke, and anemia.
- Decreased in the population with obesity, which impairs sensitivity of testing.

Clinical pearls:

People with diabetes and an elevated natriuretic peptide level without any symptoms of heart failure should be considered to have stage B heart failure. An echocardiography is recommended as the next step to screen for structural heart disease and echocardiographic doppler indices for evidence of diastolic dysfunction and increased filling pressures, and is recommended to implement a guideline-directed medical treatment strategy, which may reduce the risk of progression to symptomatic stages of heart failure.

ADA consensus report on heart failure and with current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure.

Diabetes and Peripheral arterial diseases (PAD):

Evidences:

Screening for Asymptomatic Peripheral Artery Disease (PAD)in People with Diabetes (PARTNERS) program and others: 30% of people aged 50–69 years with a history of cigarette smoking or diabetes, or aged ≥70 years regardless of risk factors, had PAD. Diabetes increased the odds of having PAD by 85%.

Symptoms/signs:

Classical symptoms of claudication are uncommon, and almost half of people with newly diagnosed PAD were asymptomatic. Conversely, up to two-thirds of people with asymptomatic PAD have been shown to have comorbid diabetes.

Risk factors: Risk factors associated with an increased risk for PAD in people with diabetes include age, smoking, hypertension, dyslipidemia, worse glycemic control, longer duration of diabetes, neuropathy, and retinopathy as well as a prior history of cardiovascular disease. The presence of microvascular disease is associated with adverse outcomes in people with PAD, including an increased risk for future limb amputation.

Screening

Is recommended for asymptomatic PAD using ankle-brachial index in people with diabetes at high risk for PAD, including any of the following:

1. age ≥50 years,
2. diabetes with duration ≥10 years,

3. Comorbid microvascular disease,
4. Clinical evidence of foot complications, or
5. Any end-organ damage from diabetes.

Cardiovascular disease risk reduction

A. Lifestyle and Pharmacologic Interventions

- Intensive lifestyle intervention (Look AHEAD) trial focusing on weight loss through decreased caloric intake and increased physical activity, as performed in the Action for Health in Diabetes, may be considered for improving glucose control, fitness, and some ASCVD risk factors.
- Pharmacotherapy: Individuals at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the individual has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class.

B. ACE inhibitor or ARB: Clear cardiovascular benefit exists for ACE inhibitor or ARB therapy in people with diabetes. (HOPE).

- reduced cardiovascular and all-cause mortality, MI, and stroke.
- have benefit in people with diabetes and diabetic kidney disease or hypertension, and
- recommended for hypertension management in people with known ASCVD (particularly coronary artery disease)

C. Finerone: People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression.

D. β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function.

E. Glucose - Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes amid concerns of increased cardiovascular risk.

Several studies (SUSTAIN, LEADER. EMPA_REG, CANVAS, DECLARE) carried on to prove cardiorenal safety of Glucose-Lowering Therapies.

Prevention and Treatment of Heart Failure

Prevention of Symptomatic Heart Failure

- lifestyle intervention with diet, physical activity, weight control, and smoking cessation.
- ACE Inhibitors/ARBs and β-Blockers: The vast majority of incident heart failure is preceded by hypertension; (up to 91%), use of ACE inhibitors or ARBs is the preferred treatment strategy for management of hypertension in people with diabetes, particularly in the presence of albuminuria or coronary artery disease.

- ACE inhibitors/ARBs plus β-blockers
- . People with diabetes and stage B heart failure who remain asymptomatic but have evidence of structural heart disease, including history of MI, acute coronary syndrome, or left ventricular ejection fraction (LVEF) ≤40%, should be treated with ACE inhibitors/ARBs plus β-blockers according to current treatment guidelines.
- The Carvedilol: Showed Post-Infarct Survival and hospitalization benefit.
- Metoprolol improved adverse cardiac remodeling (REVERT) trial.
- SGLT inhibitor treatment is recommended in asymptomatic people with type 2 diabetes at risk or with established cardiovascular disease to prevent incident heart failure and hospitalization from heart failure. EMPA - REG, CANVAS, DAPA-HFSCORED trials)
- Finerenone is a nonsteroidal MRA and has recently been studied and finerenone is recommended in people with type 2 diabetes and diabetic kidney disease to reduce the risk of progression from stage A heart failure to symptomatic incident heart failure. (FIDELIO-DKD) (FIGARO-DKD) studies.

Treatment of Symptomatic Heart Failure

In general, current guideline-directed medical therapy for a history of MI and symptomatic stage C and D heart failure in people with diabetes is similar to that for people without diabetes.

The treatment recommendations are detailed in current 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure

Glucose-Lowering Medications and Heart Failure: Thiazolidinediones have a strong and consistent relationship with increased risk of heart failure.

Metformin: Restrictions to use in people with medically treated heart failure were removed by the FDA in 2006 (9). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use .

DPP4i: The Saxagliptin is not approved, others of non-cardiovascular benefit.

GLP-1 receptor agonists: lixisenatide, liraglutide, semaglutide, exenatide once weekly, albiglutide, or dulaglutide compared with placebo showing benefit.

SGLT2: Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors primary outcome was consistent regardless of the presence or absence of type 2 diabetes (10). SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

Clinical pearl:

In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure and improvement in symptoms, physical symptoms and quality of life. Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death.

Sotagliflozin

Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, was recently approved by the FDA in the U.S. to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure in people with heart failure or type 2 diabetes, CKD, and other cardiovascular risk factors.

This drug is distinct from other SGLT inhibitors, as it lowers glucose via delayed glucose absorption in the gut via inhibition of the cotransporter SGLT1 in addition to increasing urinary glucose excretion; however, it is not currently approved by the FDA for glycemic management of type 1 or type 2 diabetes. .

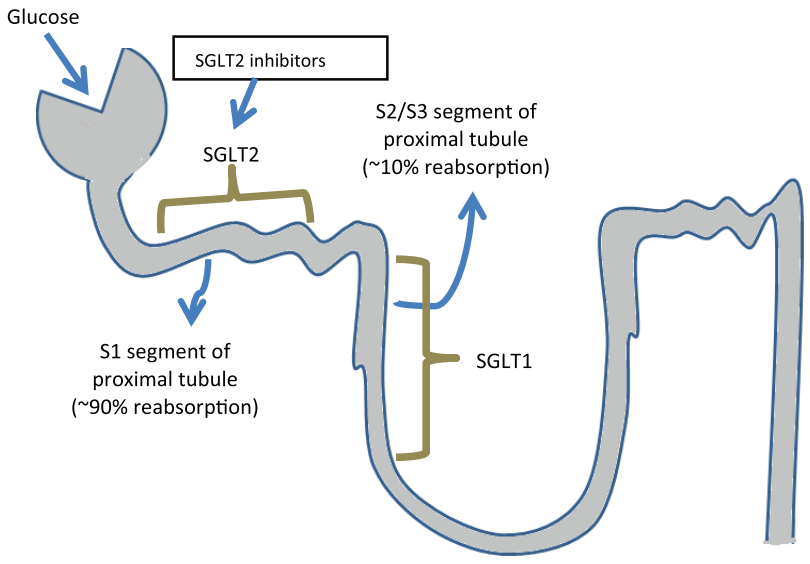


Figure 15.6: SGLT I mechanism & site of action

One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis, including the atypical presentation of euglycemic ketoacidosis.

SGLTi and Ketosis:

There are multiple proposed pathways through which SGLT inhibition results in ketosis (increased β-hydroxybutyrate and acetoacetate), such as

1. Increased production due to reduction in insulin doses,
2. Increases in glucagon levels leading to increased lipolysis and ketone production, and
3. Decreased renal clearance of ketones.

Finerone

- a selective nonsteroidal MRA, has been shown to
- improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria.
- improves cardiovascular and renal outcomes in people with type 2 diabetes
- people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of Finerenone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Clinical Approach (SGLT 2 I, GLP-1 agonist)

ADA-*endorsed American College of Cardiology "2020 Expert Consensus Decision, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.*

- Adoption of these agents (SGLT 2 I, GLP-1 agonist) should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management.
- Incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of individuals with more long-standing diabetes, with complex glucose-lowering plan. SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications.

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence. of albuminuria along with h modifiable risk factors

Suggested citation: *American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S179–S218.*

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CHAPTER

Chronic Kidney Disease in Diabetes

Screening

- Non CKD:At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] should be assessed in people with type 1 diabetes with duration of ≥5 years and in all people with type 2 diabetes regardless of treatment.
- CKD:In people with established chronic kidney disease (CKD), urinary albumin (e.g., spot UACR) and eGFR should be monitored 1–4 times per year depending on the stage of the kidney disease (Fig.16.1).

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD) | High risk
Moderately increased risk | Very high risk

Figure 16.1: Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted and adapted from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090.

Treatment of Diabetic Kidney Disease

Summary: 5 therapeutic pillars of treatment of Diabetic kidney disease-

1. Renin-angiotensin aldosterone inhibitors
2. Statins
3. SGLT2i
4. GLP-1
5. Non-steroidal selective mineralocorticoid receptor antagonist

Options of treatment of Diabetic kidney disease

A. Blood glucose: Optimize glucose management to reduce the risk or slow the progression of CKD.

B. Blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk.

C. ACEi, ARB: In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) and is strongly recommended for those with severely increased albuminuria (UACR ≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m2 to prevent the progression of kidney disease and reduce cardiovascular events. Periodically monitor for increased serum creatinine and potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists are used, or for hypokalemia when diuretics are used. Do not discontinue renin-angiotensin system blockade for mild to moderate increases in serum creatinine (≤30%) in the absence of signs of extracellular fluid volume depletion. *An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR.*

D. Sodium–glucose cotransporter 2 (SGLT2) inhibitor; For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m2 and urinary albumin ≥200 mg/g creatinine.

E. Nonsteroidal mineralocorticoid receptor antagonist As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥25 mL/min/1.73 m2). Potassium levels should be monitored. *In people with CKD who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression.*

F. Dietary protein intake: For people with non–dialysis-dependent stage G3 or higher CKD, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day. For individuals on dialysis, 1.0–1.2 g/kg/day of dietary protein intake should be

considered since protein energy wasting is a major problem in some individuals on dialysis

For cardiovascular risk reduction in people with type 2 diabetes and CKD, consider use of an SGLT2 inhibitor (if eGFR is ≥20 mL/min/1.73 m2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if eGFR is ≥25 mL/min/1.73 m2).

G. Referral to Nephrologist: Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m2. Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

Epidemiology of Diabetes Kidney Disease

Definition: Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage.

Epidemiology:

CKD attributed to diabetes (diabetic kidney disease) in adults, which occurs in 20–40% of people with diabetes. Diabetic kidney disease typically develops after a diabetes duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation and is the leading cause of ESKD in the U.S.

Assessment of Albuminuria and Estimated Glomerular Filtration Rate

UACR: Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection. Timed or 24-h collections are more burdensome and add little to prediction or accuracy. two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering an individual to have moderately or severely elevated albuminuria (1,12,13). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage

Normal level of urine albumin excretion is defined as <30 mg/g creatinine, moderately elevated albuminuria is defined as ≥30–300 mg/g creatinine, and severely elevated albuminuria is defined as ≥300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with kidney and cardiovascular outcomes.

eGFR: Traditionally, eGFR is calculated from serum creatinine using a validated formula. eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently <60 mL/min/1.73 m2 and/or an urinary albumin value of >30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 r. Thus, it was decided that the equation should be altered such that it applies to all.

Diagnosis of Diabetic Kidney Disease and controversy:

Diabetic kidney disease is a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of diabetic kidney disease may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S.

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For individuals with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered.

Acute Kidney Injury

Acute kidney injury (AKI) is diagnosed by a sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR. People with diabetes are at higher risk of AKI than those without diabetes. Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), certain intravenous dyes (e.g., iodinated radiocontrast agents) and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease or high CVD risk with normal kidney function. It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression.

Staging of Chronic Kidney Disease

Stage G1 and stage G2 CKD are defined by evidence of high albuminuria with eGFR ≥60 mL/min/1.73 m2, and stages G3–G5 CKD are defined by progressively lower ranges of eGFR (Fig. 16.1). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality. Therefore, there is an additional subclassification by level of urine albumin (Fig. 16). Furthermore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex. Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions.

Quantification of eGFR levels is essential for modifications of medication dosages or restrictions of use (Fig. 16), and the degree of albuminuria should influence the choice of antihypertensive medications.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD) · High risk · Moderately increased risk · Very high risk

Figure 16.2: Grading of Chronic Kidney diseases eGFR and Albuminuria grading

Clinical pearls:

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI. An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrated that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease. Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.

Surveillance

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose medications appropriately, and determine whether nephrology referral is needed. Serum potassium should also be monitored measured periodically. exposure to nephrotoxins should be evaluated for potential CKD complications (Table-16.1). There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE

inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure targets). Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in UACR. The prevalence of CKD complications correlates with eGFR. When eGFR is <60 mL/min/1.73 m2, screening for complications of CKD is indicated. Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESKD.

Table 16.1 Screening for selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m2 (stage G3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage G3 CKD, every 3–5 months for stage G4 CKD, and every 1–3 months for stage G5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Prevention

The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure control (blood pressure <130/80 mmHg).

Interventions

Nutrition

Daily Protein: For people with non–dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the

amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline. For individuals on dialysis, higher levels of dietary protein intake should be considered since malnutrition is a major problem for some individuals on dialysis

Sodium, Potassium: Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk, and individualization of dietary potassium may be necessary to control serum potassium concentrations. Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Goals

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes and type 2 diabetes, lowering blood glucose itself helps prevent CKD and its progression

Adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline. Therefore, in some people with prevalent CKD and substantial comorbidity, treatment may be less intensive (i.e., A1C goals may be higher to decrease the risk of hypoglycemia. A1C levels are also less reliable at advanced CKD stages.

Blood Pressure and chronic kidney disease:

Use of ACE Inhibitors and Angiotensin Receptor Blockers

- ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR <60 mL/min/1.73 m2, and UACR ≥300 mg/g creatinine because of their proven benefits for -
    1. prevention of CKD progression
    2. reduces the risk of albuminuria
    3. reduces the risk of progression to ESKD.

    ACE inhibitors and ARBs are considered to have similar benefits and risks. Moreover, antihypertensive therapy (ACEi/ARB) reduces the risk of cardiovascular events among people with diabetes, hypertension, CKD and Proteinuria.
- No renoprotective effect in normotensives: Two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs among people with type 1 and type 2 diabetes who were normotensive with or without high albuminuria (formerly microalbuminuria, 30–299 mg/g creatinine).
- ACEi/ARB maximum doses: It should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of concerns that serum creatinine will rise. Not maximizing these therapies for this reason would be

considered suboptimal care. In all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal mineralocorticoid receptor antagonist effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

- Benefit with eGFR<30: Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR <30 mL/min/1.73 m2. Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued.
- ACEi/ARB in absence of kidney disease: In the absence of kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers. Furthermore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Renal Effects of Glucose-Lowering Medications

- SGLT2i: SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia. SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity.
- Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo, although a definitive resolution as to the renoprotective effects of GLP-1 RAs is yet to be determined.
- Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease.For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia.

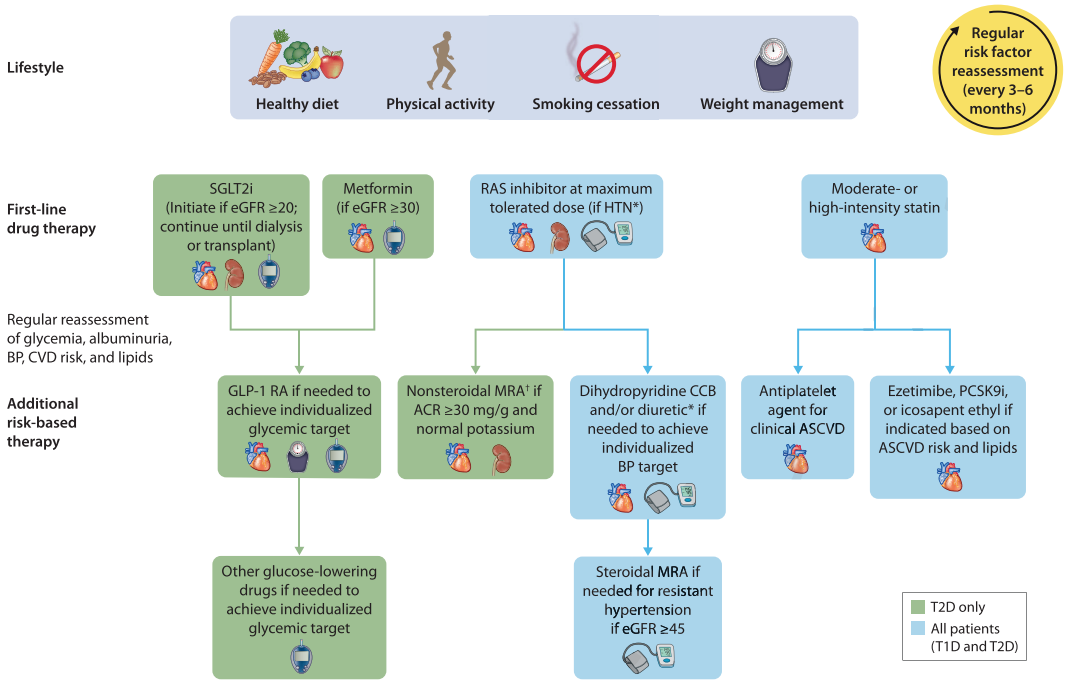


Figure 16.3: Holistic approach for improving outcomes in people with diabetes and CKD.

*Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Reprinted from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090*

Clinical pearl:

Metformin: The FDA revised its guidance for the use of metformin in CKD in 2016 , recommending use of eGFR instead of serum creatinine to guide treatment and expanding

the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that 1) metformin is contraindicated in individuals with an eGFR <30 mL/min/1.73 m2, 2) eGFR should be monitored while taking metformin, 3) the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m2 , 4) metformin should not be initiated for individuals with an eGFR <45 mL/min/1.73 m2, and 5) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30–60 mL/min/1.73 m2.

SGLT2 inhibitors & GLP-1 RAs: are recommended for people with eGFR ≥20 mL/min/1.73 m2 and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management. GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression. (EMPA-REG OUTCOME, CANVAS Study, LEADER (Results), and SUSTAIN-6 outcome) (CREDENCE evaluation). GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment .

Non-steroidal Mineralocorticoid Receptor Antagonists: Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease: The non-steroidal mineralocorticoid Finerone has been studied for cardio renal effects.

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) & Finerone in Reducing Cardiovascular Mortality and Morbidity (FIGARO-DKD) trial, which examined the renal and cardiovascular effects of Finerenone, demonstrated a significant reduction in diabetic kidney disease progression and cardiovascular events (36%-57% reduction in ESKD with incidences of hyperkalemia and cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure in people with advanced diabetic kidney disease. While using Finerenone, Serum potassium to be monitored.

Clinical pearl:

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and renal outcomes with Finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

Referral to a Nephrologist

Health care professionals should consider referral to a nephrologist if the individual with diabetes has-

- Continuously rising UACR levels and/or continuously declining eGFR,
- Uncertainty about the etiology of kidney disease,
- Difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances),

- Advanced kidney disease (eGFR <30 mL/min/1.73 m2) requiring discussion of renal replacement therapy for ESKD.

Clinical Pearl:

Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m2) has been found to reduce cost, improve quality of care, and delay dialysis. Other specialists and health care professionals should also educate people with diabetes about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

Suggested citation: American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S219–S230.

17
CHAPTER

Neuropathy in Diabetes

Diabetic peripheral neuropathy (DPN) refers to the development of peripheral nerve dysfunction in patients with diabetes when other causes are excluded. Diabetic distal symmetric polyneuropathy (DSPN) is the most representative form of DPN. As one of the most common complications of diabetes, its prevalence increases with the duration of diabetes. 10-15% of newly diagnosed T2DM patients have DSPN, and the prevalence can exceed 50% in patients with diabetes for more than 10 years.

Screening:

Somatic

- When: All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter.
- Distal symmetric polyneuropathy: History and assessment of either temperature or pinprick sensation (small-fiber function).
- Vibration sensation using a 128-Hz tuning fork (for large-fiber function).
- Annual 10-g monofilament testing to identify feet at risk for ulceration and amputation.(fig-17.1)

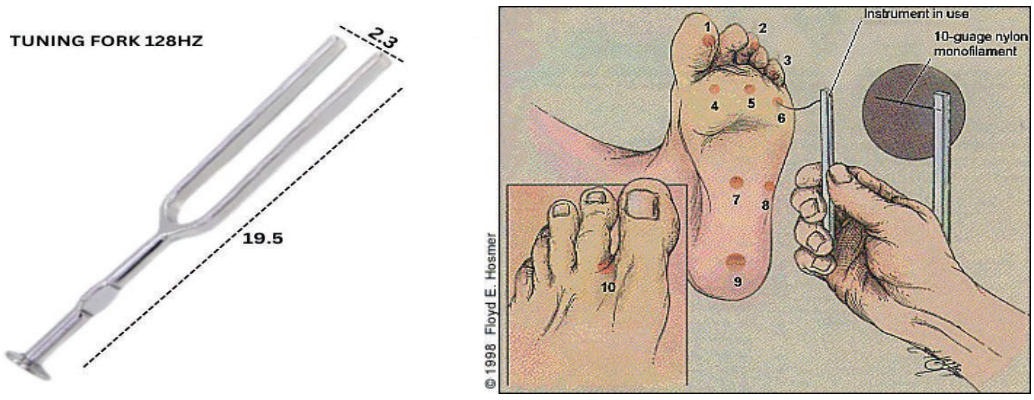


Figure 17.1: Monofilament test

Fig17.2: Bedside neurological and sensory nerve testing. (A) Vibration. Patients are notified when they cannot feel the vibrations from a 128-Hz tuning fork (first interphalangeal joint of the great toe) when the toes are extended, and the investigator feels the vibration and measures the time when the feeling disappeared. A time difference ≥10 seconds between the investigator and the patient is considered abnormal. (B) Pressure: 10-g monofilaments are pressed on 10 points on the sole and dorsum of the feet until the monofilament begins to bend (100 mN). If the patient has sensation in fewer than seven points, the results is considered abnormal. Four sites per foot, such as the hallux and metatarsal heads 1, 3, and 5, should be screened. (C) Noxious stimuli and (D) light touch. The patient is touched on the foot using a sterile pin, toothpick, and cotton wisp and asked to identify a " sharp or dull " or " light touch " with their eyes closed. (E) Warm/cold. Tip-therm (temperature discriminator; AXON GmbH) is a pen-like device with a plastic cylinder on one end and a metal cylinder on the other end, which is applied to the dorsum of each foot at irregular intervals so patients can identify the sensation as cold or not with their eyes closed. (F) Sudomotor function. Indicator tests (Neuropad, miro Verbandstoffe) are applied to both soles at the level of the first and second metatarsal heads. The time to color change from blue to pink is more than 10 seconds; the result is considered abnormal.

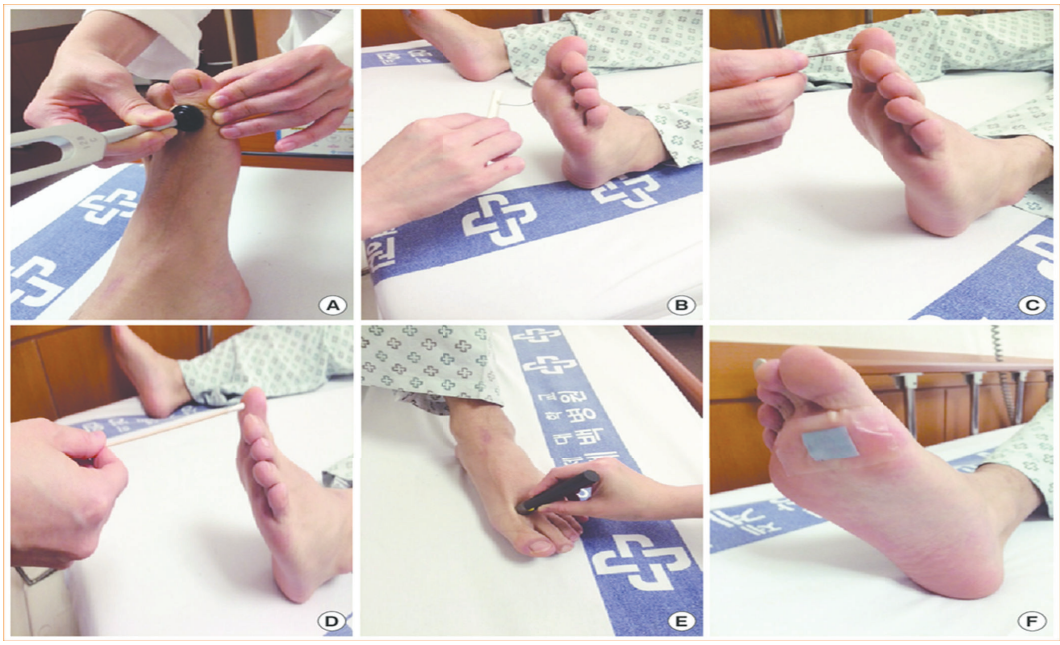


Figure 17.2: Monofilament test and bed side neurological tests

Autonomic neuropathy

When Symptoms and signs of should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic retinopathy..

- Symptoms: orthostatic dizziness, syncope, or dry cracked skin in the extremities.
- Signs: orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin.

Clinical pearls:

- Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
- Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations.
- Specific treatment to reverse the underlying nerve damage is currently not available.
- Electrophysiological testing or referral to a neurologist is rarely needed.
- No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions.

Diagnosis

Diabetic Peripheral Neuropathy

The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensory polyneuropathy and is a risk factor for diabetic foot ulceration. Bilateral limb pain, numbness, and paresthesia are the most common clinical manifestations in patients with DPN, and in severe cases, foot ulcers can occur, even leading to amputation. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

Small-fiber function: pinprick and temperature sensation.

Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.

Protective sensation: 10-g monofilament.

Somatic:

- All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter.
- Distal symmetric polyneuropathy: History and assessment of either temperature or pinprick sensation (small-fiber function)
- Vibration sensation using a 128-Hz tuning fork (for large-fiber function).
- Annual 10-g monofilament testing to identify feet at risk for ulceration and amputation.

Causes of neuropathy other than diabetes should be considered:

Non diabetic causes of PN: toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis. See the American Diabetes Association position statement “Diabetic Neuropathy” for more details.

Treatment:

The etiology and pathogenesis of diabetic neuropathy are not yet completely clarified, but hyperglycemia, disorders of lipid metabolism, and abnormalities in insulin signaling pathways are currently considered.

Glycemic management: can effectively prevent diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes and may modestly slow their progression in type 2 diabetes, but it does not reverse neuronal loss of other Dyslipidemia.

Hypertension: Treatments of modifiable risk factors can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes.

Therapeutic strategies:

Summary: There are no drugs available to reverse the progression of DPN. For chronic pain, which is often associated with DPN, current clinical options include anticonvulsants (pregabalin, gabapentin), tricyclic antidepressants (amitriptyline), and serotonin-noradrenaline reuptake inhibitors (duloxetine). The first-line drugs most often recommended for the treatment of painful DSPN are α2δ ligands (gabapentin and pregabalin).

Tricyclic antidepressants have been restricted because of their potential cholinergic adverse effects, especially in older patients.

Other drugs: used to improve symptoms include drugs to improve microcirculation (prostaglandins and prostaglandin analogues, hexoketocin, pancreatic kininogenase, Bactrim), neurotrophic drugs (methylcobalamin), drugs to improve cellular energy metabolism, drugs to combat oxidative stress (alpha-lipoic acid), inhibitors of aldose reductase activity (epalrestat), angiotensin-converting enzyme inhibitors.

Many studies have reported that these drugs, alone or in combination with other drugs, can promote peripheral nerve regeneration and improve clinical symptoms in patients with DPN, but the magnitude of their benefits remains controversial. Although a wide range of drugs are available, there is still a lack of specific drugs and treatment options for DPN due to its complex pathogenesis.

A Refer to neurologist or pain specialist when adequate pain management is not achieved within the scope of practice of the treating clinician.

Glycemic Management

Near-normal glycemic management, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people

with type 1 diabetes. Evidence for the benefit of near-normal glycemic management is not as strong that for type 2 diabetes,

Evidences:

1. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea.
2. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed clear benefit of intensive glucose and blood pressure management on the prevention of CAN in type 2 diabetes .

   Tang Y, Shah H, Bueno Junior CR, et al. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD trial. Diabetes Care 2021;44:164–173

Lipid Management

Although the evidence for a relationship between lipids and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and bariatric surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development.

Blood Pressure Management

Evidences:

1. (INTERPRET-DD): A recent meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk of DPN development with an odds ratio of 1.58.
2. ACCORD trial: In the ACCORD trial, intensive blood pressure intervention decreased CAN risk by 25%.

Neuropathic Pain

- Pharmaceutical interventions. A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN.
- The American Academy of Neurology update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, and tricyclic antidepressants (TCAs) could all be considered in the treatment of pain in DPN. These offer a supplement to a recent American Diabetes Association pain monograph.
- A recent head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN.
- The trial also supported the role of combination therapy over monotherapy for the

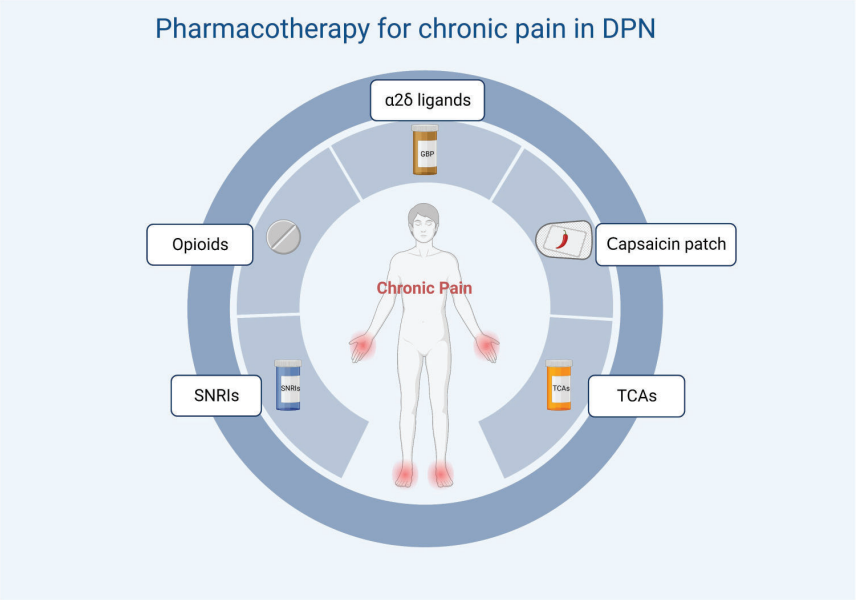


Figure 17.3: Treatment options for chronic pain in DPN. SNRIs, serotonin and norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

Gabapentinoids

- Gabapentinoids include several calcium channel α2-δ subunit ligands. Eight high-quality studies and seven medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN.
- Mirogabalin: Two medium-quality studies suggest that mirogabalin has a small effect on pain in DPN
- Adverse effects may be more severe in older individuals) and may be attenuated by lower starting doses and more gradual titration.

SNRIs

- SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs.
- Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN.
- A high-quality study supports the role of venlafaxine in the treatment of pain in DPN.
- Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN
- Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol and Tramadol

- Tapentadol and tramadol are centrally acting opioid analgesics that exert their analgesic effects through both μ-opioid receptor agonism and norepinephrine and serotonin reuptake inhibition.
- SNRI/opioid agents are probably effective in the treatment of pain in DPN. However, the use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic Antidepressants

- TCAs have been studied for treatment of pain, and most of the relevant data were acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the treatment of pain in DPN.
- Anticholinergic side effects may be dose limiting and restrict use in individuals ≥65 years of age.

Sodium Channel Blockers

- Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid.
- Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN.

Capsaicin

- Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported.
- One medium-quality study of 0.075% capsaicin cream has been reported.
- In individulas with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Lidocaine 5% Plaster/Patch

- Lidocaine patches have limited data supporting their use in DPN and are not effective in more widespread distribution of pain (although they may be of use in individuals with nocturnal neuropathic foot pain).
- Lidocaine patches cannot be used for more than 12 h in a 24-h period.

α-Lipoic Acid

- α-Lipoic acid, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN.

  Epalrestat: Epalrestat: is an aldose reductase inhibitor that is approved in Japan for the improvement of subjective neuropathy symptoms, abnormality of vibration sense, and abnormal changes in heart beat associated with diabetic peripheral

neuropathy. Epalrestat may serve as a new therapeutic option to prevent or slow the progression of diabetic neuropathy.

Clinical pearls:

Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.

Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations.

- Specific treatment to reverse the underlying nerve damage is currently not available.
- Electrophysiological testing or referral to a neurologist is rarely needed.
- No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions.

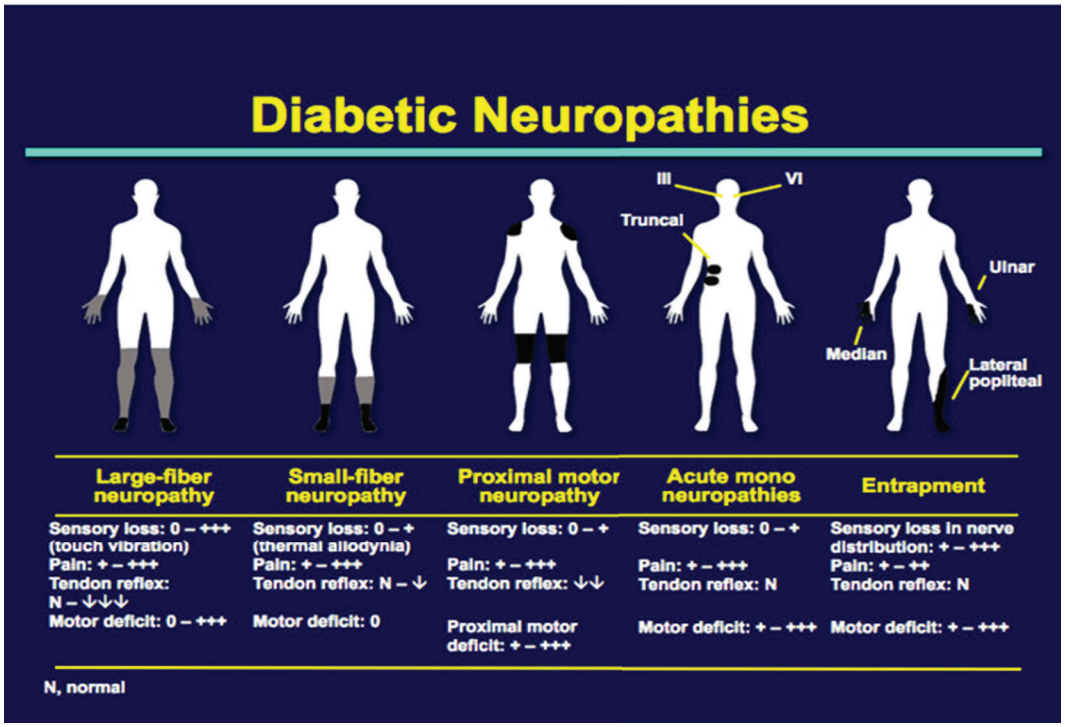


Figure 17.4: Diabetic neuropathies

Diabetic neuropathies with clinical importance:

Mononeuropathies:

- The most common diabetic mononeuropathies involve the cranial nerves with the third nerve being the most commonly affected. Due to occlusion of the vasa nervorum causing a central infarction of the cranial nerve (3^{rd},4^{th},6^{th},7^{th})

- Entrapment neuropathies due to diabetes in the upper and lower limbs may need surgical decompression to relieve muscle weakness.
- Diabetic radiculopathies occur in the dermatomes of the chest and abdomen, never cross the midline and mimic intraabdominal and intrathoracic pathologies.
- Diabetic amyotrophy and neuropathic cachexia is due to involvement of the upper and lower lumbar plexi diabetic lumbosacral radiculopathy, (diabetic myelopathy, proximal diabetic neuropathy, Bruns-Garland syndrome and femoral-sciatic neuropathy) and is a rare condition that presents with severe pain, muscle weakness and atrophy of the muscles of the upper thigh accompanied by severe weight loss. Symptoms, though often severe, are self-limited and will usually resolve without resulting in a permanent disability as there is no nerve damage like diabetic peripheral neuropathy.

Entrapment Syndromes

These start slowly and will progress and persist without intervention. A number of nerves including the median, ulnar, radial, lateral femoral cutaneous, fibular, and plantar nerves are vulnerable to pressure damage in diabetes. The etiology is multifactorial involving metabolic and ischemic factors, impaired reinnervation, and even obesity.

Carpal tunnel syndrome: Carpal tunnel syndrome occurs three times as frequently in people with diabetes compared with healthy populations and is found in up to one third of patients with diabetes. Its increased prevalence in diabetes may be related to repeated undetected trauma, metabolic changes, or accumulation of fluid or edema within the confined space of the carpal tunnel. The diagnosis is confirmed by electrophysiological studies. Treatment consists of rest, aided by placement of a wrist splint in a neutral position to avoid repetitive trauma. Anti-inflammatory medications and steroid injections are sometimes useful. Surgery should be considered if weakness appears and medical treatment fails.

Diabetic Autonomic Neuropathy

Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function.

Further Testing: cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy/colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to hypoglycemia unawareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy (CAN)

In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing.

Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate).

CAN treatment is generally focused on alleviating symptoms.

Orthostatic Hypotension

Treating orthostatic hypotension is challenging.

- The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most individuals require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen and pharmacologic measures.
- Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical.
- There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures.
- Ttreatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate,enalapril.
- Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastrointestinal autonomic Neuropathies

- Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract
- Manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence.
- Gastroparesis should be suspected in individuals with erratic glycemic management or with upper gastrointestinal symptoms without another identified cause.
- Reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease
- Esophagogastroduodenoscopy or a barium study of the stomach is needed before considering a diagnosis of or specialized testing for gastroparesis.
- The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of 13C octanoic acid breath test is an approved alternative.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging.

- A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful. Foods with small particle size may improve key symptoms
- Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, TCAs, GLP-1 RAs, and pramlintide, may also improve intestinal motility.

Pharmacologic interventions:

- Metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA.
- Other treatment: Domperidone (available outside the U.S.) and erythromycin,
- Gastric electrical stimulation: using a surgically implantable device has received approval of FDA do not support gastric stimulation as an effective therapy in diabetic gastroparesis).

Genitourinary Disturbances

- Diabetic autonomic neuropathy: Sexual dysfunction and bladder dysfunction.
- In men, diabetic autonomic neuropathy: cause erectile dysfunction and/or retrograde ejaculation). Female sexual dysfunction: decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication. Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream).

Erectile Dysfunction:

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

- Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

18
CHAPTER

Retinopathy in Diabetes

- Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control . Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries.
- Factors that increase the risk of, or are associated with, retinopathy.

1. Diabetes duration,
2. Chronic hyperglycemia,
3. Nephropathy
4. Hypertension
5. Dyslipidemia
6. Pregnancy
7. Anemia.

- Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy.
- Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy
- Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy
- GLP-1 RAs including Liraglutide, Semaglutide, and Dulaglutide have been shown to be associated with an increased risk of rapidly worsening diabetic retinopathy in randomized trials.
- Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy.

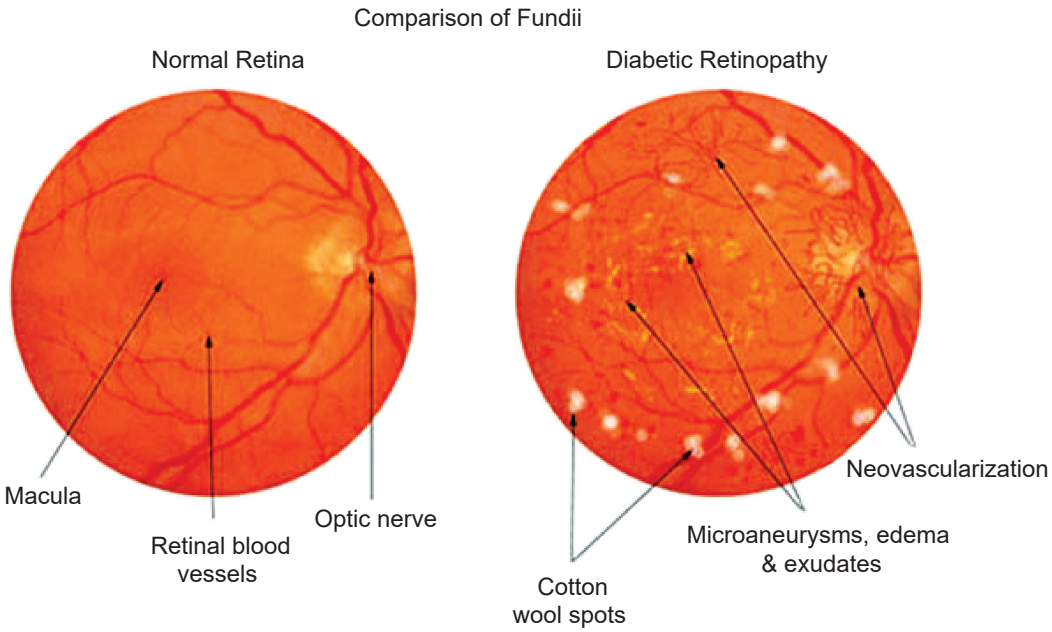


Figure 18.1: comparison of Fundus of normal and diabetic retinopathy

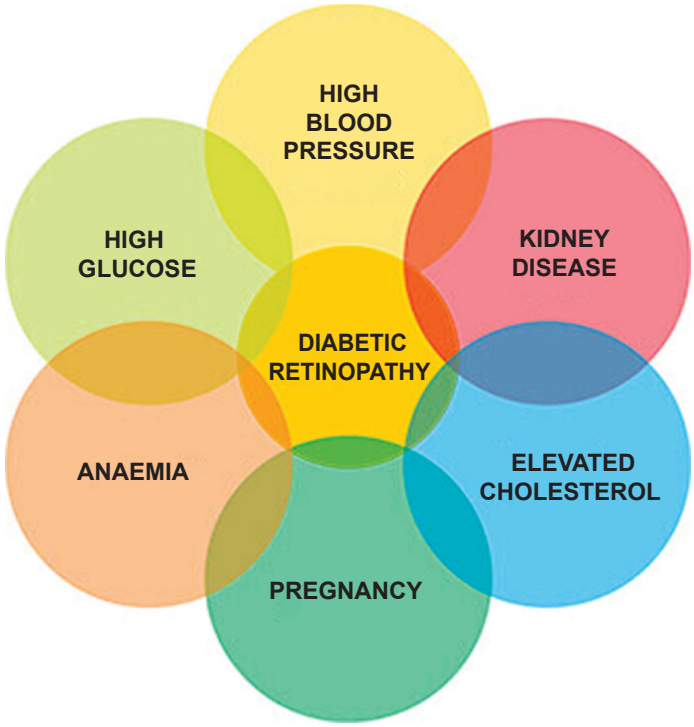


Figure 18.2: Diabetic retinopathy;Diagnosis,treatment of risks

Summary

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.
- People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis.
- If no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 years may be considered.
- Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy.
- Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy.
- Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy.

Clinical pearls:

- The preventive effects of therapy and the fact that individuals with any level of diabetic retinopathy or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.
- Diabetic retinopathy screening should be performed using validated approaches and methodologies.
- Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy.
- Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage.

Method of eye examination:

- Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available. Retinal photography may also enhance efficiency and reduce costs. Retinal photos are not a substitute for dilated comprehensive eye exams

- Fundus photographs: High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional.
- In-person exams are still necessary
- Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches.

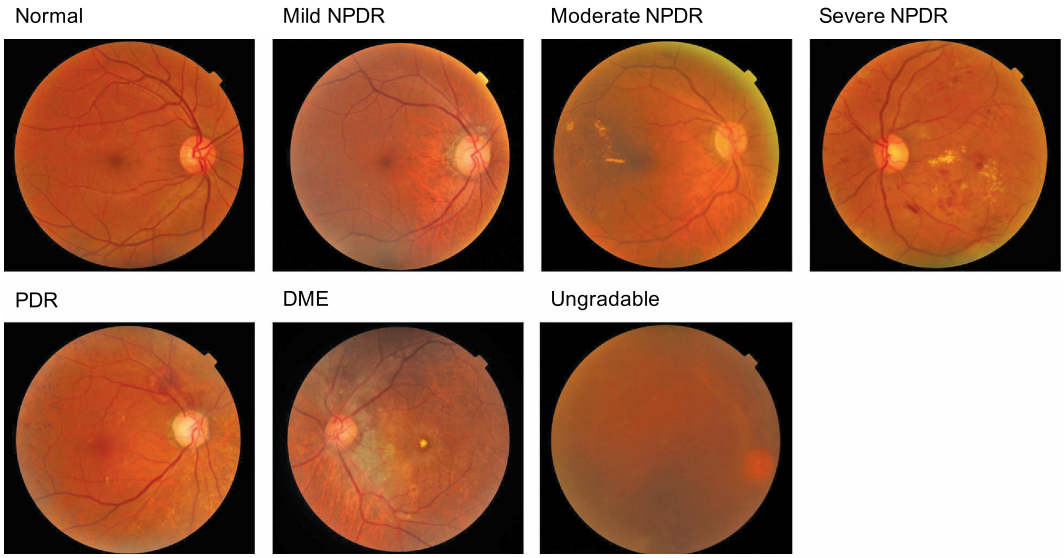


Figure 18.3: Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy.

However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy.

- Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema .
- The use of anti–vascular endothelial growth factor (anti-VEGF) injections in pregnant individuals may be justified only if the potential benefit outweighs the potential risk to the fetus and only if clearly indicated

Treatment

Symmary

- Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy.
- Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy.
- Intravitreous injections of anti–vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals.
- Intravitreous injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity.
- Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach

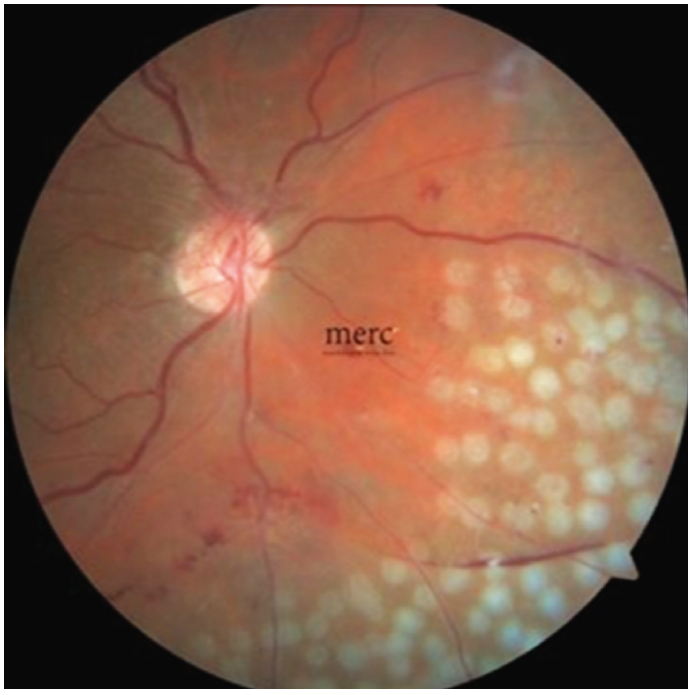


Figure 18.4: Laser marks

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although strict goals (systolic blood pressure <120 mmHg) do not impart additional benefit. In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline.

Visual Rehabilitation

Recommendations

- Referred for, a comprehensive evaluation of their visual impairment by a practitioner experienced in vision rehabilitation.
- People with vision loss from diabetes should receive educational materials and resources for eye care support in addition to self-management education (e.g., glycemic management and hypoglycemia awareness).

In the U.S., ~12% of adults with diabetes have some level of vision impairment. They may have difficulty controlling their diabetes and performing many other activities of daily living, which can lead to depression, anxiety, social isolation, and difficulties at home, workplace, school, or workplace.

People with diabetes are at increased risk of chronic vision loss, subsequent functional decline, and resulting disability. Vision impairment has physical, psychological, behavioral, and social consequences that affect people with diabetes, their families, friends, and caregivers. Health care professionals and stakeholders may not be aware of the overall impact of vision loss on an individual's health and well-being. People with diabetes-related vision loss should be evaluated to determine their potential to benefit from comprehensive vision restoration. Vision rehabilitation can help people with vision loss achieve maximum function, independence, and quality of life.

19
CHAPTER

Foot Care in Diabetes

Summary:

- Annual comprehensive foot evaluation should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, or vibration), and vascular assessment, including pulses in the legs and feet.
- Every visit**:** Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit.
- History of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication).
- PAD**:** Initial screening for peripheral arterial disease (PAD) should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate.

Management:

Interprofessional approach: An interprofessional approach facilitated by a podiatrist in conjunction with other appropriate team members is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with PAD).

- Referral: Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or PAD to foot care specialists for ongoing preventive care and lifelong surveillance.

  Foot self-care education: general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems.
- Therapeutic footwear: The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation.

- Advanced agents: For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy.

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral arterial disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Factors that are associated with the at-risk foot include the following:

- Poor glycemic management
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy

Table 19.1 International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency.

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted from Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ; IWGDF Editorial Board. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev 2020;36(Suppl. 1):e3266. LOPS, loss of protective sensation; PAD, peripheral artery disease.

*Examination frequency suggestions are based on expert opinion and person-centered requirements.

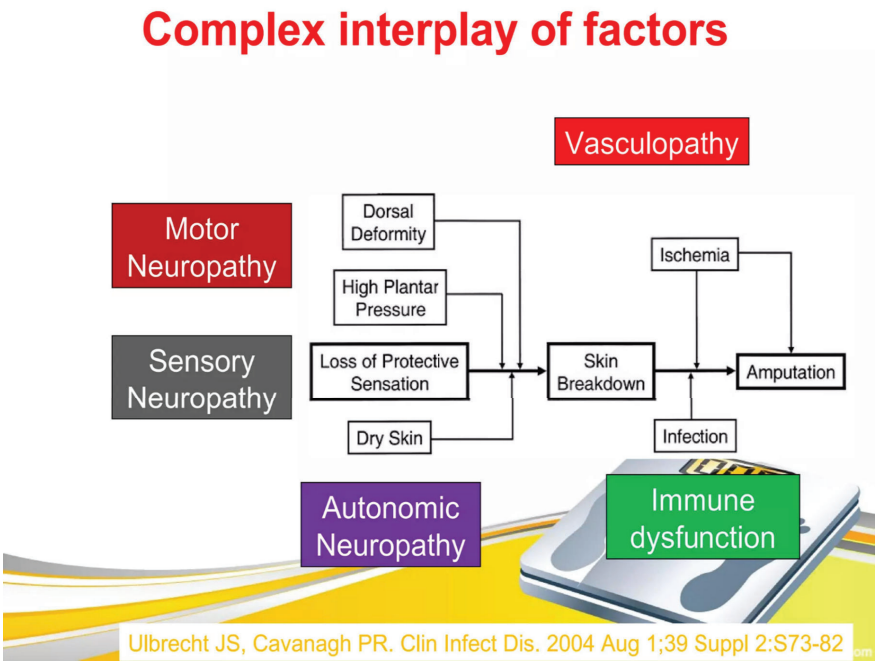


Figure 19.1: Pathophysiology of diabetic foot

Evaluation for Loss of Protective Sensation

- . One of the most useful tests to determine LOPS is the 10-g monofilament test.
- Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration
- Other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device).

Evaluation for Peripheral Arterial Disease

- History: Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency.
- Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time of Doppler ultrasound with pulse volume: Any individual exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings.
- Ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to noncompressible vessels.
- Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressures <30 mmHg are suggestive of PAD and an inability to heal foot ulcerations.

Clinical pearl:

- American Podiatric Medical Association guidelines: Due to the high prevalence of PAD in people with diabetes, the Society for Vascular Surgery and the American Podiatric Medical Association guidelines recommend that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies. If normal, these should be repeated every 5 years.
    - Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation.

Education for People with Diabetes

- All people with diabetes (and their families), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies. It is part of an annual comprehensive examination and to individuals with high-risk conditions at every visit.
- Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot inspections on a daily basis.

- Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems.
- The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes).
- Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures can reduce peak plantar pressures more significantly than insoles alone.

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals can often be managed with education and self-care. People in the moderate to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance

Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in

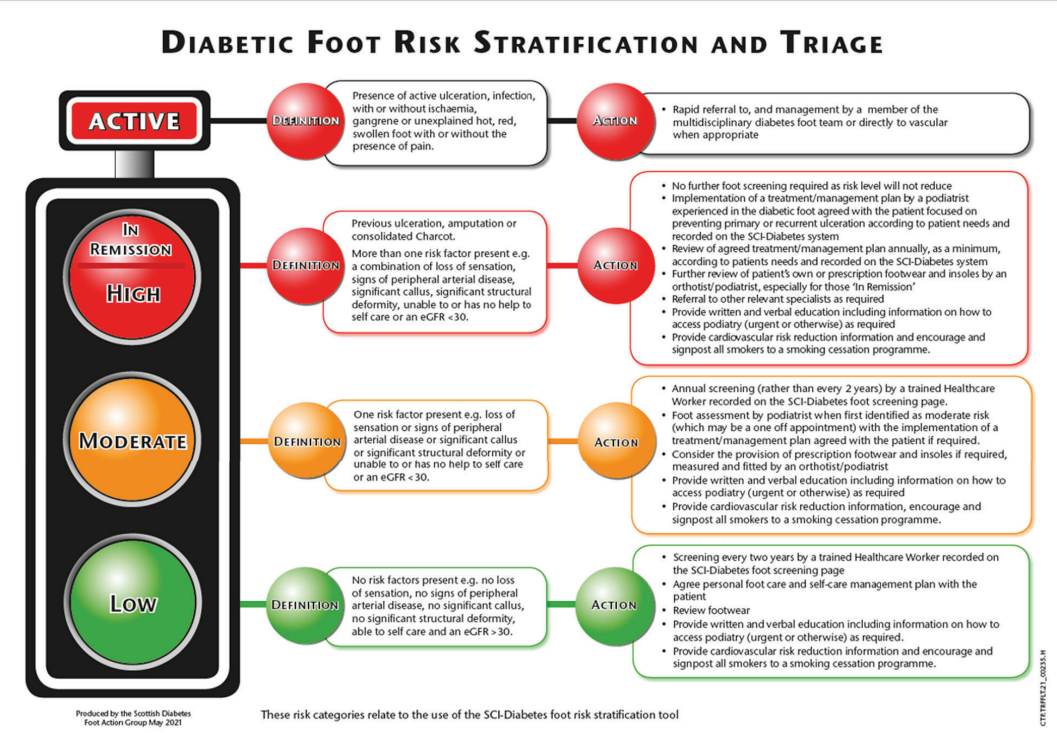


Figure 19.2: These risk categories relate to the use of the SCI-Diabetes foot risk stratification tool (Scottish guideline SIGN 116)

Charcot joint disease:

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings.

Foot Ulcer: There have been a number of developments in the treatment of ulcerations over the years. These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy. It is agreed that the initial treatment and evaluation of ulcerations include the following **five** basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal and this advanced wound therapy is challenging.

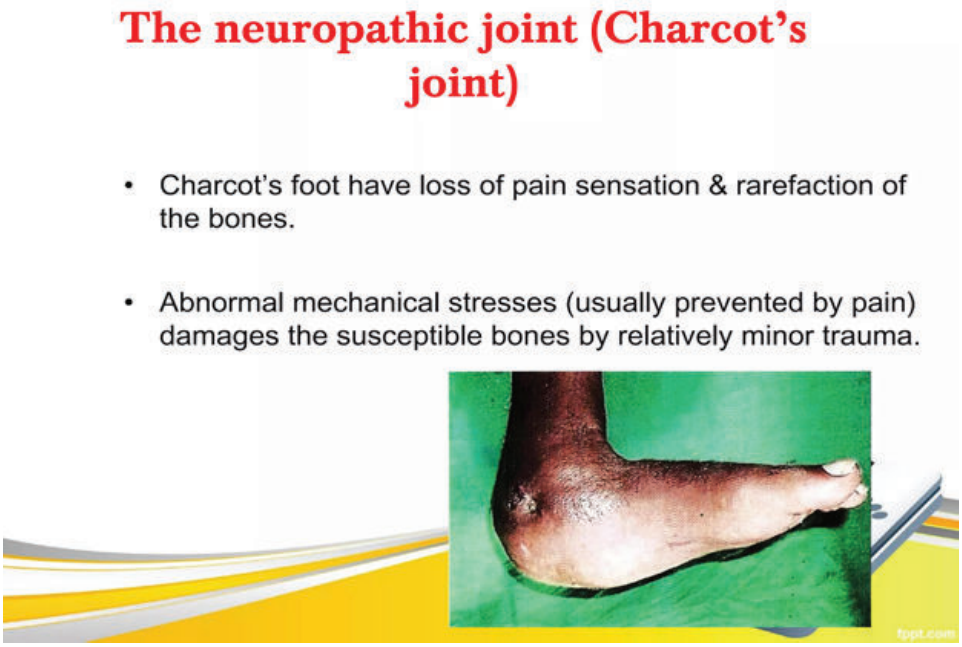


Figure 19.3: Charcot's foot

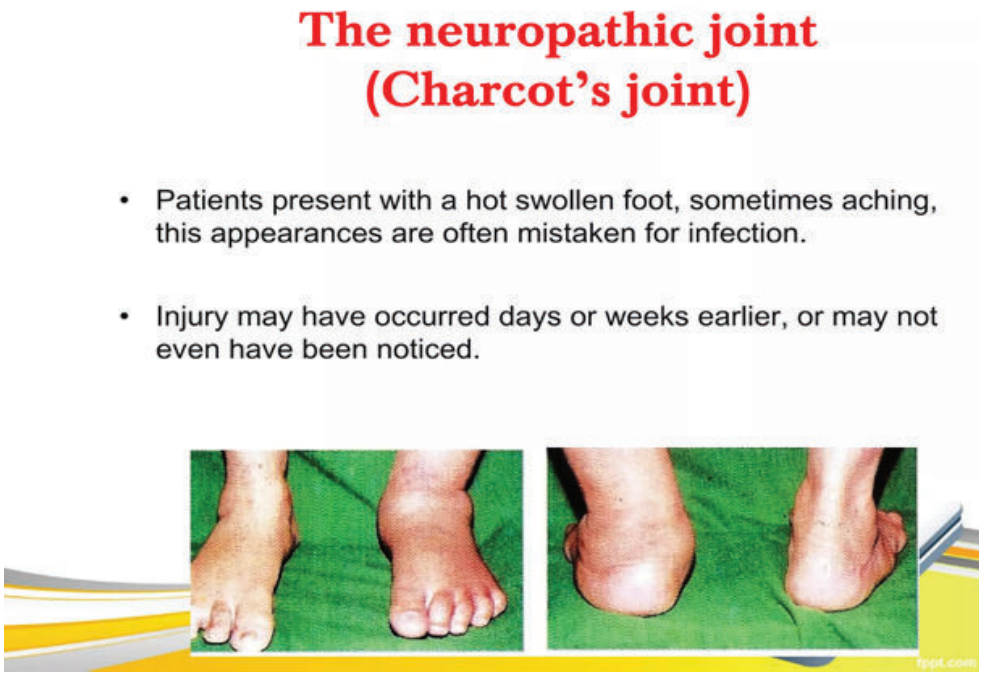


Figure 19.4: Charcot's foot

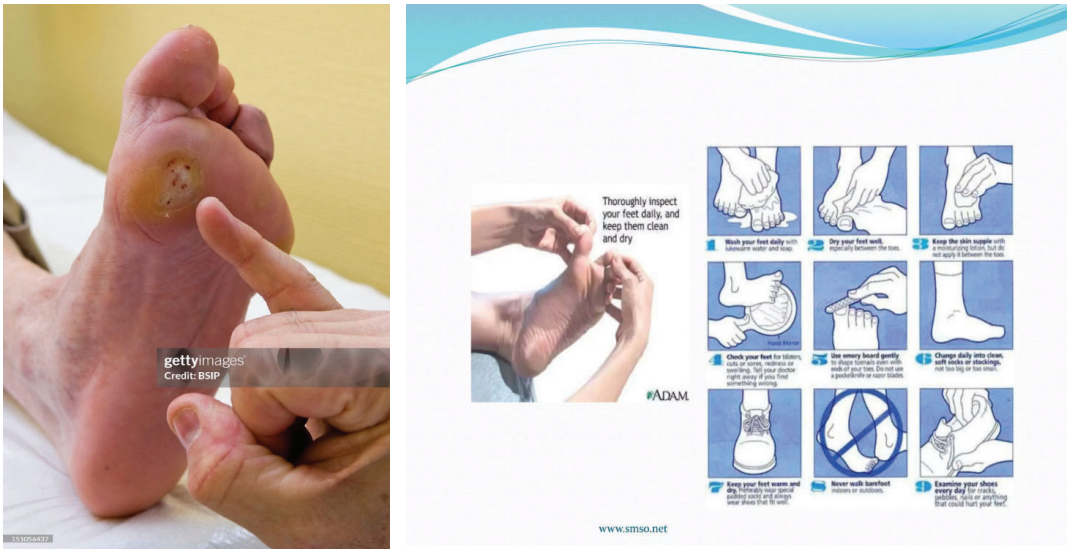
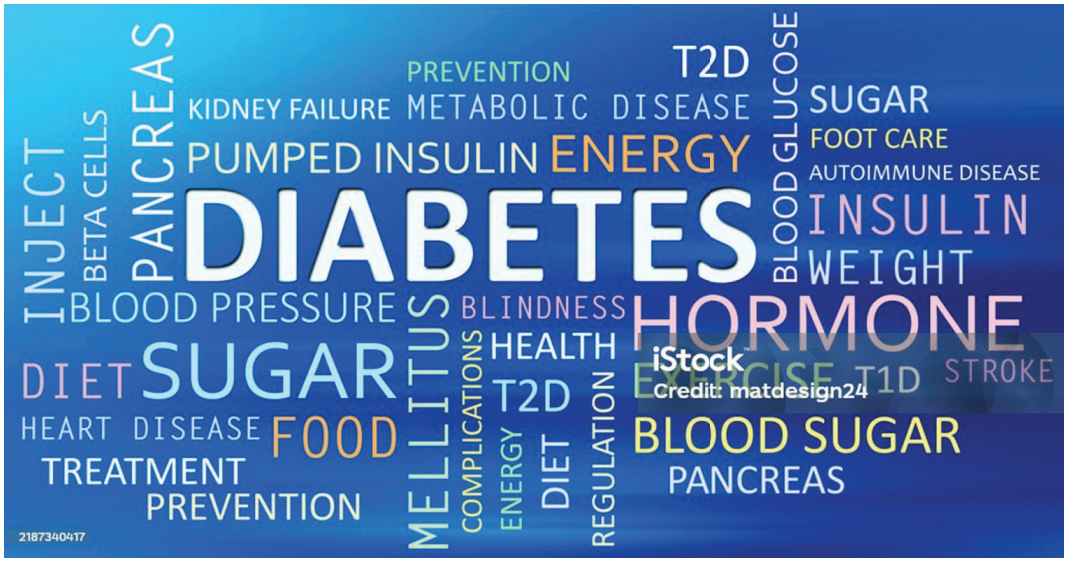


Figure 19.5: Foot ulcer and scopes of prevention

Figure 19.6: Elderly diabetes



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Diabetes in Special Situation

20
CHAPTER

Diabetes in Older Adults

Diabetes is a highly prevalent health condition in the aging population. Over one-quarter of people over the age of 65 years have diabetes and one-half of older adults have prediabetes.

- They need assessment of medical, psychological, functional (self-management abilities), and social domains
- Screening for geriatric syndromes (e.g., cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) and polypharmacy
- Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact treatment goals and therapeutic approaches.

Neurocognitive Function

- Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. Older adults with diabetes are at higher risk of cognitive decline and institutionalization.
- People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia
- . Poor glycemic management is associated with a decline in cognitive function and longer duration of diabetes is associated with worsening cognitive function.
- studies examining the effects of diabetes prevention or intensive glycemic and blood pressure management to achieve specific goals have not demonstrated a reduction in brain function decline
- In observational studies as well as post hoc analyses from randomized clinical trials, certain glucose-lowering drugs, such as metformin, thiazolidinediones, and glucagon-like peptide 1 (GLP-1) receptor agonists have shown small benefits on slowing progression of cognitive dysfunction.
- Control of blood pressure and cholesterol lowering with statins have been associated with a reduced risk of incident dementia and are, thus, particularly important in older adults with diabetes.

- The presence of cognitive impairment can make it challenging for clinicians to help people with diabetes reach individualized glycemic, blood pressure, and lipid goals
- . Simple assessment tools are available to screen for cognitive impairment , such as the Mini-Mental State Examination , Mini-Cog , and the Montreal Cognitive Assessment ,
- People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health professional for formal cognitive/neuropsychological evaluation .

Hypoglycemia

- Because older adults with diabetes have a greater risk of hypoglycemia, especially when treated with hypoglycemic agents (e.g., sulfonylureas, meglitinides, and insulin), than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. continuous glucose monitoring should be considered
- For older adults with type 1 diabetes, continuous glucose monitoring is recommended to reduce hypoglycemia. For older adults with type 1 diabetes, consider the use of automated insulin delivery (AID) systems, connected pens based on individual ability and support system.

  People with diabetes and their caregivers should be routinely queried about hypoglycemia) and impaired hypoglycemia awareness. Glycemic goals and pharmacologic treatments may need to be adjusted to minimize the occurrence of hypoglycemic events (ACCORD) (VADT) study.

Use of Continuous Glucose Monitoring and Advanced Insulin Delivery Devices

For older adults with type 1 diabetes, continuous glucose monitoring (CGM) is a useful approach to predicting and reducing the risk of hypoglycemia (WISDM) trial , DIAMOND study. (ORACL) trial .Advanced insulin delivery devices like accurate CGM dvices,Hybrid closed loop system,Automated insulin delivery(AID)have been shown to improve glycemic outcomes in both children and adults with type 1 diabetes.

declining cognitive or functional status.

Treatment Goals

Summary:

- Older adults with diabetes who are otherwise healthy with few and stable coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [<53–58 mmol/mol]).
- Less stringent goals (such as A1C <8.0% [<64 mmol/mol]) for those with significant cognitive and/or functional limitations, frailty, severe comorbidities, and a less favorable risk-to-benefit ratio of diabetes medications. Older adults with very complex or poor health receive minimal benefit from stringent glycemic control, and clinicians should avoid reliance on glycemic goals and instead focus on avoiding hypoglycemia and symptomatic hyperglycemia.

- Treatment of hypertension to individualized goal levels is indicated in most older adults with diabetes.
- Lipid-lowering therapy and antiplatelet agents may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials.

The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity and their varied prior experience with disease management.

Table 20.1 Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes.

Characteristics and health status of person with diabetes	Rationale	Reasonable A1C goal*	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (<53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses or two or more instrumental ADL impairments or mild to moderate cognitive impairment)	Variable life expectancy. Individualize goals, considering: • Severity of comorbidities • Cognitive and functional limitations • Frailty • Risk-to-benefit ratio of diabetes medications • Individual preference	<8.0% (<64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit minimal	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

- This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The characteristic categories are general concepts.
- A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

- Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. “Multiple” means at least three, but many individuals may have five or more.
- The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

Vulnerable Older Adults at the End of Life

For people with diabetes receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic hyperglycemia while reducing the burdens of glycemic management. Thus, as organ failure develops, several agents will have to be deintensified or discontinued. For a dying person, most agents for type 2 diabetes may be removed. There is, however, no consensus for the management of type 1 diabetes in this scenario. See the section END-OF-LIFE CARE below for additional information.

Beyond Glycemic Management

There is strong evidence from clinical trials of the value of treating hypertension in older adults, with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials . In the case of statins, the follow-up time of clinical trials ranged from 2 to 6 years. While the time frame of trials can be used to inform treatment decisions, a more specific concept is the time to benefit for a therapy. For statins, a meta-analysis of the previously mentioned trials showed that the time to benefit is 2.5 years.

Lifestyle Management

Summary:

- Optimal nutrition and protein intake is recommended for older adults with diabetes; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, should be encouraged in all older adults with diabetes who can safely engage in such activities.Modest weight loss (e.g., 5–7%) For older adults with type 2 diabetes, overweight/obesity should be considered Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia and/or osteopenia.
- Diabetes is also recognized as an independent risk factor for frailty.
- Frailty is characterized by decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychosocial stressors.

- Management of frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weightbearing, and resistance training. [LIFE] study) The goal of these programs is not weight loss but enhanced functional status. The Look AHEAD (Action for Health in Diabetes) trial

Pharmacologic Therapy

- In older adults with type 2 diabetes, medications with low risk of hypoglycemia are preferred, especially for those with hypoglycemia risk factors. Overtreatment should be avoided.
- deintensify hypoglycemia-causing medications (e.g., insulin, sulfonylureas, or meglitinides) or
- switch to a medication class with low hypoglycemia risk using individualized glycemic goals.
- Simplification of complex treatment plans (especially insulin) is recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the treatment burden if it can be achieved using the individualized glycemic goals.
- In older adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment plan should include agents that reduce cardiorenal risk, irrespective of glycemia.
- Consider costs of care and coverage when developing treatment plans
- Special care is required in prescribing and monitoring pharmacologic therapies in older adults

Table 20.2 Considerations for treatment plan simplification and deintensification/deprescribing in older adults with diabetes

Characteristics and health status of person with diabetes	Reasonable A1C/treatment goal	Rationale/ considerations	When may medication plan simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.0–7.5% (<53–58 mmol/mol)	• Individuals can generally perform complex tasks to maintain good glycemic management when health is stable • During acute illness, individuals may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in individuals on insulin therapy (regardless of A1C) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in indviduals on noninsulin therapies with high risk of hypoglycemia (regardless of A1C) • If wide glucose excursions are observed • In the presence of polypharmacy

(table continued)

Table 20.2 *(cont'd)*

Characteristics and health status of person with diabetes	Reasonable A1C/treatment goal	Rationale/ considerations	When may medication plan simplification be required?	When may treatment deintensification/ deprescribing be required?
Complex/intermediate (multiple coexisting chronic illnesses or two or more instrumental ADL impairments or mild to moderate cognitive impairment)	<8.0% (<64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication plan	• If severe or recurrent hypoglycemia occurs in individuals on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin plan • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If severe or recurrent hypoglycemia occurs in individuals on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling individuals receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C, glucose goal 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic management is important for recovery, wound healing, hydration, and avoidance of infections • Individuals recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the individual will receive at home	• If treatment plan increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication plan during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (LTC or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more ADL impairments)	Avoid reliance on A1C and avoid hypoglycemia and symptomatic hyperglycemia	• No benefits of tight glycemic management in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin plan and the individual would like to decrease the number of injections and finger-stick blood glucose monitoring events each day • If the individual has an inconsistent eating pattern	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or finger sticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Treatment plan simplification refers to changing strategy to decrease the complexity of a medication plan (e.g., fewer administration times and fewer blood glucose checks) and decreasing the need for calculations (such as sliding-scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether.

ADL, activities of daily living; LTC, long-term care.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes.

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in older adults at risk for heart failure, osteoporosis, falls or fractures, and/or macular edema .Lower doses of a thiazolidinedione in combination therapy may mitigate these side effects.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues such as the meglitinides (repaglinide and nateglinide) are associated with hypoglycemia and should be used with caution).

Incretin-Based Therapies

- DPP-4) inhibitors :Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal risk of hypoglycemia, but their cost may be a barrier to some older adults. DPP-4 inhibitors do not reduce or increase major adverse cardiovascular outcomes. Across the trials of this drug class, there appears to be no interaction by age-group.
- GLP-1 receptor agonists :GLP-1 receptor agonists have demonstrated cardiovascular benefits among people with diabetes and established atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk to the same degree for people over and under 65 years of age
- Tirzepatide:, a novel dual-acting GIP and GLP-1 receptor was approved by the FDA decreased A1C and weight—generally to a greater extent than other glucose-lowering drugs

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In those with established ASCVD, these agents have shown cardiovascular benefits. This class of agents has also been found to be beneficial for people with heart failure and to slow the progression of chronic kidney disease side effects such as volume depletion, urinary tract infections, and worsening urinary incontinence may be more common among older people.

Insulin Therapy

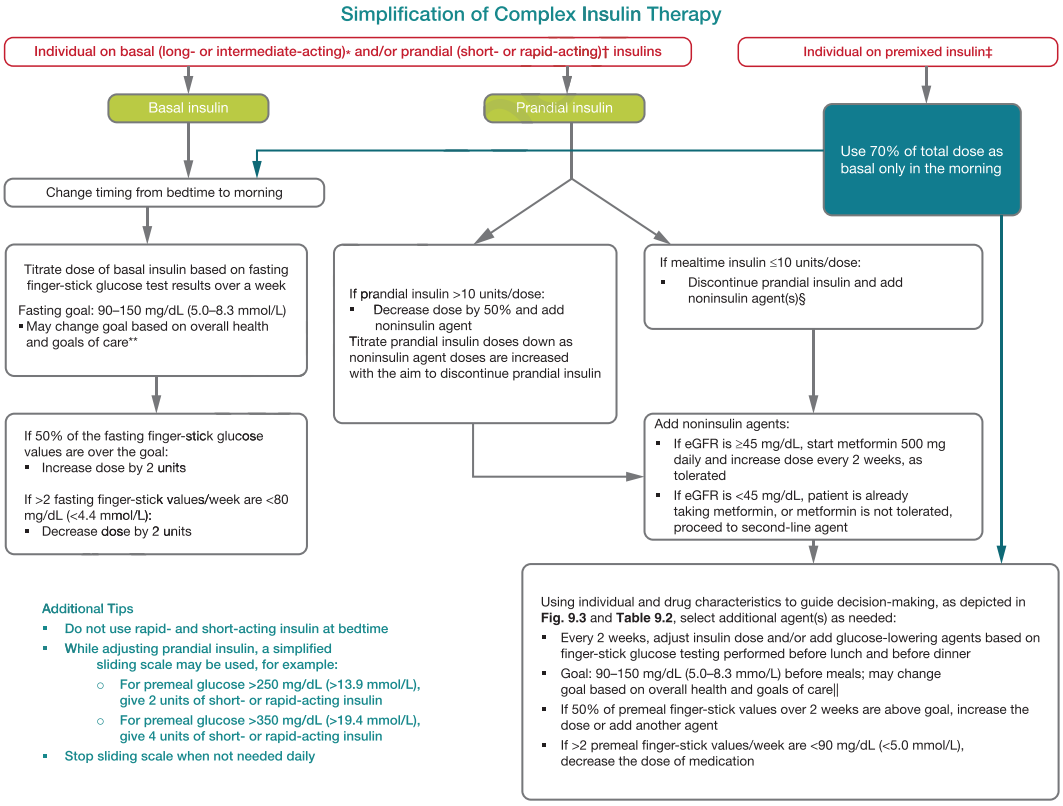


Figure 20.1: Algorithm to simplify insulin plans for older adults with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). Premixed insulins: 70/30, 75/25, and 50/50 products. §Examples of noninsulin agents include metformin, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 receptor agonists.

Once-daily basal insulin injection specially long-acting insulin analogs have been found to be associated with a lower risk of hypoglycemia compared with NPH insulin in the Medicare population therapy is associated with minimal side effects and may be a reasonable option in many older adults

Other Factors to Consider

- Impaired social support and reduced access to long-term services and support may reduce these individuals' quality of life and increase the risk of functional dependency
- The person's living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g.,

adult children and caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

Special Considerations for Older Adults with Type 1 Diabetes

Insulin is an essential life-preserving therapy for people with type 1 diabetes, unlike for those with type 2 diabetes.

To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections.

Suggested citation: American Diabetes Association Professional Practice Committee. 13. Older adults: Standards of Care in Diabetes—2024. Diabetes Care 2024;47(Suppl. 1):S244–S257

21
CHAPTER

Diabetes in Children and Adolescents

Introduction

The management of diabetes in children and adolescents (individuals <18 years of age) cannot simply be derived from care routinely provided to adults with diabetes.

There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of pediatric diabetes.

Type 1 Diabetes

- Type 1 diabetes is the most common form of diabetes in youth
- The health care professional must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA)
- Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan

The diabetes team, taking into consideration the youth's developmental and psychosocial needs, should ask about and discuss diabetes management responsibilities with youth and parents/caregivers on an ongoing basis.

Diabetes Self-Management Education and Support

Clinical pearl:

- Youth with type 1 diabetes and their parents/caregivers (for individuals aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter.

- No matter how sound the medical plan is, it can only be effective if the family and/or affected individuals are able to implement it
- It may be team work with doctor nurse patients caregiver with education entertainment and financial endorsement.

Nutrition Therapy

Summary

- Individualized medical nutrition therapy is recommended for youth with type 1 diabetes as an essential component of the overall treatment plan.
- Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is a key component to optimizing glycemic management.
- Meal composition impacts postprandial glucose excursions. Education on the impact of high-fat and high-protein meals and the adjustment of insulin dosing is necessary.
- Comprehensive nutrition education at diagnosis, with at least annual updates and as needed, by an experienced registered dietitian nutritionist is recommended to assess caloric and nutrition intake in relation to weight status and cardiovascular disease risk factors and to inform macronutrient choices.

Physical Activity and Exercise

- Physical activity is recommended for all youth with type 1 diabetes with the goal of 60 min of moderate (brisk walking or dancing) to vigorous-intensity (e.g., running or jumping rope) - aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week.
- Frequent glucose monitoring before, during, and after exercise, via blood glucose meter or continuous glucose monitoring (CGM), is important to prevent, detect, and treat hypoglycemia and hyperglycemia associated with exercise.
- Youth and their parents/caregivers should receive education on goals and management of glycemia before, during, and after physical activity, individualized according to the type and intensity of the planned physical activity.
- Youth and their parents/caregivers should be educated on strategies to prevent hypoglycemia during, after, and overnight following physical activity and exercise, which may include reducing prandial insulin dosing for the meal/snack preceding (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime snacks, and/or using CGM. Treatment for hypoglycemia should be accessible before, during, and after engaging in activity.

Youth should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program.

No exercise:

1. Hyperglycemia-. Intense activity should be postponed with marked hyperglycemia (glucose ≥350 mg/dL [≥19.4 mmol/L]), moderate to large urine ketones, and/or β-hydroxybutyrate (B-OHB) >1.5 mmol/L.
2. Hypoglycemia: The prevention and treatment- decreasing the prandial insulin for the meal/snack before exercise and/or increasing food intake. Youth on insulin pumps without automated insulin delivery (AID) can lower basal rates by ~10–50% or more or suspend for 1–2 h during exercise. Decreasing basal rates or long-acting insulin doses by ~20% after exercise may reduce delayed exercise-induced hypoglycemia. Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before, during, and after exercise, with or without continuous glucose monitoring (CGM), maximize safety with exercise. Consider additional carbohydrate intake during and/or after exercise, depending on the duration and intensity of physical activity, to prevent hypoglycemia. For low- to moderate-intensity aerobic activities (30–60 min), and if the youth is fasting, 10–15 g of carbohydrate may prevent hypoglycemia. After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (~ 30–60 g), which is similar to carbohydrate requirements to optimize performance in athletes without type 1 diabetes.

Target Blood glucose: Blood glucose goals prior to physical activity and exercise should be 126–180 mg/dL (7.0–10.0 mmol/L) but should be individualized).

Obesity: obesity is as common in youth with type 1 diabetes as in those without diabetes. Therefore, diabetes health care professionals should monitor weight status and encourage a healthy eating pattern, physical activity, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a youth's day is spent in school and/or day care, training of school or day care personnel to provide care in accordance with the child's individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school or day care–sponsored opportunities. The classmate and other associate must know his/her diagnosis and the emergency of hypoglycemia.

Psychosocial Care

- At diagnosis and during routine follow-up care, screen youth with type 1 diabetes for psychosocial concerns (e.g., diabetes distress, depressive symptoms, and disordered eating), family factors, and behavioral health. May need referal to a qualified behavioral health professional, preferably experienced in childhood diabetes, when indicated.
- Health care professionals should consider asking youth and their parents/caregivers about social adjustment (peer relationships) and school performance to determine whether further intervention is needed.

- Although cognitive abilities vary, the ethical position often adopted is the “mature minor rule,” whereby children after age 12 or 13 years who appear to be “mature” have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health.

Clinical pearls:

- Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all individuals of childbearing potential.
- Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Consider screening youth for diabetes distress, generally starting at 7 or 8 years of.
- It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight management in type 1 diabetes using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention.
- Given the complexity of treating disordered eating behaviors, collaboration between the diabetes health care team and a behavioral health professional is recommended.

Glycemic Monitoring, Insulin Delivery, and Goals

Summary:

- All youth with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or CGM), including prior to meals and snacks, at bedtime, and as needed in specific situations such as physical activity, driving, or the presence of symptoms of hypoglycemia.
- Real-time CGM or intermittently scanned CGM should be offered for diabetes management at diagnosis or as soon as possible in youth with diabetes on multiple daily injections or insulin pump therapy who can afford, who are capable of using the device safely (either by themselves or with caregivers
- Automated insulin delivery (AID) systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual’s and family’s circumstances, desires, and needs.
- Students must be supported at school in the use of diabetes technology, including continuous glucose monitors, insulin pumps, connected insulin pens, and AID systems as prescribed by their diabetes care team.
- A1C goals must be individualized and reassessed over time. An A1C of <7% (<53 mmol/mol) is appropriate for many children and adolescents.
- CGM metrics derived from continuous glucose monitor use over the most recent 14 days (or longer for youth with more glycemic variability), including time in range (70–180 mg/dL [3.9–10.0 mmol/L]), time below range (<70 mg/dL [<3.9 mmol/L]

and <54 mg/dL [<3.0 mmol/L]), and time above range (>180 mg/dL [>10.0 mmol/L] and >250 mg/dL [>13.9 mmol/L]), are recommended to be used in conjunction with A1C whenever possible.

The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus plans, insulin pumps, frequent blood glucose monitoring, CGM, AID systems, goal setting, and improved patient education has been associated with more children and adolescents reaching the blood glucose goals recommended by the ADA.

Lower A1C in adolescence and young adulthood is associated with a lower risk and rate of microvascular and macrovascular complications and demonstrates the effects of metabolic memory.

However, meticulous use of therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., CGM, sensor-augmented pump therapy, and AID systems), and intensive self-management education now make it more feasible to achieve glycemic goals while reducing the incidence of severe hypoglycemia and neurocognive impairments.

Lower goals may be possible during the honeymoon phase of type 1 diabetes.

CGM soon after type 1 diabetes diagnosis is associated with improved A1C.

It is still uncertain what the ideal goal TIR should be for children, and further studies are needed.

- Glycemic goals should be individualized, and lower goals may be reasonable based on a benefit–risk assessment.

Autoimmune Conditions

- Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if symptoms develop especially thyroid dysfunction and celiac disease.

  other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population (e.g., Trial Net)

Thyroid Disease

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of individuals with type 1 diabetes. At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies, the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of people with type 1 diabetes.

- Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis.

- Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after optimizing glycemia. If normal, suggest rechecking every 1–2 years or sooner if the youth has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability.

Celiac Disease

- Celiac disease is an immune-mediated disorder that occurs with increased frequency in people with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population). Screening people with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria
- Screen youth with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG tTG and deamidated gliadin antibodies if IgA is deficient.
- Repeat screening for celiac disease within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in youth who have symptoms or a first-degree relative with celiac disease.
- Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications.

Management of Cardiovascular Risk Factors

Hypertension Screening

Clinical pearl:

- Blood pressure should be measured at every routine visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, blood pressure ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered.

Hypertension Treatment

Summary

- Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management.
- In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects,

individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception.

- The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg.

  Blood pressure measurements should be performed using the appropriate size cuff with the youth seated and relaxed. Elevated blood pressure should be confirmed on at least three separate days, and ambulatory blood pressure monitoring should be considered.

Dyslipidemia Screening

- Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is ≥2 years. If initial LDL cholesterol is ≤100 mg/dL (≤2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. Initial testing may be done with a nonfasting lipid level with confirmatory testing with a fasting lipid panel.
- If LDL cholesterol values are within the accepted risk level (<100 mg/dL [<2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable.

Dyslipidemia Treatment

- If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutrition therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid trans fats, and aim for ~10% calories from monounsaturated fats.
- After the age of 10 years, addition of a statin may be considered in youth with type 1 diabetes who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL (>4.1 mmol/L) or LDL cholesterol >130 mg/dL (>3.4 mmol/L) and one or more cardiovascular disease risk factors. Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception.
- The goal of therapy is an LDL cholesterol value <100 mg/dL (<2.6 mmol/L).

Pathophysiology

The atherosclerotic process begins in childhood, and although ASCVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis.

Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia

efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening.

Statins are not approved for children aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age.

Statins are contraindicated in pregnancy.

The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes.

Microvascular Complications

Nephropathy Screening

Clinical pearl:

- Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the youth has had diabetes for 5 years.

Nephropathy Treatment

Summary:

- An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemia and normalize blood pressure).
- An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex, should be considered at baseline and repeated as indicated.

Retinopathy

Summary:

- An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥11 years or puberty has started, whichever is earlier. repeat dilated and comprehensive eye examination every 2 years or on advice of an eye care professional.
- Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration

Neuropathy

Clinical pearl:

- Consider an annual comprehensive foot exam at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. The examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests.

Type 2 Diabetes

The prevalence of type 2 diabetes in youth has continued to increase over the past 20 years. The CDC published projections for type 2 diabetes prevalence using the SEARCH database; assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years .

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (TODAY) study .

Screening and Diagnosis

Summary

- Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes
- If screening is normal, repeat screening at a minimum of 3-year intervals, or more frequently if BMI is increasing.
- Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population,
- Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes.

Clinical pearl:

- Overweight and obesity are common in children with type 1 diabetes, and diabetes-associated autoantibodies and ketosis may be present in pediatric individuals with clinical features of type 2 diabetes (including obesity and acanthosis nigricans. The presence of islet autoantibodies has been associated with faster progression to insulin deficiency

- . At the onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes. Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, and thus it should be part of the differential in children with suggestive symptoms.
- Obesity contributes to the development of type 1 diabetes in some individuals , which further blurs the lines between diabetes types. .
- The significant diagnostic difficulties posed by MODY
- There are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

- All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education and support that is specific to youth with type 2 diabetes and is culturally appropriate.
- Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve at least a 7–10% decrease in excess weight.
- Youth with prediabetes and type 2 diabetes, like all children and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week)
- Nutrition for youth with prediabetes and type 2 diabetes, like for all children and adolescents, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages.

Glycemic Goals

- Blood glucose monitoring should be individualized, taking into consideration the pharmacologic treatment of the youth with type 2 diabetes.
- Real-time CGM or intermittently scanned CGM should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or insulin pumps who are capable of using the device
- Glycemic status should be assessed at least every 3 months.
- A reasonable A1C goal for most children and adolescents with type 2 diabetes is <7% (<53 mmol/mol). More stringent A1C goals (such as <6.5% [<48 mmol/mol]) may be appropriate for selected

Pharmacologic Management

- Life style alteration: Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes.

- Metformin: In individuals with incidentally diagnosed or metabolically stable diabetes (A1C <8.5% [<69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal.
- Basal Insulin + metformin: Youth with marked hyperglycemia (blood glucose ≥250 mg/dL [≥13.9 mmol/L], A1C ≥8.5% [≥69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with long-acting insulin while metformin is initiated and titrated.
- IV insulin: In individuals with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued.
- In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [≥ 33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome.
- GLP-1 A/or SGLT2 A: If glycemic goals are no longer met with metformin (with or without long-acting insulin), glucagon-like peptide 1 (GLP-1) receptor agonist therapy and/or empagliflozin should be considered in children 10 years of age or older.
- Medication effect on weight: When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and the medications' effect on weight.
- Intensifying Insulin**:** For youth not meeting glycemic goals, maximize noninsulin therapies (metformin, a GLP-1 receptor agonist, and empagliflozin) before initiating and/or intensifying insulin therapy plan.
- Insulin tapering: In individuals initially treated with insulin and metformin and/or other glucose lowering medications who are meeting glucose goals based on blood glucose monitoring or CGM, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days.

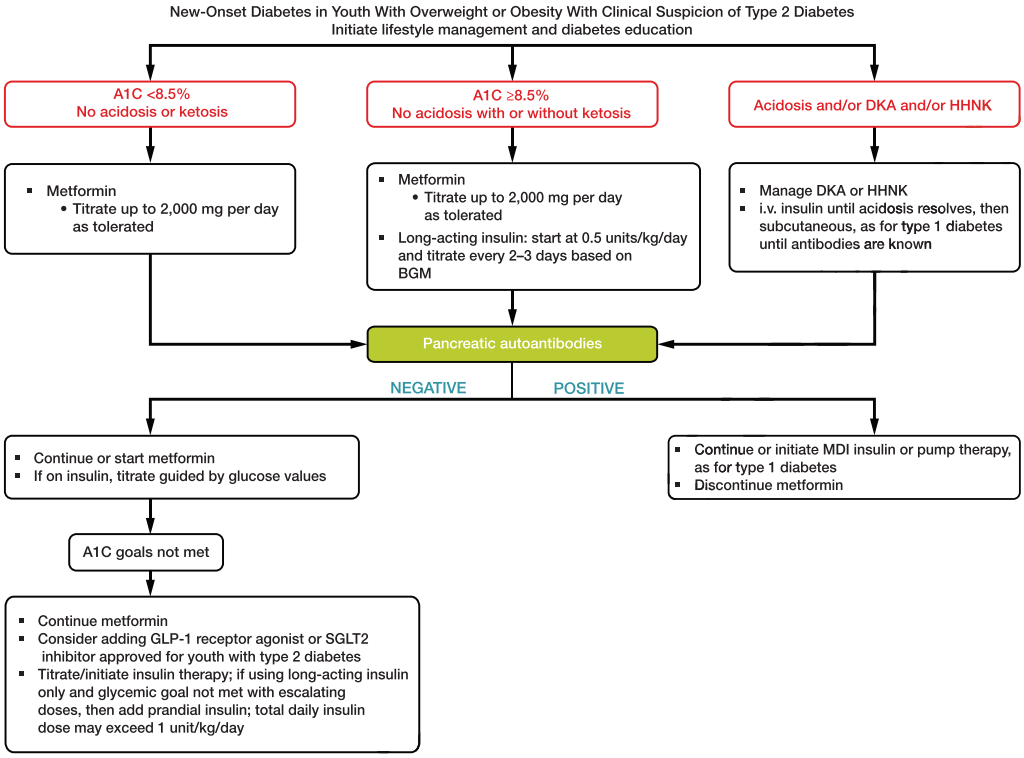


Figure 21.1: Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes". BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide 1; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; i.v., intravenous; MDI, multiple daily injections; SGLT2, sodium–glucose cotransporter 2.

Metabolic Surgery

- Metabolic surgery: may be considered for the treatment of adolescents with type 2 diabetes who have class 2 obesity or higher (BMI >35 kg/m^2 or 120% of 95th percentile for age and sex, whichever is lower) and who have elevated A1C and/or serious comorbidities despite lifestyle and pharmacologic intervention.

The results of weight loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and treatment options as adjuncts to lifestyle therapy are limited. Recent U.S. Food and Drug Administration–approved medications for youth ages 12 and older include phentermine and topiramate extended-release capsules and GLP-1 receptor agonists.

Indication for metabolic surgery in adolescents

- Class 2 obesity or higher (BMI >35 kg/m^2 or 120% of 95th percentile for age and sex, whichever is lower, with comorbidities)

- BMI >40 kg/m^2 with or without comorbidities.
- A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents

Prevention and Management of Diabetes Complications

Hypertension

- Blood pressure should be measured at every clinic visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered.
- Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management.
- In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg).
- Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception.
- The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg.

Nephropathy

Summary:

- Protein intake should be at the recommended daily allowance of 0.85–1.2 g/kg/day (according to age).
- Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples.
- Estimated glomerular filtration rate (GFR) should be determined at the time of diagnosis and annually thereafter.
- In youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated GFR <60 mL/min/1.73 m^2.

- Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception.
- For youth with nephropathy, continue monitoring (yearly and/or as indicated by urinary albumin-to-creatinine ratio and estimated GFR) to detect disease progression.
- Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated GFR.

Neuropathy

- Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests.
- Prevention of neuropathy should focus on achieving glycemic goals.

Retinopathy

- Screening for retinopathy should be performed by dilated fundoscopy at or soon after diagnosis and annually thereafter.
- Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy.
- Less frequent examination (every 2 years) may be considered if achieving glycemic goals and a normal eye exam.
- Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy.

Nonalcoholic Fatty Liver Disease

Obligations:

- Evaluation of youth with type 2 diabetes for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter.
- Referral to gastroenterology should be considered for persistently elevated or worsening transaminases.

Obstructive Sleep Apnea

- Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented.

Polycystic Ovary Syndrome

- Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies, when indicated.
- Metformin, in addition to lifestyle modification, is likely to improve the menstrual cyclicity and hyperandrogenism in female individuals with type 2 diabetes.

Cardiovascular Disease

- Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood.

Dyslipidemia

- Lipid screening should be performed initially after optimizing glycemia and annually thereafter.
- Optimal goals: Optimal goals are LDL cholesterol <100 mg/dL (<2.6 mmol/L), HDL cholesterol >35 mg/dL (>0.91 mmol/L), and triglycerides <150 mg/dL (<1.7 mmol/L).
- Diet: If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutritional therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid trans fats, and aim for ~10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, medical nutrition therapy should also focus on decreasing simple sugar intake and increasing dietary n-3 fatty acids in addition to the above changes.
- Statin: If LDL cholesterol remains >130 mg/dL (>3.4 mmol/L) after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL <100 mg/dL (<2.6 mmol/L). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception.
- Hypertriglyceridemia: If triglycerides are >400 mg/dL (>4.7 mmol/L) fasting or >1,000 mg/dL (>11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL (<4.7 mmol/L) fasting to reduce risk for pancreatitis.

Cardiac Function Testing

- ECG, ETT, Echocardiogram**:** Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes.

Comperison with T1 DM:

Complications: ASCVD-The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes than with type 1 diabetes of similar duration, including ischemic heart disease and stroke.

Hypoglycemia-There is a low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin,

These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C.

In youth with type 2 diabetes and polycystic ovary syndrome, oral contraceptives are appropriate agents.

Psychosocial Factors

- Health care professionals should screen for food insecurity, housing instability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions.
- Use age-appropriate standardized and validated tools to screen for diabetes distress, depressive symptoms, and behavioral health in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating, and refer to a qualified behavioral health professional when indicated.
- Adolescents and young adults should be screened for tobacco/nicotine, electronic cigarettes, substance use, and alcohol use at diagnosis and regularly thereafter.

Substance Use in Pediatric Diabetes

Tobacco and Electronic Cigarettes

- Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke as these are well recognized with respect to future cancer and CVD risk
- Electronic cigarette use should be discouraged
- efforts are warranted to reduce alcohol use and increase education about the risks of alcohol use and strategies to minimize risks.

Transition from Pediatric to Adult Care

- Pediatric diabetes care teams should implement transition preparation programs for youth beginning in early adolescence and, at the latest, at least 1 year before the anticipated transfer from pediatric to adult health care.
- Interprofessional adult and pediatric health care teams should provide support and resources for adolescents, young adults, and their families prior to and during the transition process from pediatric to adult health care.
- Pediatric diabetes specialists should partner with youth with diabetes and their caregivers to decide on the timing of transfer to an adult diabetes specialist.
- During this period of major life transitions, youth may begin to move out of their parents' or caregivers' homes and become increasingly responsible for their diabetes care.

It is clear that comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care Suggested citation: American Diabetes Association Professional Practice Committee. 14. Children and adolescents: *Standards of Care in Diabetes—2024*. Diabetes Care 2024;47(Suppl. 1):S258–S281

22
CHAPTER

Diabetes in Pregnancy

In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal respiratory distress syndrome. In addition, diabetes in pregnancy increases the risks of obesity, hypertension, and type 2 diabetes in offspring later in life.

Preconception Counseling

- Starting at puberty and continuing in all people with diabetes and childbearing potential, preconception counseling should be incorporated into routine diabetes care.
- Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until an individual's treatment plan and A1C are optimized for pregnancy.
- Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C <6.5% (<48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications.

Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy. optimize glycemia prior to conception with an A1C <6.5% (<48 mmol/mol), as this is associated with the lowest risk of congenital anomalies (given that organogenesis occurs primarily at 5–8 weeks of gestation), preeclampsia, and preterm birth, preconception care for pregnant individuals with preexisting diabetes was associated with lower A1C and reduced risks of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admissions

There are opportunities at any health care visit to educate all adults and adolescents with diabetes and childbearing potential about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning

all adults and adolescents with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies and even with mild hyperglycemia and *2*) the use of effective contraception at all times when trying to prevent a pregnancy.

Preconception Care

Individuals with preexisting diabetes who are planning a pregnancy should ideally begin receiving interprofessional care for preconception, which includes an endocrinology health

care professional, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception, care should be augmented with extra focus on nutrition, physical activity, diabetes self-care education, and screening for diabetes comorbidities and complications. A key point is the need to incorporate a question about plans for pregnancy into the routine primary and gynecologic care of people with diabetes

- Individuals with preexisting type 1 or type 2 diabetes who are planning a pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then pregnant individuals should be monitored every trimester and for 1 year postpartum
- Prescription of prenatal vitamins with at least 400 µg of folic acid and 150 mg of potassium iodide is recommended prior to conception.
- abstinence of use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes
- screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications, herbal supplements, and non-herbal supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus.
- Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to -creatinine ratio

Table 22.1 Checklist for preconception care for people with diabetes (ACOG)

Preconception education should include:
Comprehensive nutrition assessment and recommendations for: • Overweight/obesity or underweight • Meal planning • Correction of dietary nutritional deficiencies • Caffeine intake • Safe food preparation technique
Lifestyle recommendations for: • Regular moderate exercise • Avoidance of hyperthermia (hot tubs) • Adequate sleep
Comprehensive diabetes self-management education • Counseling on diabetes in pregnancy per current standards, including: natural history of insulin resistance in pregnancy and postpartum; preconception glycemic goals; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
Supplementation • Folic acid supplement (400 µg routine) • Appropriate use of over-the-counter medications and supplements

(table continued)

Table 22.1 *(cont'd)*

Health assessment and plan should include:

- General evaluation of overall health
- Evaluation of diabetes and its comorbidities and complications, including DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- Evaluation of obstetric/gynecologic history, including a history of cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- Review of current medications and appropriateness during pregnancy

Screening should include:

- Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine albumin-to-creatinine ratio
- Anemia
- Genetic carrier status (based on history):
- Cystic fibrosis
- Sickle cell anemia
- Tay-Sachs disease
- Thalassemia
- Others if indicated
- Infectious disease
- *Neisseria gonorrhoeae/Chlamydia trachomatis*
- Hepatitis B and hepatitis C
- HIV
- Pap smear
- Syphilis

Immunizations should include:

- Inactivated influenza
- Tdap (tetanus, diphtheria, and pertussis)
- COVID-19 (certain populations)
- Hepatitis A and hepatitis B (certain populations)
- Others if indicated

Preconception plan should include:

- Nutrition and medication plan to achieve glycemic goals prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
- Contraceptive plan to prevent pregnancy until glycemic goals are achieved
- Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

Glycemic Goals in Pregnancy

- **Blood Glucose**: Glucose goals are:
- Fasting plasma glucose <95 mg/dL (<5.3 mmol/L) and either 1-h postprandial *glucose* <140 mg/dL (<7.8 mmol/L) or 2-h postprandial glucose <120 mg/dL (<6.7 mmol/L).

A_1C: Due to increased red blood cell turnover, A_1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C goal in pregnancy is <6% (<42 mmol/mol) if this can be achieved without significant hypoglycemia, but the goal may be relaxed to <7% (<53 mmol/mol) if necessary to prevent hypoglycemia. Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

CGM: CGM is recommended in pregnancies associated with type 1 diabetes. CGM metrics may be used in addition to but should not be used as a substitute for blood glucose monitoring to achieve optimal pre- and postprandial glycemic goals. There are insufficient data to support the use of CGM in all people with type 2 diabetes or GDM. The decision of whether to use CGM in pregnant individuals with type 2 diabetes or GDM should be individualized based on treatment regimen, circumstances, preferences, and needs.

Nutrition: Nutrition counseling should endorse a balance of macronutrients including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern.

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental factors. In people with preexisting diabetes, glycemic goals are usually achieved through a combination of insulin administration and medical nutrition therapy. Processed foods, fatty red meat, and sweetened foods and beverages should be limited.

Insulin Physiology

- Early pregnancy: Given that early pregnancy may be a time of enhanced insulin sensitivity and lower glucose levels, many people with type 1 diabetes will have lower insulin requirements and an increased risk for hypoglycemia.
- At around 16 weeks: insulin resistance begins to increase, and total daily insulin

doses increase linearly ~5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. While there is an increase in both basal and bolus insulin requirements, bolus insulin requirements take up a larger proportion of overall total daily insulin needs in individuals with preexisting diabetes as pregnancy progresses.

- The insulin requirement levels off toward the end of the third trimester.
- A rapid reduction in insulin requirements can indicate the development of placental insufficiency
- Hypoglycemia: Current recommendations for hypoglycemia thresholds include blood glucose <70 mg/dL (<3.9 mmol/L) and sensor glucose <63 mg/dL (<3.5 mmol/L). In practice, it may be challenging for a person with type 1 diabetes to achieve these goals without hypoglycemia, particularly those with a history of recurrent hypoglycemia or hypoglycemia unawareness. If an individual cannot achieve these goals without significant hypoglycemia, the ADA suggests less stringent goals based on clinical experience and individualization of care.

Continuous Glucose Monitoring in Pregnancy

Selection of CGM device should be based on an individual's circumstances, preferences, and needs.

- Target sensor glucose range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- Time below range (<63 mg/dL [<3.5 mmol/L]): level 1 TBR, goal <4%
- Time below range (<54 mg/dL [<3.0 mmol/L]): level 2 TBR, goal <1%
- Time above range (>140 mg/dL [>7.8 mmol/L]): TAR, goal <25%

The international consensus on TIR endorsed the same sensor glucose target ranges for individuals with type 2 diabetes in pregnancy and GDM but could not quantify the goal of amount of time spent within each category because of insufficient data.

Management of Gestational Diabetes Mellitus

- Lifestyle behavior change is an essential component of management of gestational diabetes mellitus (GDM) and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic goals.
- Insulin is the preferred medication for treating hyperglycemia in GDM.
- OHA: Metformin and glyburide, individually or in combination, should not be used as first-line agents, as both cross the placenta to the fetus. Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.
- Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester.

- Telehealth visits used in combination with in-person visits for pregnant people with GDM can improve outcomes compared with standard in-person care alone.

GDM is characterized by an increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and abnormal glucose metabolism of offspring in childhood.

- Offspring with exposure to untreated GDM have reduced insulin sensitivity and β-cell compensation and are more likely to have impaired glucose tolerance in childhood."
- Prevention of GDM: Although there is some heterogeneity, many RCTs and a Cochrane review suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester. There are no intervention trials in offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk individuals with obesity, polycystic ovary syndrome, or preexisting insulin resistance

Lifestyle and Behavioral Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined before for preexisting type 2 diabetes, as well as glucose monitoring aiming for the goals recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus

- Fasting glucose <95 mg/dL (<5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (<7.8 mmol/L) or
- Two-hour postprandial glucose <120 mg/dL (<6.7 mmol/L)

The glycemic goal lower limits defined above for preexisting diabetes apply for GDM treated with insulin. Depending on the population, studies suggest that 70–85% of people diagnosed with GDM under Carpenter-Coustan criteria can manage GDM with lifestyle modification alone.

Medical Nutrition Therapy

- Medical nutrition therapy for GDM is an individualized nutrition plan developed between the pregnant person and an RDN familiar with the management of GDM.
- The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate weight gain, according to the 2009 National Academy of Medicine recommendations
- There is no definitive research that identifies a specific optimal calorie intake for people with GDM or suggests that their calorie needs are different from those of pregnant individuals without GDM.
- The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate (~35% of a 2,000-calorie diet), a minimum of 71 g of protein, and 28 g of fiber

- The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats.
- Promoting higher-quality, nutrient-dense carbohydrates result in controlled fasting/postprandial glucose, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity.

Physical Activity

A systematic review demonstrated improvements in glucose outcomes and reductions in need to start insulin or insulin dose requirements with an exercise intervention.

There was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity).

Pharmacologic Therapy

Insulin is the first-line agent recommended for the treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin and glyburide in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews and RCTs. However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels.

Metformin in Gestational Diabetes:

- The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin for the treatment of GDM in the Auckland cohort were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin. This difference was not found in the Adelaide cohort. A meta-analysis demonstrated that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood.
- There are some people with GDM requiring medical therapy who may not be able to use insulin safely or effectively during pregnancy due to cost, language barriers, comprehension, or cultural influences. Oral agents may be an alternative for these

individuals after discussing the known risks and the need for more long-term safety data in offspring.

- However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in pregnant people with hypertension or preeclampsia or those at risk for intrauterine growth restriction.

Insulin

Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy

Management of Preexisting Type 1 Diabetes and Type 2 Diabetes in Pregnancy:

- Insulin should be used to manage type 1 diabetes in pregnancy. Insulin is the preferred agent for the management of type 2 diabetes in pregnancy.
- Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes.

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. Due to the complexity of insulin management in pregnancy, referral to a specialized center centers may still be beneficial.

While many health care professionals prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections. None of the current automated insulin delivery (AID) systems approved by the U.S. Food and Drug Administration (FDA) have algorithms set to achieve pregnancy goals.

Partial closed-loop therapy, such as predictive low-glucose suspend (PLGS) technology, has been shown in nonpregnant people to be better than sensor-augmented insulin pumps (SAP) for reducing low glucose values.

Type 1 Diabetes

- Pregnant individuals with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all pregnant people, have altered counter-regulatory response in pregnancy that may decrease hypoglycemia awareness. Education for people with diabetes and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help prevent and manage hypoglycemia risk. Insulin resistance drops rapidly with the delivery of the placenta.
- Pregnancy is a ketogenic state, and people with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Pregnant people with type 1 diabetes should be advised to obtain ketone test strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth.

Those in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

- Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (Meta-analyses have also demonstrated a high risk of new-onset retinopathy and progression of existing retinopathy in pregnant individuals with type 1 or type 2 diabetes.

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for people with overweight is 15–25 lb (6.8–11.3 kg) and for those with obesity is 10–20 lb (4.5–9.1 kg), losing weight is not recommended because of the increased risk of small-for-gestational age infants.

Optimal glycemic goals are often easier to achieve during pregnancy with type 2 diabetes than with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. Insulin is the preferred treatment for type 2 diabetes in pregnancy.

An RCT of metformin added to insulin for the treatment of type 2 diabetes found less maternal weight gain and fewer cesarean births. There were fewer macrocosmic neonates, but there was a doubling of small-for-gestational-age neonates.

As in type 1 diabetes, insulin requirements drop dramatically after delivery.

The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes compared with type 1 diabetes, even if diabetes is better managed and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in those with type 2 diabetes, compared with the first trimester in those with type 1 diabetes.

Preeclampsia and Aspirin

- Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia

Pregnancy and Drug Considerations

- In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy. (ACOG)
- There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure <90/60 mmHg.
- A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension.
- Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor

blockers, statins should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception.

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction.

Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β-blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion. statins should also be avoided in pregnancy.

Postpartum Care

- Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum.
- A contraceptive plan should be discussed and implemented with all people with diabetes of childbearing potential.
- Screen individuals with a recent history of GDM at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria.
- Individuals with overweight/obesity and a history of GDM found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes.
- Breastfeeding efforts are recommended for all individuals with diabetes. Breastfeeding is recommended for individuals with a history of GDM for multiple benefits, including a reduced risk for type 2 diabetes later in life.
- Individuals with a history of GDM should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years.
- Individuals with a history of GDM should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations.
- Postpartum care should include psychosocial assessment and support for self-care.

Gestational Diabetes Mellitus Postpartum Care

The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥126 mg/dL [≥7.0 mmol/L]) and 2-h plasma glucose (≥200 mg/dL [≥11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets

Individuals with a history of GDM should have ongoing screening for prediabetes or type 2 diabetes every 1–3 years, even if the results of the initial 4–12 week postpartum 75-g OGTT are normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using thresholds for nonpregnant individuals).

Individuals with a history of GDM have an increased lifetime maternal risk for diabetes estimated at 50–60%, and those with GDM have a 10-fold increased risk of developing type 2 diabetes compared with those without GDM. Absolute risk of developing type 2 diabetes after GDM increases linearly through a person's lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years. Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy weight gain is associated with increased risk of adverse pregnancy outcomes and higher risk of GDM. In addition, postdelivery lifestyle interventions are effective in reducing risk of type 2 diabetes.

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in individuals with prediabetes and a history of GDM.

Preexisting Type 1 and Type 2 Diabetes Postpartum Care

Insulin sensitivity increases dramatically with the delivery of the placenta, roughly 34% lower than prepregnancy insulin requirements. Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. For individuals taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules.

Lactation

Considering the immediate nutritional and immunological benefits of breastfeeding for the baby, all mothers, including those with diabetes, should be supported in attempts to breastfeed. Breastfeeding was associated reduced infant mortality due to infectious diseases at <6 months of age , reduced respiratory infections in children aged <2 years, and reduced asthma or wheezing in children aged 5–18 years . breastfeeding was associated with improved maternal health outcomes including reduced risks of breast cancer, ovarian cancer and type 2 diabetes. Breastfeeding may also confer longer-term metabolic benefits to both mother and offspring. Breastfeeding reduces the risk of developing type 2 diabetes in mothers with previous GDM. However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Contraception

Therefore, all individuals with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to individuals in the immediate postpartum period. Individuals with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversible contraception may be ideal for individuals with diabetes and childbearing potential.

Management of diabetes in pregnancy (27%):

GDM and pregnant in diabetic women:

Summary:

Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice as treatment for many individuals.

Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus.

Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus.

Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.

Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester.

Low dose aspirin to prevent Pre-Eclampsia E.

Telehealth visits for pregnant people with gestational diabetes mellitus improve outcomes compared with standard in-person care.

Management of diabetes in pregnancy: *Standards of Care in Diabetes—2024*. Diabetes Care 2024;47(Suppl. 1): S282–S294

23
CHAPTER

Diabetes in Hospital Care

- Perform an A1C test on all people with diabetes or hyperglycemia (random blood glucose >140 mg/dL [>7.8 mmol/L]) admitted to the hospital if no A1C test result is available from the prior 3 months.
- Institutions should implement protocols using validated written or computerized provider order entry sets for management of dysglycemia in the hospital (including emergency department, intensive care unit [ICU] and non-ICU wards, gynecology-obstetrics/delivery units, dialysis suites, and behavioral health units) that allow for a personalized approach, including glucose monitoring, insulin and/or noninsulin therapy, hypoglycemia management, diabetes self-management education, nutrition recommendations, and transitions of care.

Considerations on Admission

COPE:Medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized provider order entry (CPOE). Institutions are encouraged to perform audits regularly to monitor proper use and institute educational/training programs to keep staff up to date.

Initial evaluation: Initial evaluation should state the type of diabetes (i.e., type 1, type 2, gestational, pancreatogenic, drug related, or nutrition related) when it is known. Because inpatient treatment and discharge planning are more effective when preadmission glycemia is considered, A1C should be measured for all people with diabetes or dysglycemia admitted to the hospital if no A1C test result is available from the previous 3 months.

DSMES: Diabetes self-management knowledge and behaviors should be assessed on admission, and diabetes self-management education provided (if available), especially if a new treatment plan is being considered. Diabetes self-management education should include knowledge and survival skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia.

Diabetes Care Specialists in the Hospital

Recommendation

- When caring for hospitalized people with diabetes (with an existing or new diagnosis) or stress hyperglycemia, consult with a specialized diabetes or glucose management team when accessible.

In a cross-sectional study comparing usual care to specialists reviewing diabetes cases and making recommendations virtually through the EHR, rates of both hyperglycemia and hypoglycemia were reduced by 30–40%. Providing inpatient diabetes self-management education and developing a diabetes discharge plan that includes continued access to diabetes medications and supplies and ongoing education and support are key strategies to improve outcomes. (Joint British Diabetes Societies (JBDS) for Inpatient Care Group.

Glycemic Goals in Hospitalized Adults

- Non critical ill: Insulin and/or other therapies should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L) (confirmed on two occasions within 24 h) for noncritically ill (non-ICU) individuals.
- Critically ill: Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill (ICU) individuals with hyperglycemia.
- More stringent glycemic goals: More stringent glycemic goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected critically ill individuals and are acceptable if they can be achieved without significant hypoglycemia.

Standard Definitions of Glucose Abnormalities

Hyperglycemia:

- Hyperglycemia in hospitalized individuals is defined as blood glucose levels >140 mg/dL (>7.8 mmol/L).
- An admission A1C value ≥6.5% (≥48 mmol/mol) suggests that the onset of diabetes preceded hospitalization.
- Level 1 hypoglycemia is defined as a glucose concentration of 54–69 mg/dL (3.0–3.8 mmol/L).
- Level 2 hypoglycemia is defined as a glucose concentration <54 mg/dL (<3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms.
- Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery
- Levels 2 and 3 require immediate intervention and correction of low blood glucose.
- Prompt treatment of level 1 hypoglycemia is recommended as an effort to prevent progression to more significant level 2 and level 3 hypoglycemia.

Glycemic Goals in hospitalized patients:

Critically ill: Based on these results, insulin and/or other therapies should be initiated for the treatment of persistent hyperglycemia ≥180 mg/dL (≥10.0 mmol/L). Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended (NICE-SUGAR) trial for most critically ill individuals with hyperglycemia. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized individuals without critical illness.

More stringent glycemic goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected individuals (e.g., critically ill individuals undergoing surgery) if it can be achieved without significant hypoglycemia.

Noncritical care: For inpatient management of hyperglycemia in noncritical care, settings a glycemic goal of 100–180 mg/dL (5.6–10.0 mmol/L) is recommended, whether it is new hyperglycemia (e.g., newly diagnosed diabetes or stress hyperglycemia) or hyperglycemia related to diabetes prior to admission. It has been found that fasting glucose levels <100 mg/dL (<5.6 mmol/L) are predictors of hypoglycemia within the next 24 h. Glycemic levels up to 250 mg/dL (13.9 mmol/L) may be acceptable in selected populations (terminally ill individuals with short life expectancy, advanced kidney failure [and/or on dialysis], high risk for hypoglycemia, and/or labile glycemic excursions.

Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), may be incorporated into the day-to-day decisions regarding treatment dosing.

Glucose Monitoring

In hospitalized individuals with diabetes

Who are eating: Who are eating, point-of-care (POC) blood glucose monitoring should be performed before meals;

Those not eating: glucose monitoring is advised every 4–6 h. More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin therapy.

Hospital blood glucose monitoring should be performed with U.S. Food and Drug Administration (FDA)–approved POC hospital-calibrated glucose monitoring systems. POC blood glucose meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifacts due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital

Clinical pearl: best practice dictates that any glucose result that does not correlate with the individual's clinical status should be confirmed by measuring a sample in the clinical laboratory, particularly for asymptomatic hypoglycemic events.

Continuous Glucose Monitoring-CGM

- In people with diabetes using a personal continuous glucose monitoring (CGM) device, the use of CGM should be continued during hospitalization if clinically appropriate, with confirmatory point-of-care (POC) glucose measurements for insulin dosing decisions and hypoglycemia assessment, (if according to an institutional protocol).
- AID, AID&CGM: For people with diabetes using an automated insulin delivery (AID) system along with CGM, the use of AID and CGM should be continued during hospitalization if clinically appropriate, with confirmatory POC blood glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol.

Glucose-Lowering Treatment in Hospitalized Patients

An individualized approach for glycemic management is encouraged throughout the hospital stay.

Insulin Therapy

Summary:

- Basal insulin or a basal plus bolus correction insulin plan is the preferred treatment for noncritically ill hospitalized individuals with poor oral intake or those who are taking nothing by mouth.
- An insulin plan with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized individuals with adequate nutritional intake.
- Sole use of a correction or supplemental insulin without basal insulin (formerly referred to as a sliding scale) in the inpatient setting is discouraged.

Critical Care Setting

Continuous intravenous insulin infusion is the most effective method for achieving specific glycemic goals and avoiding hypoglycemia in the critical care setting. Intravenous insulin infusions should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and immediate past and current insulin infusion rates.

For diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) (Fig. 23.2) management, continuous intravenous insulin infusion is given for correction of hyperglycemia, hyperketonemia, and acid-base disorder following a fixed-rate intravenous insulin infusion or nurse-driven protocol with a variable rate based on glucose values.

Individuals with mild and uncomplicated DKA can be managed with subcutaneous rapid-acting insulin doses given every 1–2 h.

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized individuals.

- OHA: In certain circumstances, it may be appropriate to continue home oral glucose-lowering medications, such as dipeptidyl peptidase 4 inhibitors (DPP-4i). If oral medications are held in the hospital but will be reinstated after discharge, there should be a protocol for guiding resumption of home medications 1–2 days prior to discharge.
- Subcutaneous insulin: Outside of critical care units, scheduled subcutaneous insulin orders are recommended for the management of hyperglycemia in people with diabetes and hyperglycemia.
- Analog vs Human insulin: Use of insulin analogs or human insulin results in similar glycemic outcomes in the hospital setting but may increase severe hypoglycemic events.
- Rapid- or short-acting insulin Subcutaneous rapid- or short-acting insulin: The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if the individual is receiving ***continuous enteral/parenteral nutrition***, is indicated to correct or prevent hyperglycemia.

- Basal insulin, or a basal plus bolus correction schedule: is the preferred treatment for noncritically ill hospitalized individuals with inadequate or restricted oral intake.
- Basal, prandial, and correction insulin: An insulin schedule with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized people with diabetes with adequate nutritional intake.

A randomized controlled trial has shown that basal plus bolus treatment improved glycemic outcomes and reduced hospital complications compared with a correction or supplemental insulin without basal insulin (formerly known as sliding scale) for people with type 2 diabetes admitted for general surgery.

- Mixture Insulin: Therefore, insulin mixtures such as 75/25, 70/30, or 50/50 insulins are not routinely recommended for in-hospital use.
- Concentrated insulin: Data on the use of glargine U-300 and degludec U-100 or U-200 in the inpatient and perioperative settings are limited.
- Weekly insulin: At this time, there is no available evidence for weekly insulin use in hospital or surgical settings.

Type 1 Diabetes

An insulin schedule with basal and correction components is necessary for all hospitalized individuals with type 1 diabetes, even when taking nothing by mouth, with the addition of prandial insulin when eating.

Transitioning From Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is recommended, as it is associated with less morbidity and lower costs of care. Subcutaneous basal insulin should be given 2 h before intravenous infusion is discontinued, with the aim of minimizing rebound hyperglycemia.

Emerging data from several studies show that the administration of a low dose (0.15–0.3 units/kg) of basal insulin analog in addition to intravenous insulin infusion may reduce the duration of insulin infusion and length of hospital stay and prevent rebound hyperglycemia without increased risk of hypoglycemia.

For transitioning, the total daily dose of subcutaneous insulin can be calculated based on the insulin infusion rate during the prior 6–8 h when stable glycemic goals were achieved, based on prior home insulin dose, or following a weight-based approach

Noninsulin Therapies

- For people with type 2 diabetes hospitalized with heart failure, it is recommended that use of a sodium–glucose cotransporter 2 inhibitor be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness. SGLT2 inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures.. The FDA has warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin.

- DPP-4i: The use of DPP-4i with or without basal insulin may be a safer and simpler plan for people with mild to moderate hyperglycemia on admission (e.g., admission glucose <180–200 mg/dL), with reduced risk of hypoglycemia (consider discontinuing saxagliptin and alogliptin in people who develop heart failure).
- (GLP-1) receptor agonists: Data on the inpatient use of glucagon-like peptide 1 (GLP-1) receptor agonists are still mostly limited to research studies and select populations that are medically stable.

Hypoglycemia

- A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system.
- Treatment plans should be reviewed and changed as necessary to prevent hypoglycemia and recurrent hypoglycemia when a blood glucose value of <70 mg/dL (<3.9 mmol/L) is documented.
- Many episodes of inpatient hypoglycemia are preventable.
- All hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues

Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention

Risk factors: Iatrogenic errors with insulin treatment, iatrogenic hypoglycemia may be induced by a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin doses in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the individual to report symptoms, Kidney failure is an important risk factor for hypoglycemia in the hospital

CGM and AID: Recent inpatient studies show promise for CGM as an early warning system to alert of impending hypoglycemia, offering an opportunity to mitigate it before it happens. The use of personal CGM and AID devices, such as insulin pumps that can automatically deliver correction doses and change basal delivery rates in real time, should be supported for ongoing use during hospitalization for individuals who are capable of using their devices safely and independently when proper oversight supervision is available. Hospitals should be encouraged to develop policies and protocols to support inpatient use of individual- and hospital-owned diabetes technology and have expert staff available for safe implementation and evaluation of continued use during the hospital stay.

Predictors of Hypoglycemia

In people with diabetes, it is well established that an episode of severe hypoglycemia increases the risk for a subsequent event, partly because of impaired counter regulation

- In a study of hospitalized individuals, 84% of people who had an episode of severe hypoglycemia (defined as <40 mg/dL [<2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [<3.9 mmol/L]) during the same admission.

- In another study of hypoglycemic episodes (defined as <50 mg/dL [<2.8 mmol/L]), 78% of individuals were taking basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of individuals did not have their dose of basal insulin changed before the next basal insulin administration.
- In one retrospective cohort study, a fasting blood glucose of <100 mg/dL was shown to be a predictor of next-day hypoglycemia.

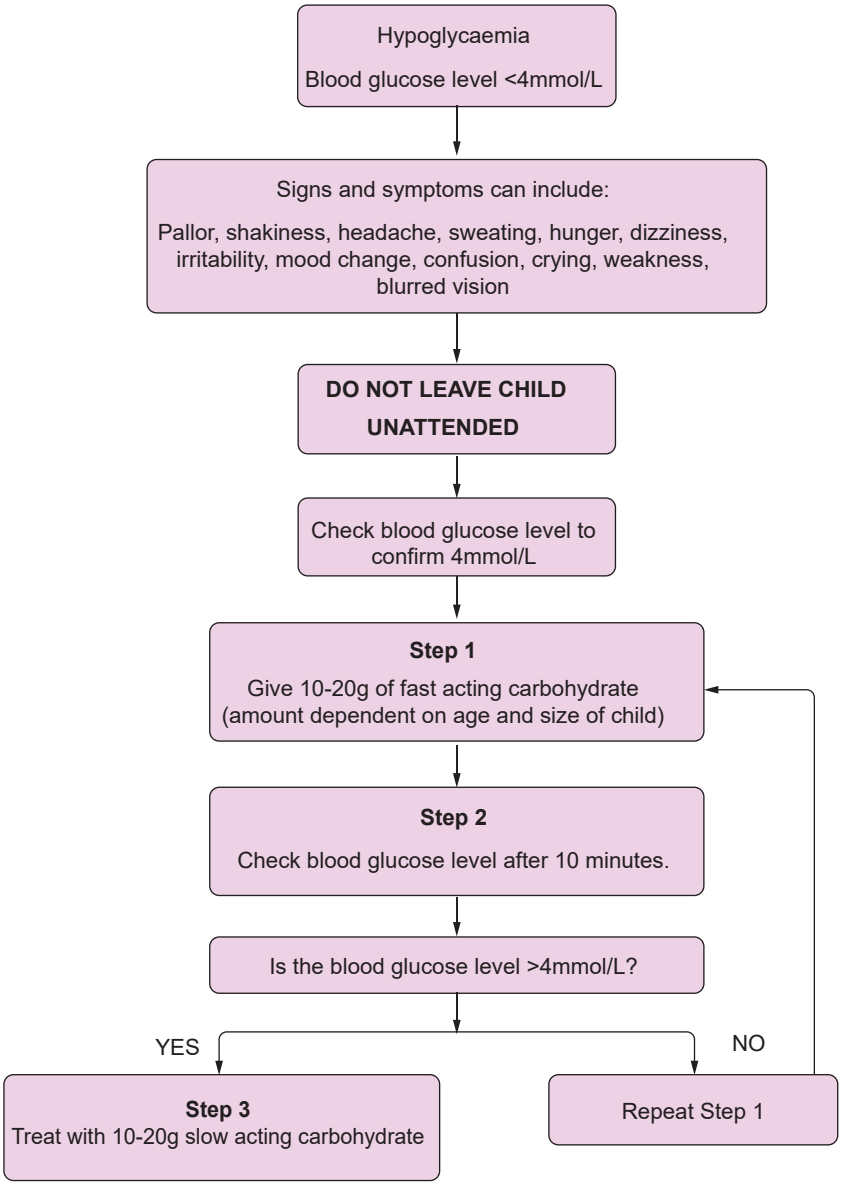


Figure 23.1: Treatment of hypoglycemia in hospitalized patient ( )

Medical Nutrition Therapy in the Hospital

The American Diabetes Association does not endorse any single meal plan or specified percentages of macronutrients.

Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use.

Controlled carbohydrate meal plans, where the amount of carbohydrate on each meal tray is calculated, are preferred by many hospitals, as they facilitate matching the prandial insulin dose to the amount of carbohydrate given.

Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events.

Some hospitals offer “meals on demand,” where individuals may order meals from the menu at any time during the day. This option improves patient satisfaction but complicates insulin–meal coordination and can lead to insulin stacking if meals are too close together.

Self-Management in the Hospital

Diabetes self-management in the hospital may be appropriate for specific individuals who wish to continue to perform self-care while acutely ill. Candidates include children with parental supervision, adolescents, and adults who successfully perform diabetes self-management at home and whose cognitive and physical skills needed to successfully self-administer insulin and perform glucose monitoring are not compromised In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, take multiple daily insulin injections or wear insulin pumps, have stable insulin requirements, and understand sick-day management

Standards for Special Situations

Enteral/Parenteral Feedings:

- For individuals receiving enteral or parenteral feedings who require insulin, the insulin orders should include coverage of basal, prandial, and correctional needs. It is essential that people with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.
- Most adults receiving basal insulin should continue with their basal dose, while the insulin dose for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g of carbohydrate in the enteral and parenteral formulas.
- All of this must be considered when calculating insulin doses to cover the nutritional component of enteral nutrition.
- Giving NPH insulin two or three times daily (every 8 or 12 h) to cover individual requirements is a reasonable option. Adjustments in insulin doses should be made frequently.
- Correctional insulin should also be administered subcutaneously every 6 h with regular human insulin. If enteral nutrition is interrupted, a dextrose infusion should

be started immediately to prevent hypoglycemia and to allow time to determine more appropriate insulin doses.

- For adults receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per every 10–15 g of carbohydrate should be given subcutaneously before each feeding.
- To mitigate any hyperglycemia, correctional insulin should be added as needed before each feeding.
- In individuals receiving nocturnal tube feeding, NPH insulin administered along with the initiation of the feeding is a reasonable approach to cover this nutritional load.
- For individuals receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h.
- A starting dose of 1 unit of regular human insulin for every 10 g of dextrose has been recommended and should be adjusted daily in the solution. Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted.
- Correctional insulin should be administered subcutaneously to address any hyperglycemia.
- Because continuous enteral or parenteral nutrition results in a continuous postprandial state, efforts to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increase the risk of hypoglycemia in these individuals.

Glucocorticoid Therapy

The prevalence of consistent use of glucocorticoid therapy in hospitalized individuals can approach 10–15%, and these medications can induce hyperglycemia in 56–86% of these individuals with and without preexisting diabetes

Prednisolone: Daily-ingested intermediate-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h but have pharmacologic actions that can last throughout the day. Individuals placed on morning steroid therapy have disproportionate hyperglycemia during the day but frequently reach blood glucose goals overnight regardless of treatment.

- In individuals on once- or twice-daily steroids, administering NPH insulin is a standard approach. NPH is usually administered in addition to daily basal-bolus insulin or in addition to oral glucose-lowering medications, depending on the type of diabetes and recent diabetes medication prior to starting steroids.
- Because NPH action peaks about 4–6 h after administration, it is recommended that it be administered concomitantly with intermediate-acting steroids.

Dexamethasone and multidose or continuous glucocorticoid: For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use,

- Long-acting basal insulin may be required to manage fasting blood glucose levels. For higher doses of glucocorticoids, increasing doses of prandial (if eating) and correction insulin, sometimes as much as 40–60% or more, are often needed in addition to basal insulin.
- Increasing the ratio of insulin to steroids was positively associated with improved time in range (70–180 mg/dL); however, there was an increase in hypoglycemia.

If insulin orders are initiated, daily adjustments based on levels of glycemia and anticipated changes in type, dosages, and duration of glucocorticoids, along with POC blood glucose monitoring, are critical to reducing hypoglycemia and hyperglycemia.

Perioperative Care

It is estimated that up to 20% of individuals undergoing general surgery have diabetes, and 23–60% have prediabetes or undiagnosed diabetes. Surgical stress and counterregulatory hormone release increase the risk of hyperglycemia as well as mortality, infection, and length of stay There are little data available to guide care of people with diabetes through the perioperative period

The following approach may be considered:

1. A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
2. The A1C goal for elective surgeries should be <8% (<63.9 mmol/L) whenever possible.
3. The blood glucose goal in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) within 4 h of the surgery. CGM should not be used alone for glucose monitoring during surgery.
4. Metformin should be held on the day of surgery.
5. SGLT2 inhibitors should be discontinued 3–4 days before surgery.
6. Hold other oral glucose-lowering agents the morning of surgery or procedure and give one-half of NPH dose or 75–80% doses of long-acting analog insulin or adjust insulin pump basal rates based on the type of diabetes and clinical judgment.
7. Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.
8. There are little data on the safe use and/or influence of GLP-1 receptor agonists on glycemia and delayed gastric emptying in the perioperative period.
9. Stricter perioperative glycemic goals are not advised, as perioperative glycemic goals stricter than 80–180 mg/dL (4.4–10.0 mmol/L) may not improve outcomes and are associated with more hypoglycemia.
10. Compared with usual dosing, a reduction by 25% of basal insulin given the evening before surgery is more likely to achieve perioperative blood glucose goals with a lower risk for hypoglycemia.

11. In individuals undergoing noncardiac general surgery, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing.

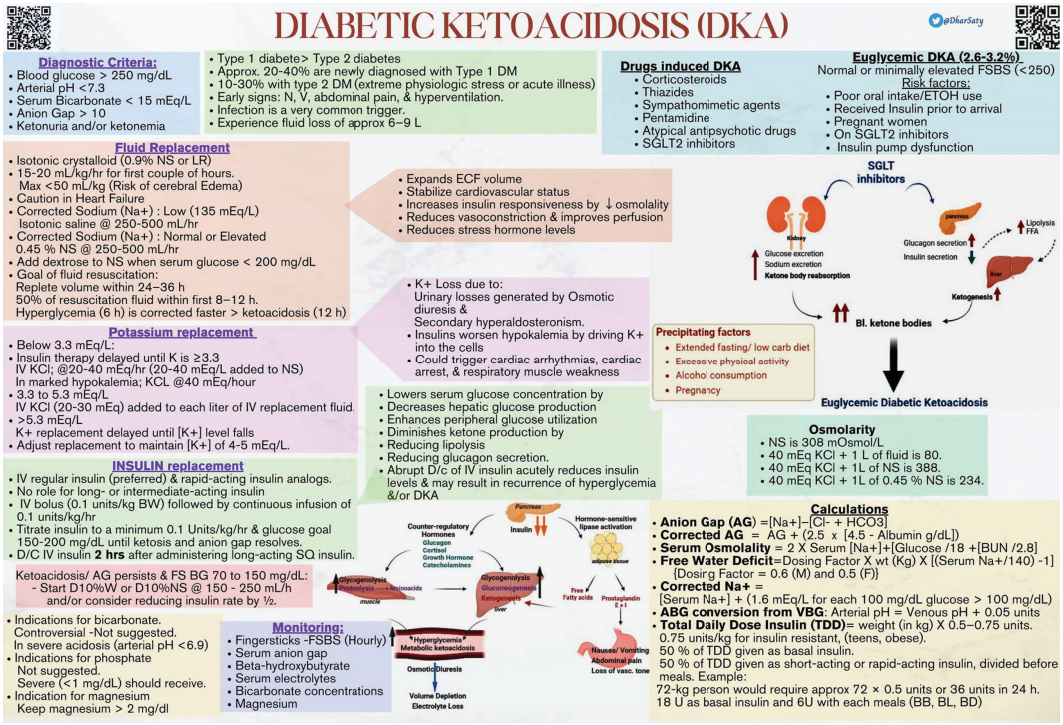


Figure 23.2: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

There is considerable variability in the presentation of DKA and HHS, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed.

Management goals include restoration of

1. Circulatory volume and tissue perfusion,
2. Resolution of ketoacidosis,
3. Correction of electrolyte imbalance and acidosis.
4. Treat any correctable underlying cause of DKA, such as sepsis, myocardial infarction, or stroke.

Intravenous insulin: In critically ill and mentally obtunded individuals with DKA or HHS, continuous intravenous insulin is the standard of care.

Transition from IV to SC insulin:

Successful transition from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h before the intravenous insulin is stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia.

Recent studies have reported that the administration of a low dose of basal insulin analog in addition to intravenous insulin infusion may prevent rebound hyperglycemia without increased risk of hypoglycemia. There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA.

Subcutaneous rapid-acting insulin analogs: Individuals with uncomplicated DKA may sometimes be treated with subcutaneous rapid-acting insulin analogs in the emergency department or step-down units. This approach may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide an adequate fluid replacement, frequent POC blood glucose monitoring, treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA.

HCO3: Several studies have shown that the use of bicarbonate in people with DKA made no difference in the resolution of acidosis or time to discharge, and its use is generally not recommended

Transition from the Hospital to the Ambulatory Setting

- A structured discharge plan tailored to the individual with diabetes. may reduce the length of hospital stay and readmission rates and increase satisfaction with the hospital experience. Discharge planning should begin at admission and be updated as individual needs change.

For individuals discharged to home or assisted living, the optimal discharge plan will need to consider diabetes type and severity, effects of the illness on blood glucose levels, and the individual's circumstances, capabilities, and preferences

An outpatient follow-up visit with the primary care clinician, endocrinologist, or diabetes care and education specialist within 1 month of discharge is advised for all individuals experiencing hyperglycemia and/or hypoglycemia in the hospital.

If glycemic medications are changed or glucose management is not optimal at discharge, an earlier appointment/contact (in 1–2 weeks) is preferred,

Medication Reconciliation

- Home and hospital medications must be cross-checked to ensure that no chronic medications are stopped and to ensure the safety of new and old prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the individual and care partners at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient health care professionals.
- Discharge summaries should be transmitted to the primary care clinician as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge with people with diabetes agreeing to the time and place increases the likelihood that they will attend.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.

People with diabetes must be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips or CGM sensors), prescriptions, and appropriate education at the time of discharge to avoid a potentially dangerous hiatus in care.

Preventing Admissions and Readmissions

Successful proactive care transitions from inpatient to outpatient is a key strategy for preventing readmission

Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; factors that may reduce readmission rates include scheduled home health visits and timely ambulatory follow-up care

There is no standard to prevent readmissions, several successful strategies offer some possible solutions

1. Reaching out to people with ketosis-prone diabetes,
2. Insulin treatment of individuals with admission A1C >9% (>75 mmol/mol), use of a transitional care model
3. People with diabetic kidney disease, collaborative person-centered medical centres may decrease risk-adjusted readmission rates.
4. Age is also an important risk factor in hospitalization and readmission among people with diabetes. They need special attention

Suggested citation: American Diabetes Association Professional Practice Committee. 16. Diabetes care in the hospital: *Standards of Care in Diabetes—2024*. Diabetes Care 2024;47(Suppl).

24
CHAPTER

Diabetes in Ramadan

Obligation for Muslims:

- Ramadan is one of the five pillar of Islam.
- Every Muslim if able must fast Diabetics are to fast and are to control blood glucose as well.
- To keep good health, they are to control also blood pressure blood cholesterol and weightl They are to manage inherent kidney, heart nerve and blood vessels complications.
- For every diabetic is to see his /her physician from one to three
- months before the start of Ramadan.

Summary:

- There is no such chronic disease which renders someone excused
- from fasting in Ramadan. Some might have risk or very high risk.
- albeit if wishes he/she may fast physician is to help only.
- A diabetic can test blood during his day time fast.
- Needs to do exercises with moderation avoiding exhaustion.
- Tablets specifically single evening dose is preferred to control diabetes if possible.
- Analogue basal is preferred insulin.
- Diet is adjusted keeping the daily calorie requirement as before Ramadan.
- It is possible to customise type of meals honoring the religious attitude and appetite in Ramadan.

77% of 1.8 billion (24%global population) muslim all over the world fast. Fasting is not only a religious ritual. it helps in brain kidneys heart and hormone health.

Fasting during Ramadan is of highest risk in type1 diabetes and diabetes with pregnancy.

Introduction: Fact is diabetic are not exempted from fasting during Ramadan simply because he or she is diabetic. If 10% of whiole population is diabetic then big number of diabetic muslims are fasting one moth fasting is blessings to muslim in all perspectives. Most muslim wish to fast during Ramadan even those who could seek exemption such as

elderly, children and the pregnant women. As per EPIDIAR study(15) 89.8% of Bangladeshi type -2 diabetes persons fast during Ramadan. 1 Day time non meal instead of night hours may not cause any problem. Less office time, lesser manual labor during day offers ambient atmosphere for fasting.

Risk of fasting for diabetics:

We can grade the risk by using the parameters. It may be mild ,moderate and high.

Higher risk: Type -1 diabetes and pregnancy diabetic are of highest risk. Like wise elderly people who can't take care of himself, patients having unstable angina or recent MI, recent strokes and TIA are of highest risk. Unawareness of hypoglycaemia, recent severe hypoglycaemia are at higher risks. Similarly grade 4 and more advanced chronic kidney disease, patients on dialysis and those with kidney transplant are of higher risk 2 Rest are mild or moderate risk who must fast. Those who have acute conditions like diarrhoea, vomiting, fever are exempted but they must have compensatory fast after recovery at their convenient time. Many people with mild or moderate risk do not fast with vague excuses. They take advantage of Fidya without knowing it. In fact they are to face Kaffara .

Risk means, worsening the disease, worsening to health conditions, imposing to death. Efforts to control diabetes imposes risk to acute complications.In pregnancy risk of baby at ohom, risk to mother. Fidya means feeding some one equivalent days. One for one. But not fast must for a valid reason. Kaffara means compensation for 60 days of fast or sixty persons feeding Sixty for one (by a insulin for breaking a fast).

Truly speaking during Ramadan people fast for 12-13 hour at day time. While usual days they fast 11-12 hours night time .Just change cycle. One must be aware of complications specially hypoglycaemia. Responsibly of doctor is to inform and teach about risks and strength or depth of risk. Responsibly of the patient is to

attend clinic one to three 3,4 months before Ramadan to have the idea about the situation of diabetes and situation of his or her health. Along with risk one must know about the diet patterns, exercise, blood tests and monitoring during Ramadan.

Iindividualise treatment and monitoring ensures safe completion Ramadan fasting.

Blood glucose test and monitoring during Ramadan: Matter of one month. If someone has good control before target HbA1C it is not an issue.

All Islamic intellectuals says blood glucose test during Ramadan fasting does not brake the fast. Every able person must learn self monitoring blood glucose (SMBG)tests from finger tip.Three [15] times tests may be needed. To apprise the status of control two hours after food in morning and night ; in the afternoon to appreciate hypoglycaemia. More test for people with more risk; Better to keep a chart of tests.

No test.: Some controlled with diet only, having good A1C beforehand, don't feel bad may not need a single prick for test.

Once a day test: One with single dose OHA may need one test at later part of day

Test Twice a day: people with insulin, two doses of OHA may need to test night and day 2 hour after meal

Test thrice a day: Once more for Hypoglycaemia identification.

May follow a directive: Every day first 3 days then every 4th days. Again in last week alternate days

Food and meals:

Same calorie food to maintained during Ramadan as was before.45-60% of total calories should come from carbohydrate,20-25% from protein and 20-30% from fat. Three main meals viz iftar (breakfast), midnight after Tarawi (lunch) and sohur (dinner) may be equally divided with two snacks at intervals. low GI foods preferable. Exchange food ,choice of items and taste should be respected. Keeping required daily calories meals to be customised. One egg with yellow, one sweet fruit and one cup of milk must be ensured daily. No sugar no glucose. Excess fat to be avoided.2-3 L fluid throughout night .Adequate fibre, fruits ,vegetables is good for health.3 dates contain 41 gm carbohydrates. It also has like other fruits contains fibres, minerals and anti oxidants. Fibers in meals delays absorption of carbohydrate and which then act like low GI foods. Fibers also soften stool helps to avoid constipation. Drinks and tea coffee better to avoid this month specifically at sahur as theses causes polyuria. Ramadan may be the best month to quit smoke.

Exercise In Ramadan:

Exercise in this month is to maintain habit. Keep the fitness and off course the hormones.

All 3 types of exercise may be done

Cardio: Which increase heart rate. Brisk walking is best. Dancing, gardening same. One must avoid exhaustion. Swimming cycling possible .Trade mill, bicycle ergometry at home also better if can be managed. Exercise period is to be shortened than that of non ramadan days.

Muscle strengthening: Standing in one place instrument hand exercise better in Ramadan as dehydration is less. Twice in a week for ten minutes good.

Tai chi is similar., Stretching or yoga also good

How long :150 hours in a week (minimum). If possible 45 minutes daily. This is for cardio.

How much: so long heart rate increases, breathing more or you get tired or hungry or thirsty, 3 miles or 4 Kilometres in 45 minutes. Target formula =220x-age in years and 70-80% of it one sitting. This is for usual non ramadan days.

When Research says better time is afternoon (145 pm -6pm).Any time you do try to have daily same time.

Keeping tarwi one and half hour into account one must calculate time. Apparently best time is after tarawi, if it is one hour after meal. Elderly people can change their schedule. For young people evening before iftar is possible. At that time dehydration can be managed .while in non Ramadan periodwe walk in morning after long time no food at night. So theoretically it is possible to walk in the evening.

During Ramadan one can also increase the rest period. Every alternate day can be done. But not two consecutive days rest is permitted.

Drug treatment for diabetes in Ramadan:

If well controlled from pre diabetic period it is very easy to adjust. Some principles may be adopted:

1. If possible without insulin,that is most desirable
2. No new regimen or drug during this month
3. Single dose or maximum two doses tablets preferable (MR XR ER, combination has made it possible)
4. Long acting insulin specifically basal analogue, basal-bolus analogue .5.to respect patient preferences and capacity

Sulphonylurea (SU): Chance of hypoglycaemia is maximum. Glibenclamide is to be avoided. Single dose and evening dose at iftar preferred. When with single dose insulin or SU to given in evening .

Metformin: Hypoglycaemia does not happen.Combination with SU should be at Iftar.

DPP4 inhibitors: Very low potential for hypoglycaemia when used singly. These are not cardiac friendly.

Combination with Metformin sometimes causes trouble because of the bigger size tablet.

Gliflogen: In Newer patient or older not to initiate with it.Causes diuresis, extra intake of water to be ensured. So first part of night is better time to take Gliflogen.

Insulin: Insulin has the highest capacity to reduce blood glucose and cause all range of hypoglycaemia. If on insulin beforehand practice is morning (breakfast)dose at evening (ifter), night dose at sahur.

Basal Insulin: Same dose at sahur: NPH (single or two doses): not comfortable insulin at Ramadan. If control beforehand insulin dose to be Reduced by 25-50%z. If two doses dose; sohur dose should be reduced to 50%.

Premixed: If on one dose same as pre-Ramadan at Iftar. For two doses sohur dose should be curtailed to half. Take a fingertip random glucose test 10 am. If it is more than 10 dose to be increased.

If one dose insulin and any combination (except SU) tablet at any time night keeps blood glucose control it is acceptable.

25/75 mixed may be switched to over 50/50 cover blood glucose of first half of the day.

Rapid/short acting insulin. Short/rapid with basal single dose at Iftar best option at Ramadan. Lunch dose to add at dinner after tarawi.

If blood glucose before Iftar 3.9-5 mmol/L reduce dose by 2 units, if less than 3.9 reduce by 4 units. with 5-7.2 mmol no change and with 7.2 to 11.1(130-200)or more add 2-4 units more.

All drugs to be taken at Iftar after drinking water. After completion only of Iftar meal a diabetic should go for magrib prayer not that meal after prayer. Adequate water to be ensured. Insulin can be taken zero to 22 minutes before food.

So no need to wait for food after injection or tablet.

GLP-1agonist (Dulalglutides, Semaglutide): Same single weekly dose as before Ramadan.

Not to initiate during Ramadan fasting considering inevitable side effects of GI upset.

Tablet and injections combined: Insulin and secretatogouge dose to be adjusted to keep blood glucose 6.7 to 8 mmol/L.

Diabetes comorbidities in Ramadan:

Most of T2 DM have high blood pressure high cholesterol, many of them are overweight. These things to be taken care in management.

Hypertension (HTN): anti-hypertensive drugs to be divided if needed and major portion in the evening. Diuretic s should be in the evening if can't be omitted.

Night dip of pressure is natural this to be kept in mind. Postural hypotension is not uncommon this to be kept in mind while treating. Dose and drugs should be selected accordingly. Drugs for heart disease stroke can be adjusted in single or two doses. Antilipid drugs (Statins others), Blood thinners to be taken after food preferably after sohur. Anti thyroid drugs to be taken in between dinner and sohur (keeping interval between food and drug for half to one hour).

Non-essential drugs: Calcium and combination calcium Vit D may be omitted for one month during Ramadan. Non-essential alternatives may be left for post Ramadan.

Ramadan in Elderly:

Those who can't move on his own, having dementia or memory disturbances need special attention. At this age many have complications like kidney disease, heart disease brain diseases, fractures for fall amputation for arterial diseases. Naturally they have visual and hearing problems, giddiness, dehydration, systolic hypertension, Postural hypertension. DAR global survey found.

Elderly people are comparatively more eager to fast and they are more prone to develop hypoglycaemia. The dose and schedule of sulphonylurea and insulin to be changed and adjusted. Beta blockers, Salicylates, Warferin, TCAs needs to be changed or omitted.

Many of the elderly diabetic have the disease of hypoglycaemia unawareness. They may refrain form fasting.

Drugs for elderly: SU may be avoided. If needed glibenclamides omitted. Single at Iftar dose advocated. Gliflogen not to initiate at Ramadan. Those who are on diuretics, those who have history of fall, eGFR less than 45 Gliflogen not good. If Gliflogen is to be given only at Iftar dose. Extra water intake should be ensured. Analogue is superior to human insulin. Basal only preferred. Basal/Basal-bolus whichever it is, best time is first half of night.

Ramadan and complications of diabetes:

Heart Brain arterial disease: Excess carbohydrate intake, lesser active works, sleep

disturbances, inadequate water intake, omission or maladjustment of essential medications increase the risk of atherosclerotic diseases in Ramadan. These factors are avoidable.

Stable disease: For Stable heart Brain arterial disease Ramadan is beneficial. Fasting increases nitric oxide. Biomarkers of oxidative stress are reduced, resulting decreased LDL, blood pressure. High sensitive CRP (hCRP)indicates healthy effects of Ramadan's fasting.

Unstable angina TIA: Study and evidence insufficient. Recent stroke TIA and acute coronary syndromes are with high risk while fasting in Ramadan.

Kidney diseases and Ramadan fasting: chronic kidney disease (CKD) and kidney transplant patients do not show changes in eGFR and blood biochemistry. [16] Patients on dialysis can fast except the days on dialysis.

Heart, stroke ,kidney patients should have their anti glycemic and anti hypertension drugs adjusted to maintain stable glucose and blood pressure levels. They are to avoid dehydration and postural hypotension. CKD patients should monitor serum electrolytes.

Acute emergencies of diabetes during Ramadan fasting:

Hypoglycaemia: Mild hypoglycaemia which patient can manage himself. (BG 3-3.9 mmol/L;54-70 mg/dL). Patient feels hungry, becomes tremulous and sweats. This urges patient to take suger without waiting for any body(doctor/relatives).

Severe hypoglycaemia:Patients become unconscious ,can't manage himself. Incidences of hypoglycaemia is 1.5 times during Ramadan. [EPIDIAR] Reasons of hypoglycaemia during Ramadan.

- Inappropriate adjustment of drug and labour
- Inadequate meals during Iftar and sahari
- In appropriate adjustments of tablet and/or injection schedule with period of Iftar or sahari.
- Dysfunction of kidneys and/or liver

Prevention: To look for the reasons to take appropriate measures 2. To acquire knowledge about diabetes before the start of Ramadan. 3 .To take idea about adjustments of insulin or tablet and quantities of dose modification as per sahari or Iftar schedule.

Treatment of hypoglycaemia: To take glucose or sugar in any form. To test RBS 15 minutes after and onwards till RBS comes 10. After that patient would take complex carbohydrates food like rice bread fruits. Milk and similar protein products to be omitted as these contain protein which stimulate insulin secretion. If severe hypoglycaemia and glucose/sweet can't be put into mouth rush to hospital emergency.

Hyperglycaemia: Higher blood glucose in range of 16.7 mmol/L(300 mg) in fasting Ramadan is not infrequent and is a big problem.

Unsual omission or reduction of tablet or injection for fear of hypoglycaemia is the main reason. Heavy meal ,excess and unaccustomed sweet eating is also a cause

Hyperglycaemia may be manifested as diabetic Ketoacidosis or as hyperosmolar state.

Both this condition needs treatments with hospitalisation. In fasting state insulin is diminished in body. There is excess ketone body production in the body which may lead to ketoacidosis.

Dehydration: Less water intake and excess work, high temperature high humidity, high blood glucose all may lead to dehydration. Extreme dehydration increases concentration of blood coagulation factors in blood resulting thrombus. Dehydration compels breaking fast. During Ramadan adequate drinking water to be ensured. Drinks containing caffeine may be abstained.

Health benefits of fasting in Ramadan: EU Studies showed cholesterol specifically LDL is minimised in ramadan which beneficial for heart and heart disease. Hunger hormone grelin is decreased in Ramadan which is weight friendly. American studies say brain renovates it's protein during fasting. Neurotropic hormones in brain increases. Brain cells increased. Brain becomes active, lively. Brain remains excited with

mental peace in Ramadan fasting. Stress hormones remain settled in Ramadan as there is less stress. Whole day fasting keep stomach empty. Body burns toxins. Fasting uses and burns fat. So fat and fat related nonessential substances are reduced. Eating at Iftar and sohur after whole day noneating(fasting) results surge in Adiponectin. Adiponectin helps in absorption of nutrients in muscle and other tissues. Fasting can help restrain from smoking &drinking alcohol, caffeine. All these increases thirst and induces polyurea. Diabetes compels someone to be disciplined .Ramadan fasting may a good rehearsal of refurbished discipline.

Ramadan can eliminate diabetics distress and depression by bringing mental peace through observation of teaching of Islam and the Quran in this best month.

Conclusion:

Ramadan fasting is one of the five pillars of Islam is. Diabetes does not exempt someone from fasting. We should learn that fasting is possible in any chronic disease with awareness and remedies of risks. Doctors and patients and those involved in care must learn how to reschedule day time food, drugs ,work and exercise of usual day time into a Ramadan fasting period of one month.Practice and learning should be started one to three months before the ensuing days of fasting.

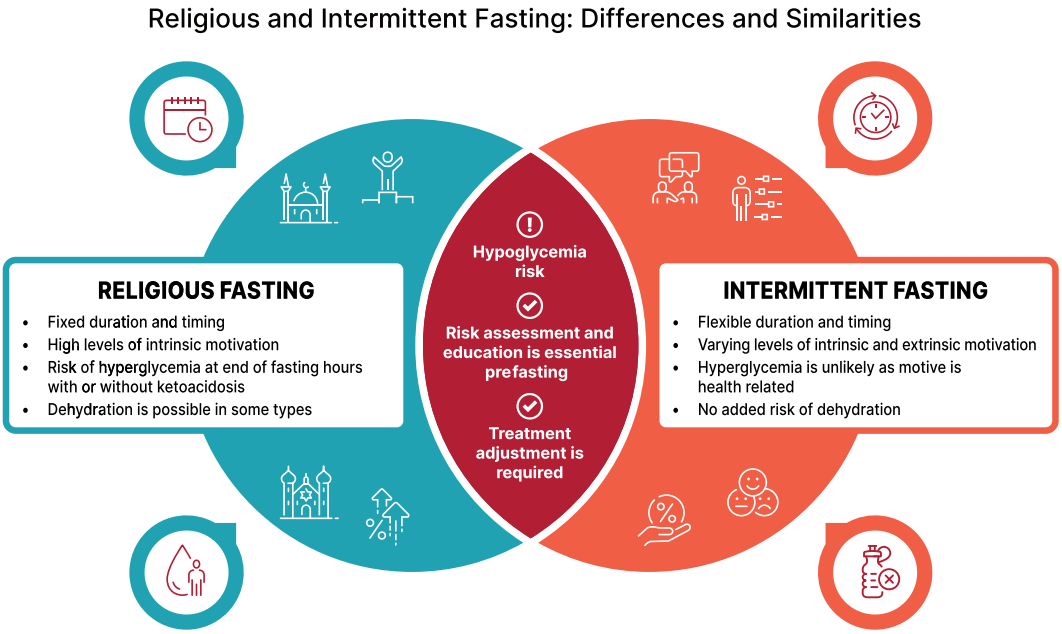


Figure 24.1: Differences and similarity of religious and intermittent fasting for people with diabetes

25
CHAPTER

Skin Diseases in Diabetes

Between thirty and seventy percent of patients with diabetes mellitus, both type 1 and type 2, will present with a cutaneous complication of diabetes mellitus at some point during their lifetime.

1. Diabetic dermopathy

Mostly heals spontaneously.Associated with uncontrolled diabetes and other complications of DM

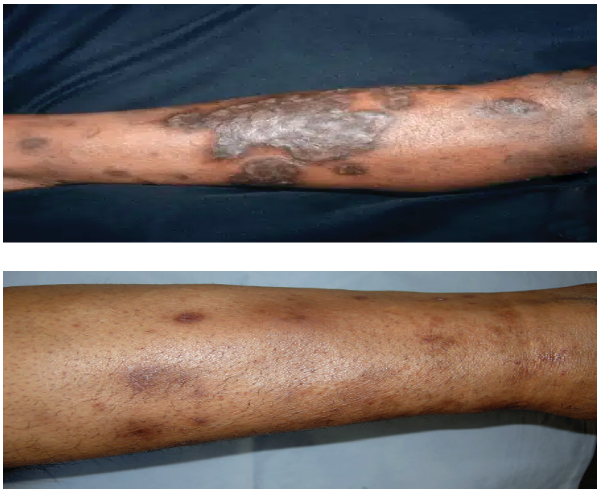


Figure 25.1: Diabetic dermopathy

2. Acanthosis nigricans :Darker area of skin that feels like velvet

A dark patch (or band) of velvety skin on your neck, armpit, groin, or elsewhere could be a sign of pre-diabetes.

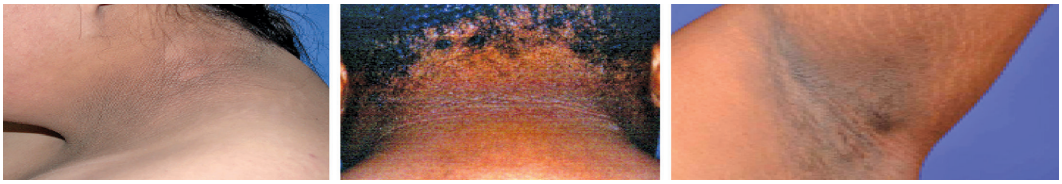
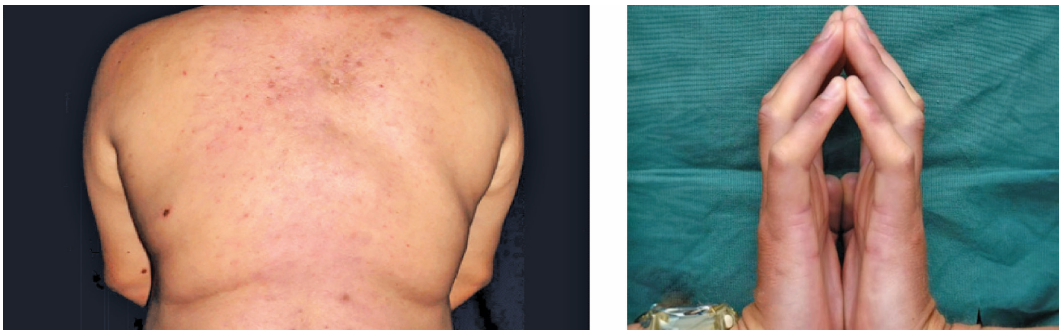


Figure 25.2: Acanthosis nigricans on the neck



A B

Figure 25.3: (A) Scleroedema, (B) Stiff skin

3: Scleredema diabeticorum

While the skin hardens and thickens, the condition is painless. Often developing on the upper back, the skin thickens and tightens slowly over months or years. This condition can also occur on the shoulders, neck, or elsewhere, but never on the hands or feet.

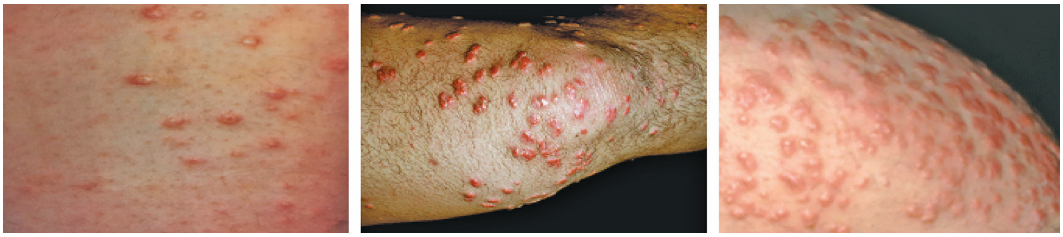


Figure 25.4: Eruptive xanthoma

4: Eruptivexanthoma: bumps can appear on your skin suddenly.

Uncontrolled diabetes can cause extremely high levels of triglycerides,Blood glucose is controlled it disappears

5:Xanthelasma: The yellowish bumps and patches usually appear in about the same place on (or around) both eyelids. These bumps and patches can feel soft or somewhat hard. Controlling diabetes may clear the bumps and patches.

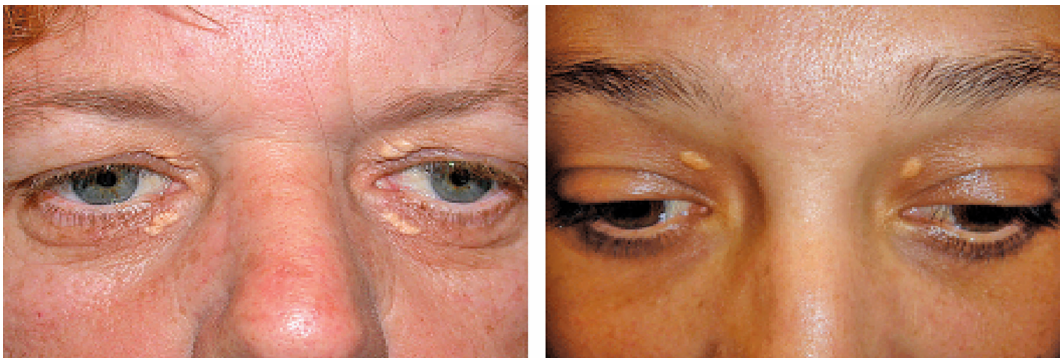


Figure 25.5: Xanthelasma

6.Infections: Diabetes weakens your immune system, which reduces your body's ability to fight off harmful germs and increases your risk of developing infections.

Some diabetes infections are:1.Oral thrush 2.Genital infections-pruritus valve 3.Malignant otitis externa 4.Mucormycosis 5.Paronychia 6.curbuncle

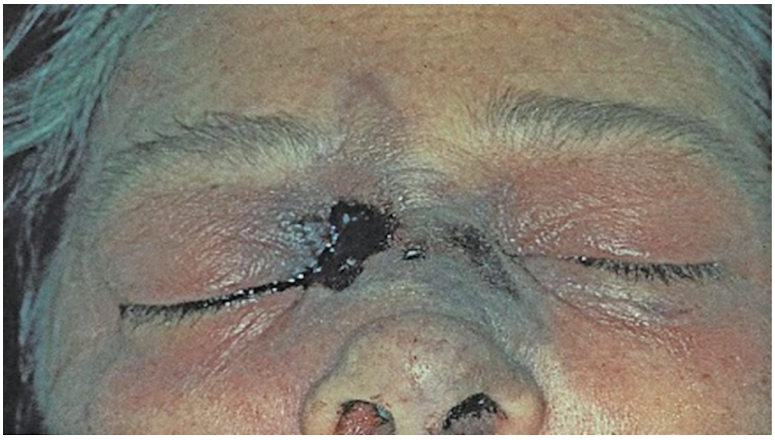


Figure 25.6: Rhino-orbital mucormycosis

7.Skin tags (**Acrochordons)**

While harmless, having many skin tags may be a sign that you have type 2 diabetes.

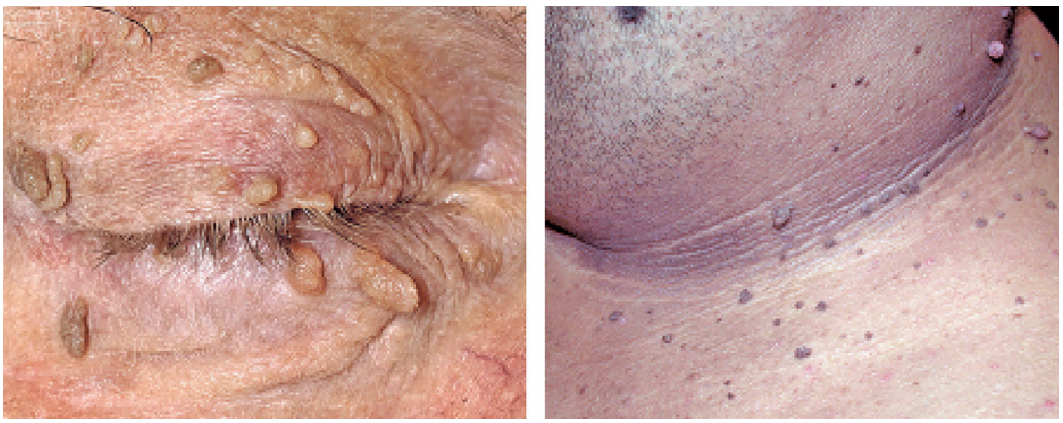


Figure 25.7: Several skin tags on neck of person with diabetes.

8. Granuloma annulare

This skin condition causes bumps and patches that may be skin colored, red, pink, or bluish purple. Whether this skin condition is associated with diabetes is controversial

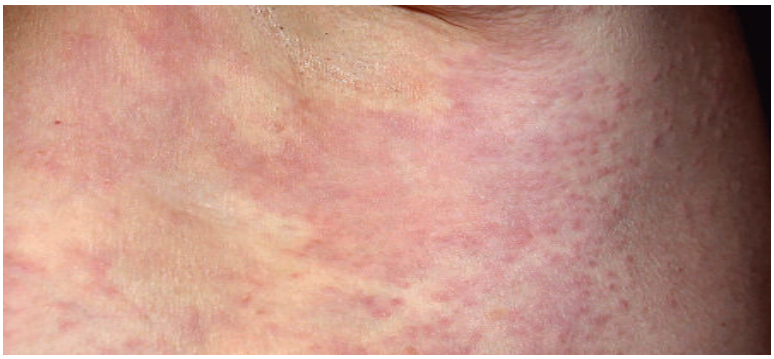


Figure 25.8: Granuloma annulare:Cluster of small bumps or a raised patch

9.Necrobiosis diabeticorum lipoidica: Yellow, reddish, brown, or purplish patches on your skin. The lighter areas in the reddish patches are waxy-feeling skin. These spots aren't itchy or painful. Necrobiosis lipoidica is harmless, but it can lead to complications.It is pathognomic of diabetes. The pathogenesis of NL is not well understood. The relationship between diabetes and NL has led some to theorize that diabetes-related microangiopathy is related to the development of NL .Difficult to manage

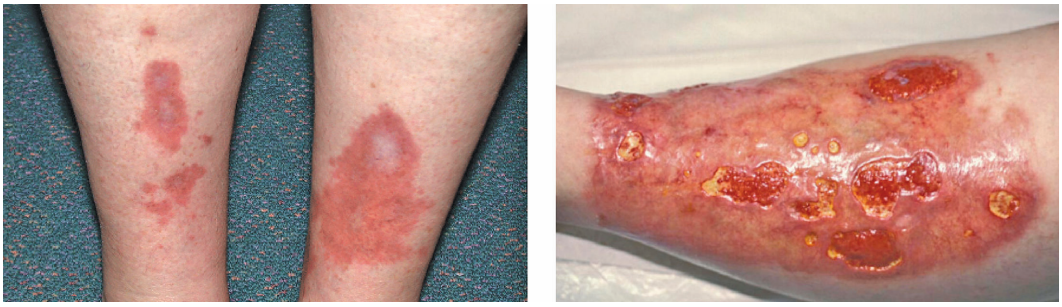


Figure 25.9: Necrobiosis lipoidica on a person's shins

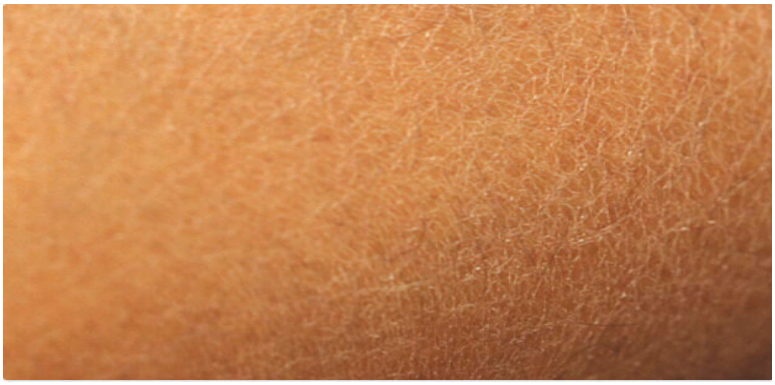


Figure 25.10: Ichthyosis

10.Acquired ichthyosiform changes

11. Xerosis

Xerosis is one of the most common skin presentations in patients with diabetes and has been reported to be present in as many as 40% of patients with diabetes . Xerosis refers to skin that is abnormally dry. Affected skin may present with scaling, cracks, or a rough texture. These skin changes are most frequently located on the feet of patients with diabetes. xerosis occurs often in the context of microvascular complications

12. Acquired Perforating Dermatosis

Perforating dermatoses refers to a broad group of chronic skin disorders characterized by a loss of dermal connective tissue. A subset of perforating dermatoses, known as acquired perforating dermatoses (APD), encompasses those perforating dermatoses that are associated with systemic diseases. Although APD may be seen with any systemic diseases, it is classically observed in patients with chronic renal failure or long-standing diabetes

13. Bullosis Diabeticorum(Diabetic bullae)

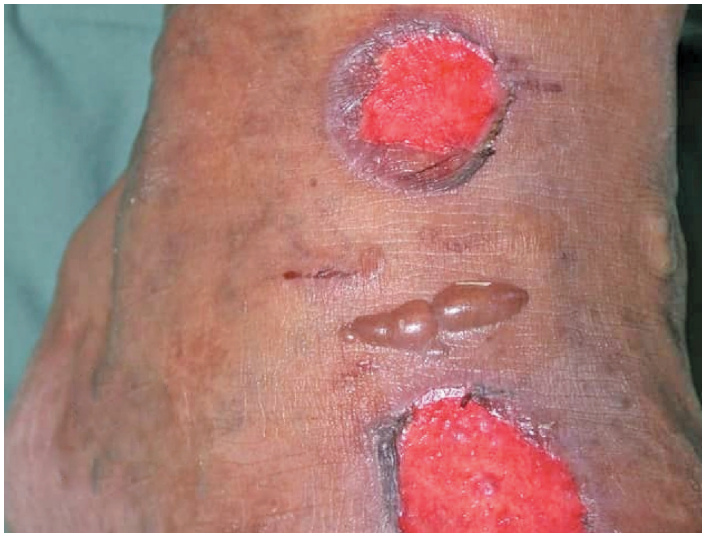


Figure 25.11: Diabetic bullae

The average age of onset is between 50 and 70 years of age (59).

BD presents at sites of previously healthy-appearing skin with the abrupt onset of one or more non-erythematous, firm, sterile bullae. Shortly after forming, bullae increase in size and become more flaccid, ranging in size from about 0.5 cm to 5 cm. Bullae frequently present bilaterally involving the acral areas of the lower extremities.. The bullae and the adjacent areas are nontender. BD often presents acutely, classically overnight, with no history of trauma to the affected area. Generally, the bullae heal within two to six weeks, but then commonly reoccur.. Histology, typically shows an intraepidermal or subepidermal blister, spongiosis, no acantholysis, minimal inflammatory infiltrate, and normal immunofluorescence. There is an incomplete understanding of the underlying

pathogenesis of BD and no consensus regarding a leading theory. Resolve without treatment and are therefore managed by avoiding secondary infection and the corresponding sequelae

14. Keratosis Pilaris

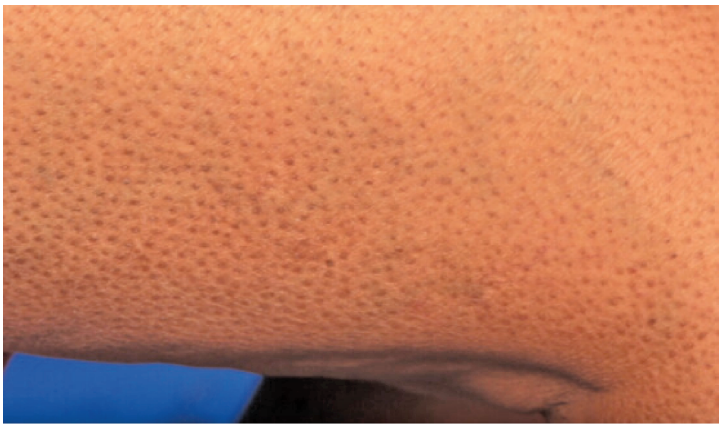


Figure 25.12: Keratosis Pilaris

14 Keratosis pilaris is a very common benign keratotic disorder. Patients with keratosis pilaris classically present with areas of keratotic perifollicular papules with surrounding erythema or hyperpigmentation . The posterior surfaces of the upper arms are often affected but involvement of the thighs, face, and buttocks can also be seen. Compared to the general population, keratosis pilaris occurs more frequently and with more extensive involvement of the skin in those with diabetes. Keratosis pilaris can be treated with various topical therapies, including salicylic acid, moisturizers, and emollients.

Steps to prevent skin problems:

- Check your skin daily for signs of rashes, redness, infections or sores.
- Use warm (not hot) water and moisturizing soap in the shower. (Soaking in a tub dries out skin.)
- Pat skin dry with a towel (don’t rub), making sure to dry in between fingers, toes and skin folds.
- Apply fragrance-free moisturizers after showering while skin is still damp and soft. Look for creams and ointments (not lotions) with ceramide to help skin retain moisture.
- Apply creams containing 10% to 25% urea(an emollient) to cracked, dry heels at bedtime.
- Prevent dehydration and keep skin hydrated by drinking plenty of fluids.
- Treat cuts and wounds immediately with soap and water. Use antibiotic ointments only if your healthcare provider gives the OK. Bandage the wound daily. Call your provider if you notice signs of redness, pain, drainage or infection.
- Use a humidifier to add moisture to the air in your home.

26
CHAPTER

Rheumatological Diseases and Diabetes

Classification of Rheumatological Manifestations in Diabetic Patients

The musculoskeletal structures involved in diabetes-associated rheumatological diseases

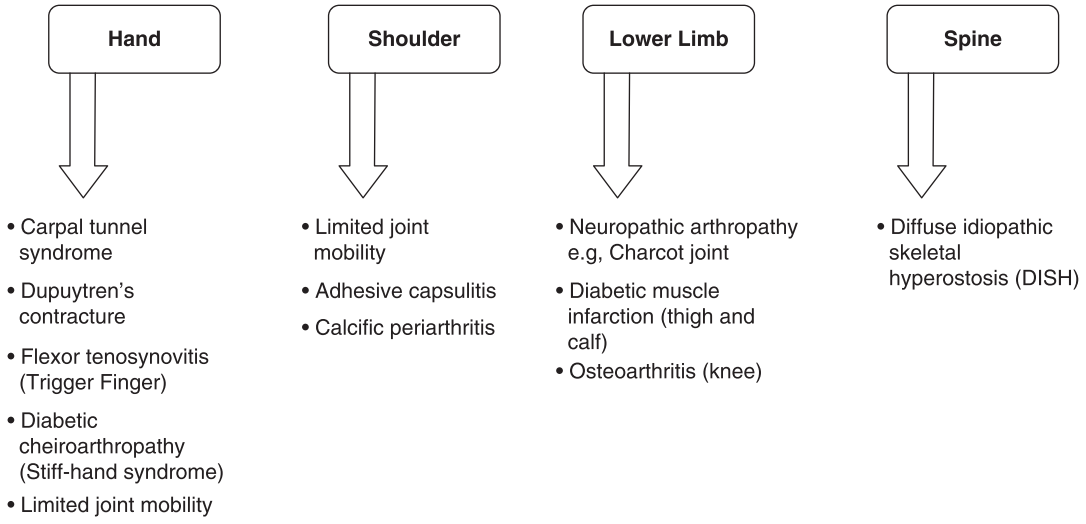


Figure 26.1: Musculoskeletal structures involved in diabetes associated rheumatological diseases

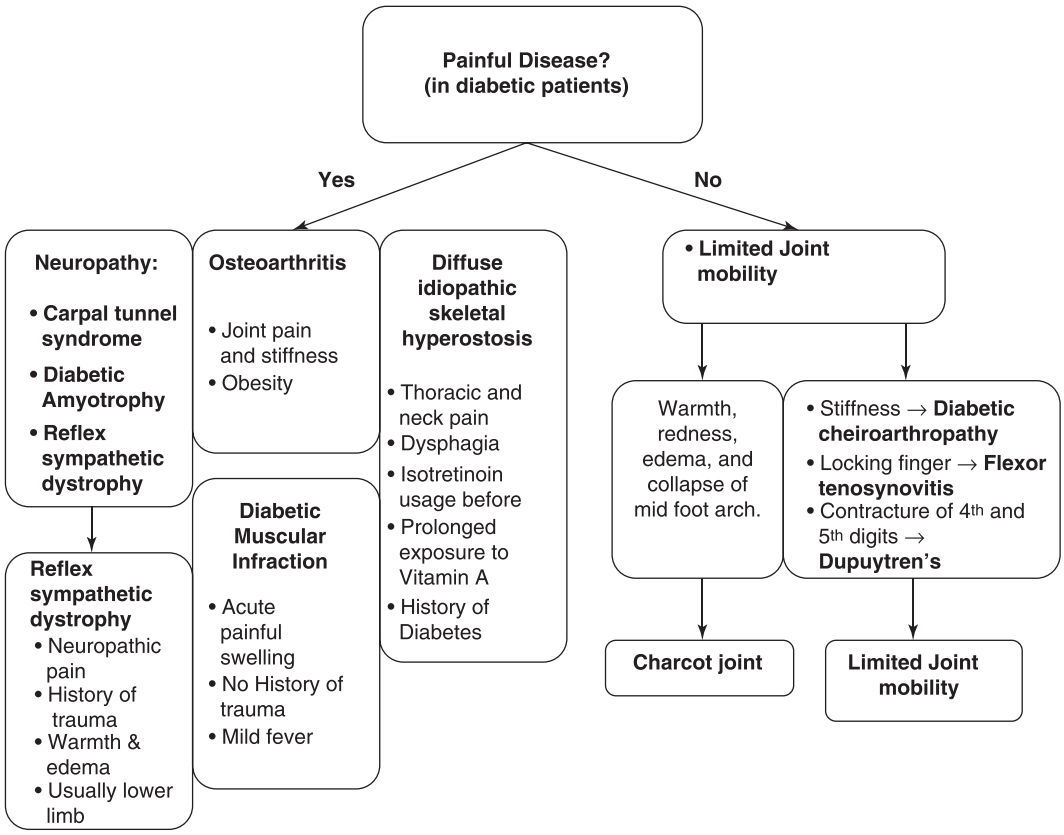


Figure 26.2: Painful and painless rheumatic diseases associated with diabetes mellitus

Table 26.1 Frozen shoulder (theoretical 3 progressive phases

Painful freezing phase	Adhesive phase	Resolution phase
▪ 10-36 weeks ▪ Pain and stiffness around the shoulder with no history of injury ▪ Constant pain with little response to NSAIDs	▪ 4-12 months ▪ Pain gradually subsides but still apparent at extremes ▪ Stiffness continues ▪ Near total loss of external rotation	▪ 12-42 months ▪ Spontaneous improvement in the range of motion ▪ Mean duration of overall impairment > 30 months

Treatment

In most cases, frozen shoulder is a self-limited condition, although a complete resolution does not occur in many patients.

Physical therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics.

Intra-articular steroid injections.

Surgery in severe non-responding cases.

Flexor Tenosynovitis

Flexor tenosynovitis, also known as trigger finger, is a non-infectious inflammation of the flexor tendon sheath of the finger leading to finger blocking in flexion with failure of active extension.

The prevalence of flexor tenosynovitis is estimated at 11% in diabetic patients, compared with less than 1% in nondiabetics [16]. The occurrence of flexor tenosynovitis correlates significantly with the duration of DM, but not with glycaemic control

Physical Examination

It is a clinical diagnosis

Local tenderness and palpable swelling at the base of the finger, where the tendon crosses over the metacarpal head.

Pain usually gets worse by stretching the tendon in extension or by resisting flexion isometrically.

Prayer sign test: the ability to flatten the hands together as in prayer, facilitating recognition of contractures in the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints.

Table top test: assesses the ability to flatten the palm against the surface of a table, facilitating recognition of contractures in the metacarpophalangeal joints.

Treatment

Activity modifications to avoid the triggers.

Splinting.

NSAIDs.

Steroid injections into tendon sheath.

Surgical release.

Diabetes osteoporosis: previous chapter

Neuropathic Osteoarthropathy (Charcot Joint) **Previous chapter-diabetic foot

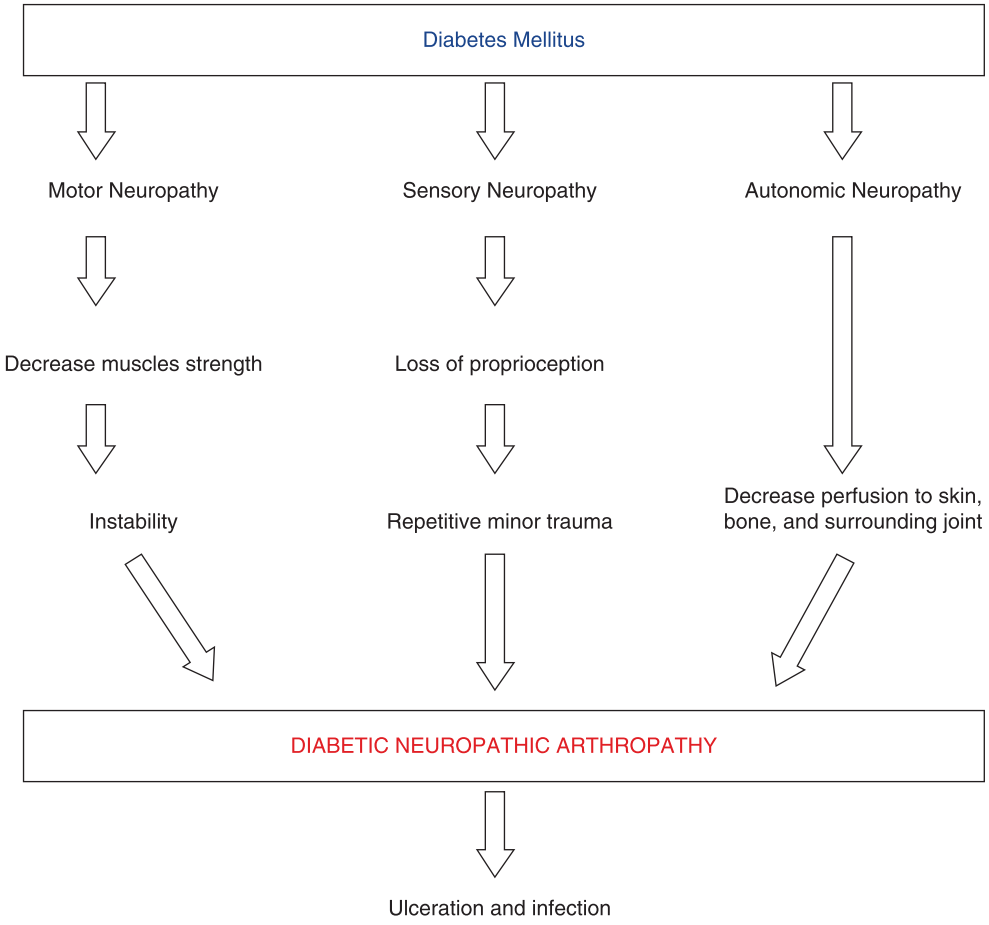


Figure 26.3: Pathogenesis of diabetic neuropathic arthropathy

Table 26.2 Stages of progression of Charcot's joint

Inflammatory (Stage 0)	Development (Stage 1)	Coalescence (Stage 2)	Remodeling (Stage 3)
▪ Localized swelling, erythema, and warmth ▪ No radiological abnormalities	▪ Persistent swelling, redness, and warmth ▪ Bony changes such as fracture, subluxation, dislocation ▪ Bony debris starts to appear radiologically	▪ Inflammatory signs decrease ▪ Radiological signs of fracture healing, bony debris resorption ▪ New bone formation	▪ Clinical inflammatory signs have settled ▪ Bony deformity ▪ Radiologically, may show mature fracture and decreased sclerosis

Table 26.3: Summary of complications of Diabetic rheumatological conditions

	Rheumatological diseases		Pathophysiology	Symptoms	Investigations	Treatment
Rheumatological complication of diabetes	Syndromes of limited joint mobility	***Diabetic cheiroarthropathy (Stiff-hand syndrome)*** (8-50% among diabetics)	Binding of advanced *glycosylation end products* to collagen that is deposited around joints	- Painless stiffness of small joints in the hand - Decreased grip strength - Prayer sign test - Table top test	- Glucose level - Imaging: U/S MRI	- Improve glycemic control - NSAID - Corticosteroid injection - Physiotherapy - Surgery
		Dupuytren's contracture	Same as other limited joint, leading to fibroblastic proliferation and collagen deposition	- Finger stiffness, usually the 3rd & 4th digits in DM - Thickening or a palpable nodule in the palm - Loss of motion of the affected fingers	Clinical diagnosis	Mild disease: - physiotherapy Moderate: - corticosteroid injection Contracture: - surgery
		Trigger finger (Stenosing flexor tenosynovitis)	Inflammation of flexor tendons in hand leading to thickening	- Finger pain - Locking of finger in flexed position	- Clinical diagnosis - X- ray - Biopsy	- Active movement - Splinting - NSAIDs - Steroid injection
		Adhesive capsulitis (Frozen shoulder)	Same as other limited joint mobility	- Shoulder stiffness - Painful shoulder - Loss of motion	- Clinical diagnosis - U/S, MRI, and plain X-rays	- Physiotherapy - NSAID - Steroid injection - Surgery
	Neuropathy	***Neuropathic arthritis (Charcot joints)***	Mechanical and vascular factors resulting from diabetic peripheral neuropathy	- Arthritis - Swollen foot - Foot arch collapse	- Clinical diagnosis - X- ray - MRI	- Weight-bearing limitation - NSAIDs - Surgery
		Carpal tunnel syndrome (CTS)	Neuropathy of diabetes causes nerve compression	- Numbness - Pain - Weakness	- Phalen test - Tinnel test - Nerve conduction study+/-EMG	- Splinting - NSAIDs - Steroid injection - Surgery
		Diabetic Amyotrophy	Ischemic injury from a non-systemic micro vasculitis	- Acute local pain, followed by weakness in the proximal leg - Autonomic failure and weight loss	- CBC, FBS, HbA1C ESR - EMG, nerve conduction study - MRI and CT	- Tricyclic antidepressant - Steroids - Immunotherapy
		Reflex sympathetic dystrophy	Neuropathic complication of DM with autonomic symptoms	1st stage: burning throbbing pain & edema 2nd stage: ↑ edema & skin thickening 3rd stage: limitation of movement and contracture, waxy trophic skin changes, and brittle nails	- Autonomic tests - X-ray, CT, MRI - Bone scintigraphy	- Education - Physical therapy - Analgesics, corticosteroids, oral muscle relaxants, bisphosphonates, and calcium-channel blockers - Invasive: intravenous percutaneous sympathetic blockade, surgical sympathectomy, spinal cord stimulation, and amputation

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome I (CRPS I), is characterized by localized or diffuse neuropathic pain of the upper or lower extremity usually associated with swelling, vasomotor disturbances and trophic skin changes which include loss of hair, skin colour changes, temperature changes and skin thickening (autonomic involvement).

History:Neuropathic pain following an injury (tissue trauma or bony fracture). It is described as burning, throbbing, aching, squeezing or shooting pain.

Vasomotor and sudomotor changes in the affected limb (colour changes, temperature changes and excessive sweating).:

-Trauma or immobilization following trauma to limb.

Bone fractures of extremities.Diabetes mellitus. Hyperthyroidism. Hyperparathyroidism. Nerve injury. Medications, e.g. ACE inhibitors.

Physical Examination

Skin: may be shiny, swollen, thinned, erythematous or cyanotic, with scaling. Temperature may be increased or decreased.

Extremities:

Joint may be stiff with decreased range of motion.Signs of chronic lymphoedema.

Neurologically:Sensory changes and weakness may be present.Tremor or dystonia in the affected limb.

Table 26.4 Diagnostic criteria of reflex sympathetic dystrophy, also known as complex regional pain syndrome

Bruehl's criteria
Continuing pain disproportionate to any inciting event. **1. Patient must report at least 1 symptom in each of the 4 following categories** a) Sensory: hyperesthesia b) Vasomotor: temperature asymmetry, skin color changes or skin color asymmetry c) Sudomotor/edema: edema, sweating changes or sweating asymmetry d) Motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin) **2. Must display at least 1 sign in 2 or more of the following categories** e) Sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch) f) Vasomotor: evidence of temperature asymmetry, skin color changes or asymmetry g) Sudomotor/edema: evidence of edema, sweating changes or sweating asymmetry h) Motor/trophic: evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)
Veldman's criteria
1. Presence of 4 out of 5 symptoms: a) Diffuse pain during exercise b) Temperature differences between affected and unaffected extremity c) Color differences between affected and unaffected extremity d) Volume differences between affected and unaffected extremity e) Limitations in active range of movement of the affected extremity **2. Occurrence or increase of symptoms during or after use** **3. Symptoms in an area larger than the area of the primary injury**

Treatment

There are different medical and surgical treatment modalities, but they have no strong evidence to support their use.

The best treatment of RSD is prevention by early mobilization following an injury or stroke and use of supplemental vitamin C for patients with wrist fractures. A typical dose is 500–1500 mg daily, and the duration is 50 days.

Physical therapy.

Medical therapy:Analgesics,e.g.,topical capsaicin cream.Bisphosphonates.

=Anticonvulsants, e.g., gabapentin.

Tricyclic antidepressant.

Vasodilator medication or percutaneous sympathetic blockades.Glucocorticoids.

Invasive therapy for non-improving on non-invasive therapy.

-Regional sympathetic nerve block.Electrical nerve stimulation.

Sympathectomy.

Spinal cord stimulation.

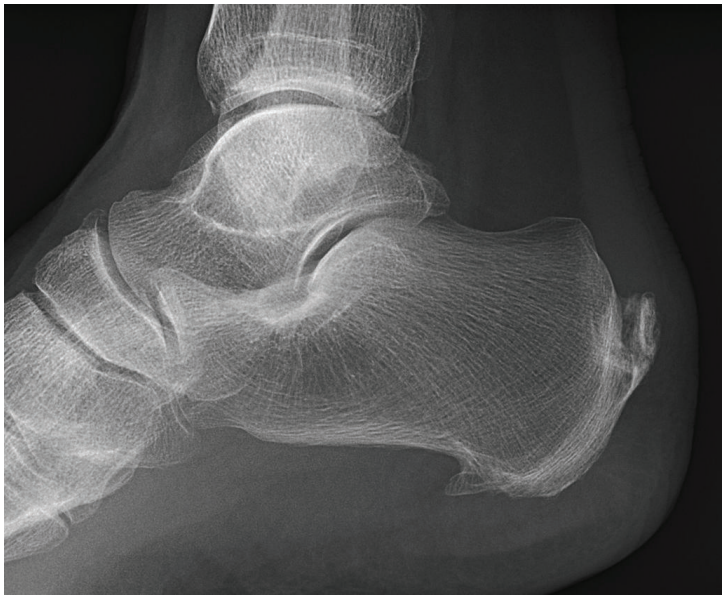


Figure 26.4: Calcaneal spur.

Calcification deposits forming an enthesophyte within the Achilles tendon at its calcaneal insertion, in a 68 year old woman with pain and swelling by the heel, further pointing to the diagnosis of Achilles tendinitis. The Achilles tendon (seen as somewhat brighter than the surrounding soft tissue in this X-ray presentation) is wider than normal, further suggesting inflammation. There is also an inferior calcaneal spur.

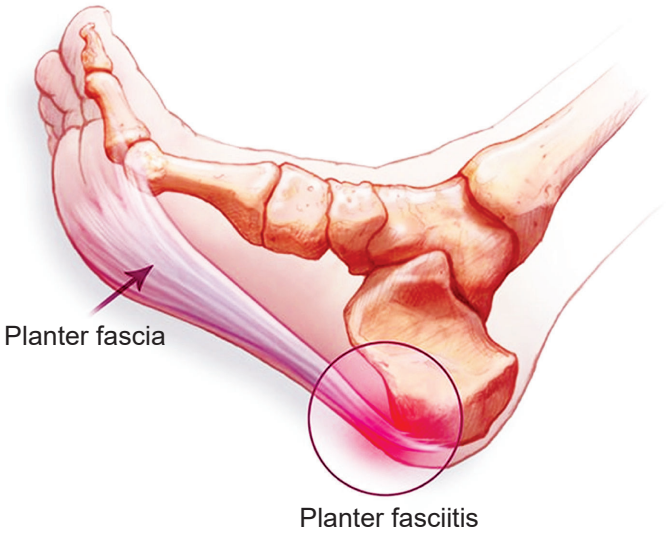


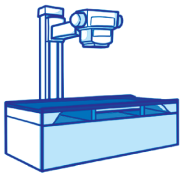
Figure 26.5:

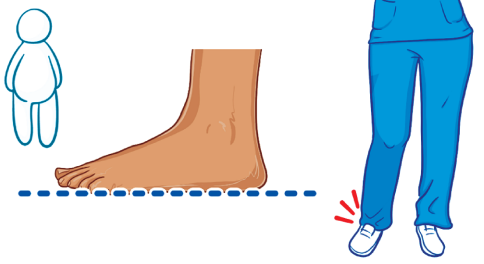
Plantar fasciitis is an inflammation of the fibrous tissue (plantar fascia) along the bottom of your foot that connects your heel bone to your toes. Plantar fasciitis can cause intense heel pain.

Background
* Bone Growths Typically at Bottom of Heel Bone
  - Heel Spurs"

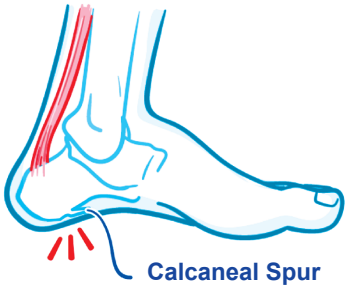
Causes
* Body's Response to Inflammation of Tendon or Ligament At Attachment
  - Triggers Formation Of New Bone
* **Risk Factors:**
  - Prolonged Standing & Working on Hard Surfaces
  - Age
  - Bone & Joint Disorders
  - Obesity & Flat Feet

Diagnosis
* X-Ray





Signs & Symptoms
* Do Not Always Cause Pain
* Heel Pain When Pressing on Surrounding Nerves or Tissues



Treatment
* Only Required If Causing Discomfort
* Anti-Inflammatory Medications
* Physical Therapy
  - Rolling Tennis Ball under Feet
* Supportive Shoes
* Surgery

Figure 26.6: Calcanean spur

27
CHAPTER

Prevention of Diabetes

Prevention or delaying the development of overt diabetes

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia .

Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood.

Diabetes is classified conventionally into several clinical categories (e.g., type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes, such as monogenic diabetes, exocrine pancreatic disorders, and high-risk medications)

Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose.

Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

Prediabetes in type 1 and Type 2 diabetes:

Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes . Moreover, the efficacy of interventions for primary prevention of type 2 diabetes (i.e., preventing conversion of prediabetes to type 2 diabetes) has been demonstrated mainly among individuals with prediabetes who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify frequency of testing based on individual risk assessment.

In people with presymptomatic type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics.

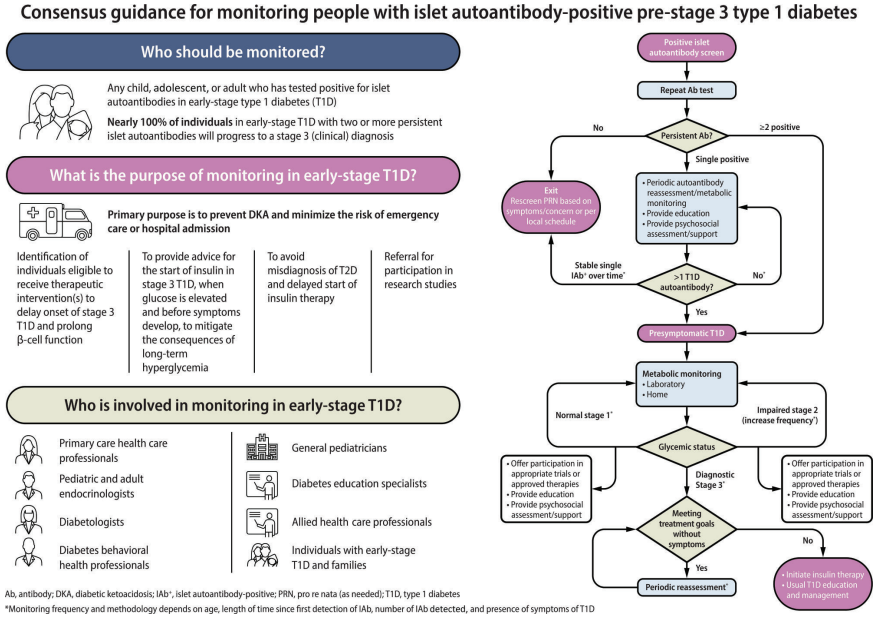


Figure 27.1: Monitoring people T_1 DM

Primary prevention: Way to prevent to develop overt Diabetes

Lifestyle Behavior Change for Type 2 Diabetes Prevention

- Intensive lifestyle behavior change program :It has been seen effective in the Diabetes Prevention Program (DPP), that an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity.
- Eating pattern:. A variety of eating patterns, such as Mediterranean style, intermittent fasting, and low carbohydrate, have shown benefit.
- Cost-effectiveness:Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes.
- Technology-assisted diabetes prevention programs : Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered.

Table 1

Risk factors for type 2 diabetes

A1C, glycated hemoglobin; CV, cardiovascular; GDM, gestational diabetes; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus-1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

∗ Associated with insulin resistance.

Schizophrenia: The incidence of type 2 diabetes is at least 3 times higher in people with schizophrenia than in the general population (34,35). Using data collected in 1991, the prevalence of diabetes was assessed in >20,000 individuals diagnosed with schizophrenia. The rate of diagnosed diabetes was 9% to 14%, exceeding rates for the general population prior to the widespread use of new antipsychotic drugs

HIV:HIV and HAART increase the risk of prediabetes (IGT) and type 2 diabetes by 1.5- to 4-fold compared to the general population .

Obstructive sleep apnea : Obstructive sleep apnea is an independent risk factor for diabetes

Age ≥40 years

First-degree relative with type 2 diabetes

Member of high-risk population (e.g. African, Arab, Asian, Hispanic, Indigenous or South Asian descent, low socioeconomic status)

History of prediabetes (IGT, IFG or A1C 6.0%–6.4%)∗

History of GDM

History of delivery of a macrocosmic infant

Presence of end organ damage associated with diabetes:>Microvascular (retinopathy, neuropathy, nephropathy) .CV (coronary, cerebrovascular, peripheral)

Presence of vascular risk factors:

HDL-C <1.0 mmol/L in males, <1.3 mmol/L in females∗>TG ≥1.7 mmol/L∗

Hypertension∗Overweight∗

Abdominal obesity∗Smoking

Presence of associated diseases:

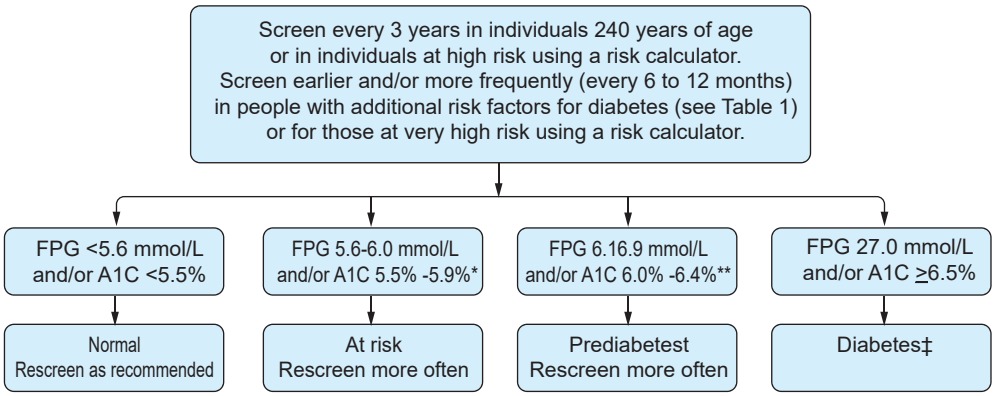
History of pancreatitis,Polycystic ovary syndrome∗, Acanthosis nigricans∗, Hyperuricemia/gout,Non-alcoholic steatohepatitis.Cystic fibrosis

Psychiatric disorders (bipolar disorder, depression, schizophrenia†

Use of drugs associated with diabetes:

Glucocorticoids, Atypical antipsychotics, Statins, Highly active antiretroviral therapy, Anti-rejection drugs

Screening and diagnosis algorithm for type 2 diabetes.



If both FPG and A1C are available, but discordant, use the test that appears furthest to the right side of the algorithm.

*Consider 75 g OGTT if ≥1 risk factors; ** Consider 75 g OGTT (see Tables 3 and 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10 for interpretation of 75 g OGTT).

†Prediabetes IFG or A1C 6.0 to 6.4% (see Table 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

In the presence of symptoms of hyperglycemia, a single test result in the diabetes range is sufficient to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is prefer-able that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. If results of two different tests are available and both are above the diagnostic cut points the diagnosis of diabetes is confirmed.

A1C, glycated hemoglobin; FPG, fasting plasma glucose; IFG, impaired fasting glucose

Figure 27.2: Screening and diagnosis algorithm T_2 DM

Screening for Diabetes in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

Jean-Marie Ekoe MD, CSPQ, PD, Ronald Goldenberg MD, FRCPC, FACE, Pamela Katz MD, FRCPC

The Diabetes Prevention Program

Several major randomized controlled trials, demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation

US Diabetes Prevention Program (DPP) trial (N Engl J Med 2002;346:393–403) Finnish Diabetes Prevention Study (DPS)-(Lancet 2006;368:1673–1679). Da Qing Diabetes Prevention Study (Da Qing study) -Lancet Diabetes Endocrinol 2014;2:474–480).

The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial. The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed a sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study , 43% reduction at 7 years in the Finnish DPS, and 34% reduction at 10 years and 27% reduction at 15 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP lifestyle intervention was goal-based. All participants were given the same weight loss and physical activity goals, but individualization was permitted to achieve the goals . The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and to partake in 150 min of moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, achieving the behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% .

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests higher benefit for prevention of diabetes with at least 7–10%weight loss with lifestyle interventions .The initial focus of the nutrition intervention was on reducing total fat rather than calories. After several weeks, the concepts of calorie balance and the need to restrict calories and fat were introduced. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal .

Physical Activity

In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training .Breaking up prolonged sedentary time may also be encouraged, as it lowers postprandial glucose levels . The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM).

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention included a reduction of total fat and calories .evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals

Mediterranean-style and low-carbohydrate eating plans , vegetarian, plant-based diet, and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes.Evidence suggests that the overall quality of food consumed with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes

Sleep Characteristics Associated With Increased Risk of Type 2 Diabetes

The latest ADA-EASD consensus report on management of hyperglycemia highlights sleep as a central component in the management of prediabetes and type 2 diabetes, placing it, for the first time, on the same level as other lifestyle behaviors (e.g., physical activity and nutrition) .

those with a preference for evenings (i.e., going to bed late and getting up late), there was a 2.5-fold higher odds ratio for type 2 diabetes than for those with a preference for mornings (i.e., going to bed early and getting up early), independent of sleep duration and sleep sufficiency (37).

Pharmacologic Interventions to Delay Type 2 Diabetes

- Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus.
- Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 level in metformin-treated individuals, especially in those with anemia or peripheral neuropathy.

Because weight loss through behavior changes in nutrition and physical activity may not be sufficient on their own and can be difficult to maintain long term, some people at high risk of type 2 diabetes may benefit from additional support and pharmacotherapeutic options.

Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, incretin receptor agonists (e.g., liraglutide and semaglutide), thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations , whereas diabetes prevention was not seen with nateglinide In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years . In individuals with previous history of GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline . Several medications evaluated for weight loss (e.g., orlistat, phentermine and topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of type 2 diabetes in those with prediabetes

Vitamin D therapy has recently been advocated by the U.S. Endocrine Society to prevent progression of high-risk prediabetes to type 2 diabetes in adults . 1) The recommended vitamin D dose is unclear. . 2) The benefit-to-risk ratio of vitamin D therapy for high-risk prediabetes remains uncertain. No pharmacologic agent has been approved by the U.S. Food and Drug Administration for prevention of type 2 diabetes.

Metformin

Metformin has the most safety data as a pharmacologic therapy for diabetes prevention Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., younger individuals, those with history of GDM, or those with BMI ≥35 kg/m2).

Decreased vitamin B12 levels are a known consequence of long-term treatment with metformin . Periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency, especially in those receiving a higher dose (e.g. ≥1,500 mg/day) or longer treatment duration and in those with existing risk factors. A person who has been taking metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan dietary pattern, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually

Prevention of Vascular Disease and Mortality

- Screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. Hypertension treatment and statin therapy are also recommended.
- Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. It is not recommended that statins be avoided or discontinued for this adverse effect.
- Pioglitazone :In people with a history of stroke and evidence of insulin resistance and prediabetes,
- Pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fractures. Lower doses may mitigate the risk of adverse effects but may be less effective.

. Tobacco cessation :Evaluation for tobacco use and referral for should be part of routine care for those at risk for diabetes.The years immediately following smoking cessation may represent a time of increased risk for diabetes , and individuals should be monitored for diabetes development and receive evidence-based lifestyle behavior change for diabetes prevention as described in this section Person-Centered Care Goals

- In adults with overweight or obesity at high risk of type 2 diabetes, care goals should include weight loss and maintenance, minimizing the progression of hyperglycemia, and attention to cardiovascular risk.
- Person-centered care goals

  Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, and cardiovascular risk reduction) should be considered to support person-centered care goals.
- More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥ 35 kg/m2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.1–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C ≥6.0% [≥42 mmol/mol]), and individuals with a history of gestational diabetes mellitus.

  Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications
- However, the new diagnosis of prediabetes in older adults (aged >70 years) is less relevant for progression to diabetes, because regression to normoglycemia or death was more frequent than progression to diabetes in the Atherosclerosis Risk in Communities (ARIC) study

Pharmacotherapy for weight management and cardiovascular risk reduction can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

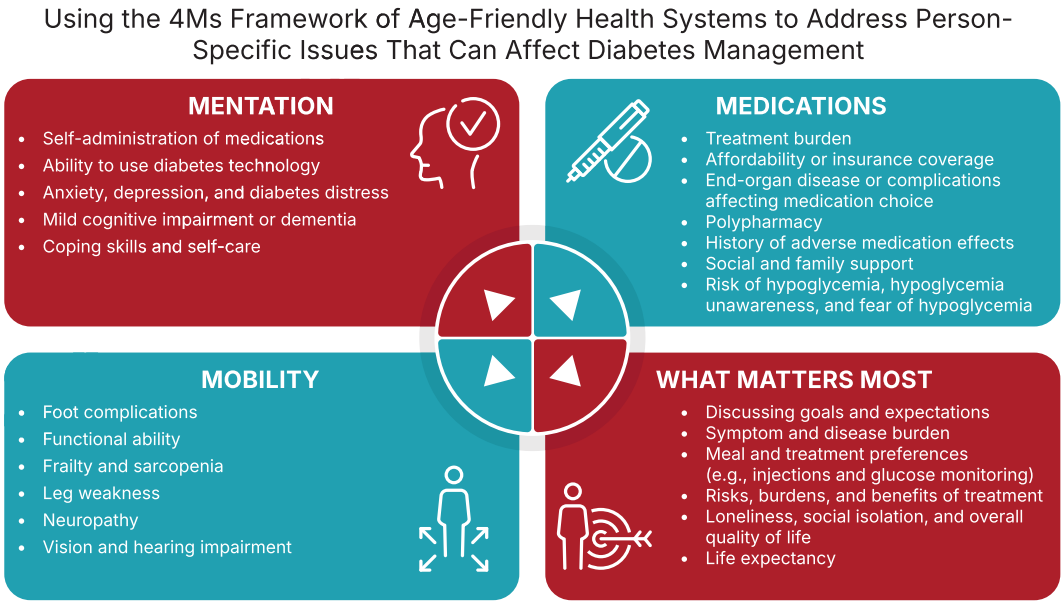
Prevention or Delay of Symptomatic Type 1 Diabetes

Lifestyle and Type 1 Diabetes Progression

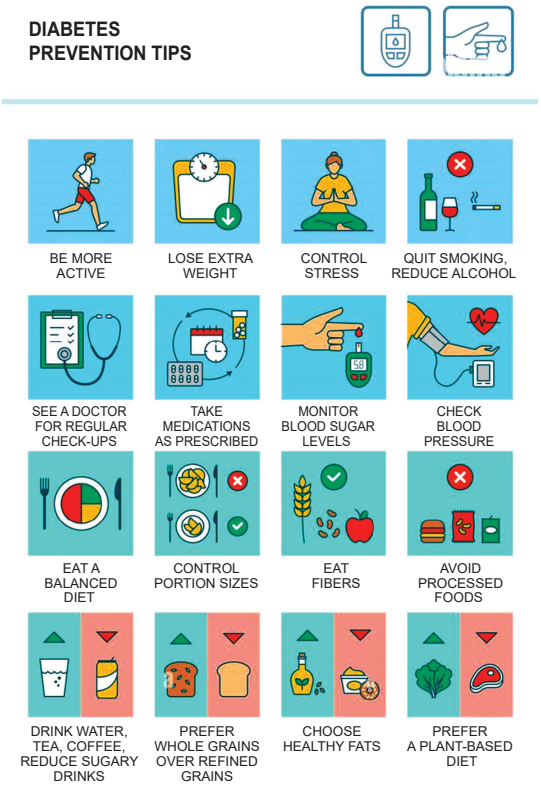
Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand, including less physical activity higher glycemic index , and total sugar intake, are associated with progression to clinical diabetes.

Pharmacologic Interventions to Delay Symptomatic Type 1 Diabetes

- Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be discussed with selected individuals aged ≥8 years with stage 2 type 1 diabetes.



(A)



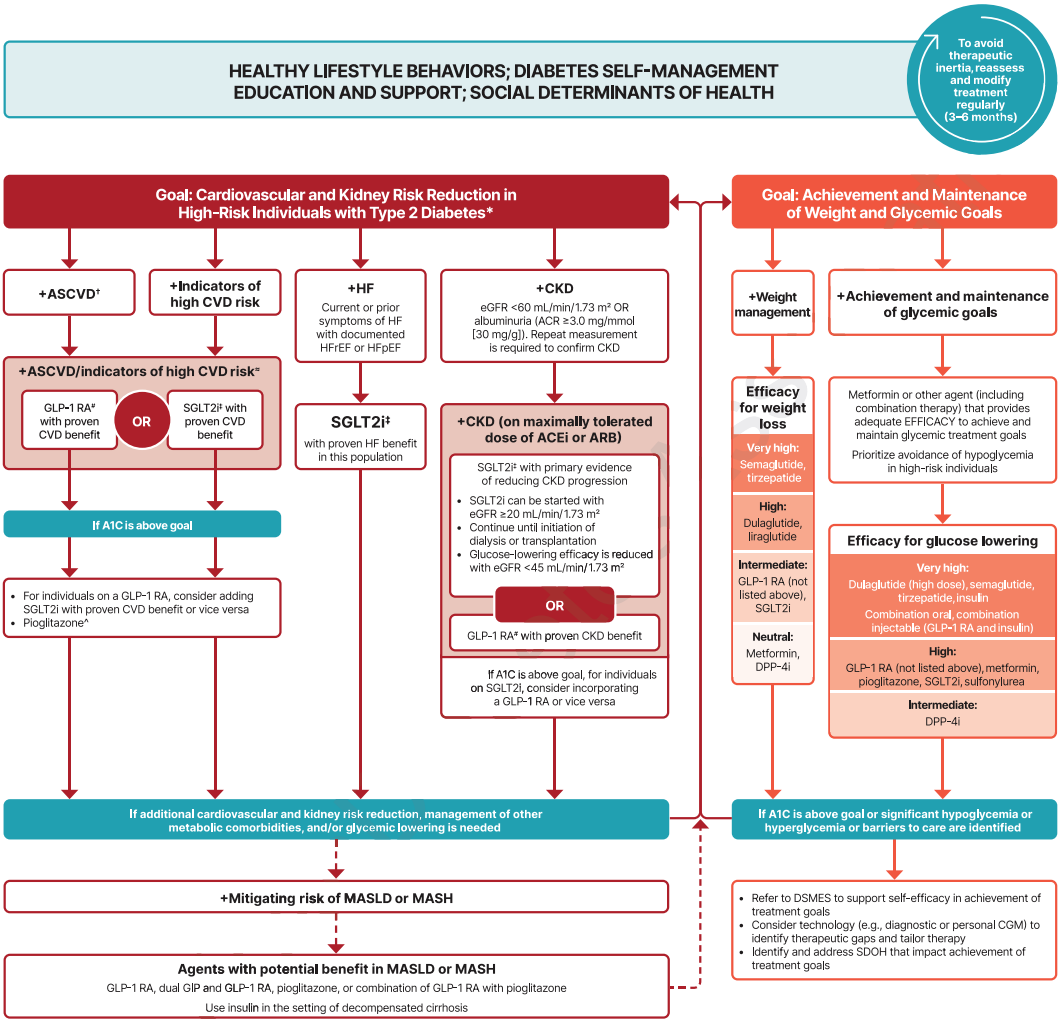
(B)

Figure 27.3: (A) Person specific issues, (B) Diabetes Prevention Tips (Universal)

Secondary prevention of diabetes:

Once control achieved ,maintenance is important.Inertia of any part of management is futile as diabetes is life time problem.

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

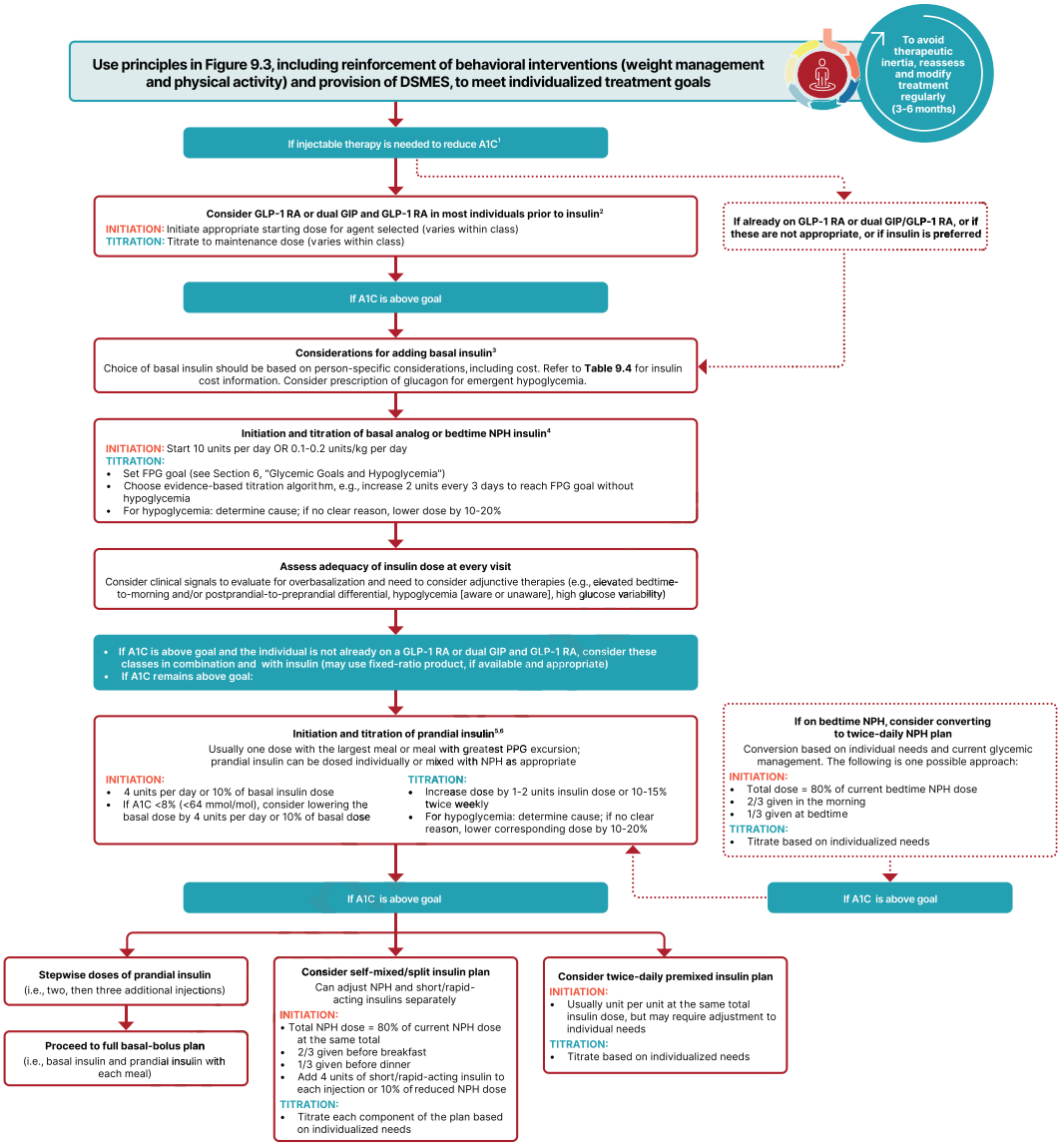
≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 27.4: Glucose lowering medication



1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal Insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal Insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 27.5 : Injectable therapy sequence

Suggested citation: American Diabetes Association Professional Practice Committee. 3. Prevention or delay of diabetes and associated comorbidities: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Suppl. 1):S50–S58

Prevention of or delay of progression of comorbidities

(NASH/MASLD)

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

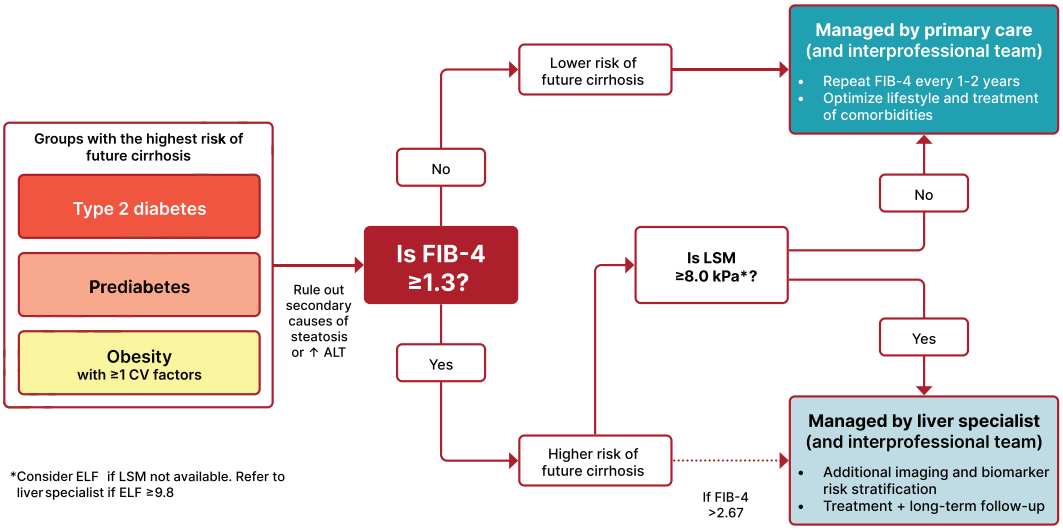
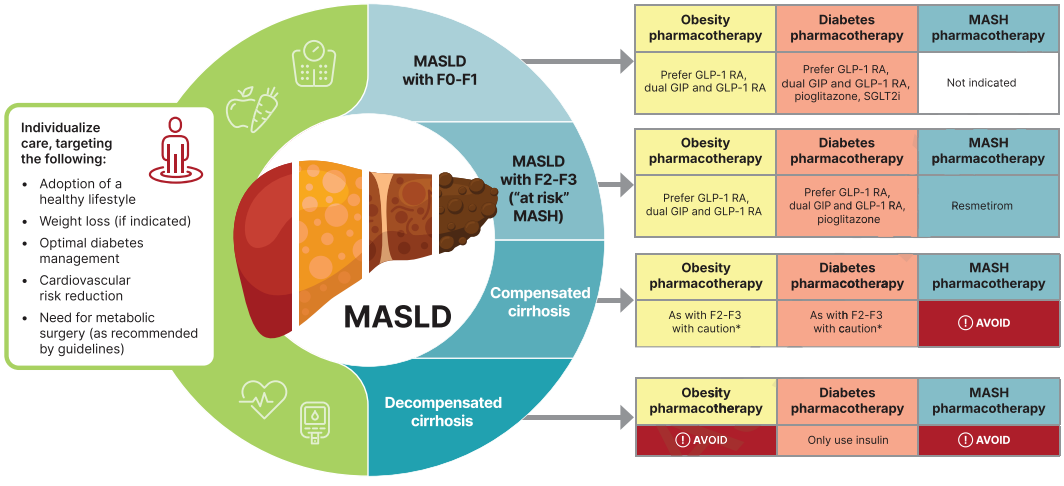


Figure 27.6: Diagnosis algorithm MASLD

Treatment and prevention to development of cirrhosis in MASLD

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 27.7: Prevention cirrhosis in MASLD

Prevention of fragility fractures

Diagnostic assessment

Individuals who should receive BMD testing

People aged ≥65 years

Postmenopausal women and men aged ≥50 years with history of adult-age fracture or with diabetes–specific risk factors:

- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylureas
- A1C >8%
- Peripheral or autonomic neuropathy, retinopathy, nephropathy
- Frequent falls
- Glucocorticoid use

Primary Prevention of Fragility Fractures in People With Diabetes.

In the general population, a T-score ≤–2.5 is the threshold to consider pharmacological treatment for osteoporosis. In type 2 diabetes, since the T-score underestimates fracture risk (as discussed above), a T-score ≤–2.0 may be more appropriate for considering the initiation of a first-line drug, including bisphosphonates (alendronate, risedronate, and zoledronic acid) or denosumab.

Denosumab is preferred in individuals with estimated glomerular filtration rate <30–35 mL/min/1.73 m^2, although the FDA has recently issued a boxed warning for increased risk of severe hypocalcemia in individuals with advanced chronic kidney disease. Self-management abilities of the person with diabetes should be considered in medication selection, recommending strict medication-taking behavior, as there can be rebound bone loss causing multiple vertebral fractures with missed doses of denosumab or delays in care. Bisphosphonate therapy (oral or intravenous) may be more appropriate in individuals with poor medication-taking behavior or gaps in access to medical care.. Romosozumab received FDA approval with a box warning because it may increase risk of myocardial infarction, stroke, or cardiovascular death and should not be prescribed in women who experienced a myocardial infarction or a stroke within the past year .

Secondary Prevention of Fragility Fractures.

The risk of subsequent fracture in individuals with hip or vertebral fracture is high, especially in the first 1–2 years after a fracture. Antiosteoporosis treatment reduces the risk of fracture in older individuals with prior hip or vertebral fracture.

As in the general population, people with diabetes who experience fragility fracture should *1*) be given the diagnosis of osteoporosis regardless of DXA data and *2*) receive the

appropriate work-up and therapy to prevent future fractures . It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation (if required) as soon as possible

Risk reduction of ASCVD:

Lipid management and primary prevention of ASCVD

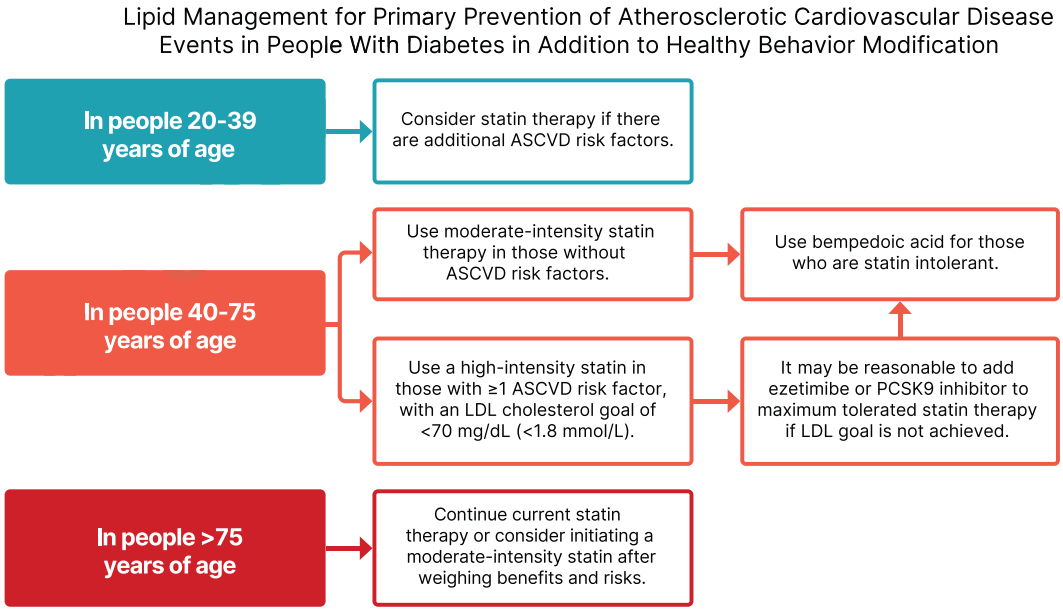


Figure 27.8: Lipid management primary prevention ASCVD

Lipid management and secondary Prevention of ASCVD

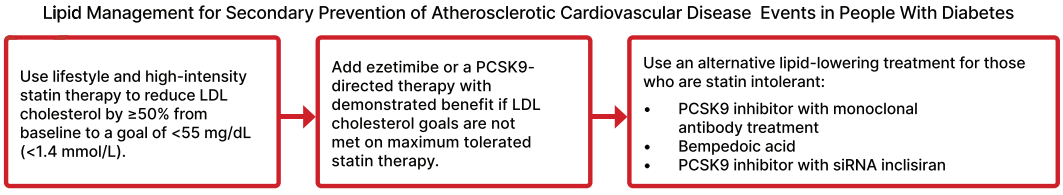


Figure 27.9: Secondary Prevention ASCVD

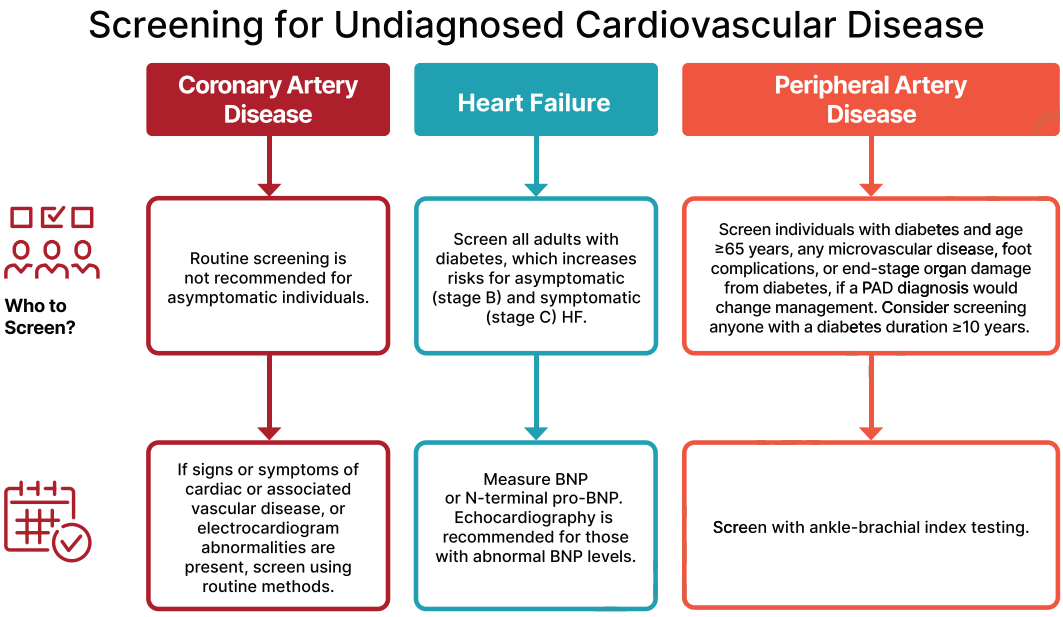


Figure 27.10: Screening CVD

Reduction of risk of symptomatic heart failure :

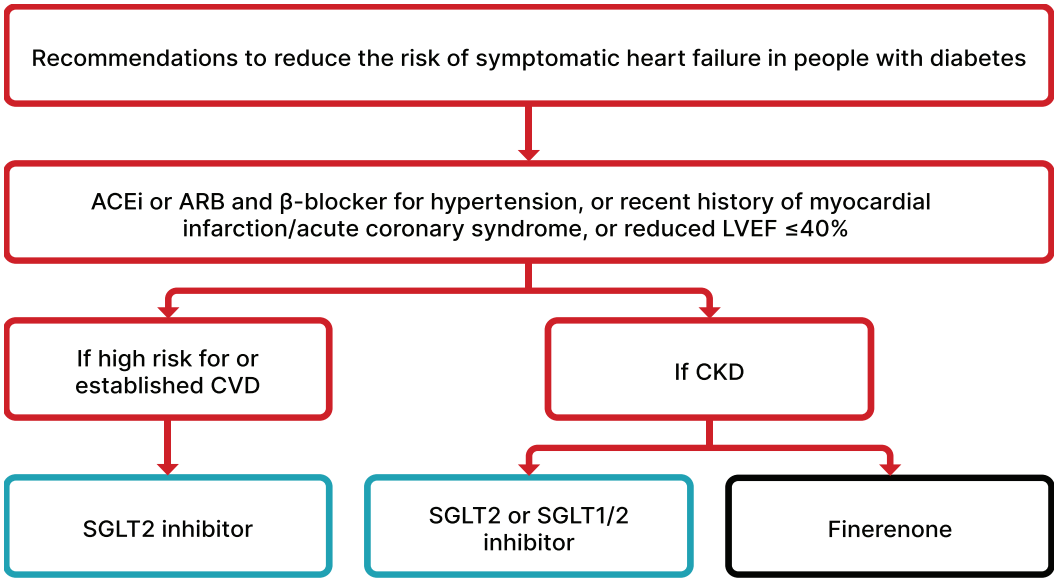
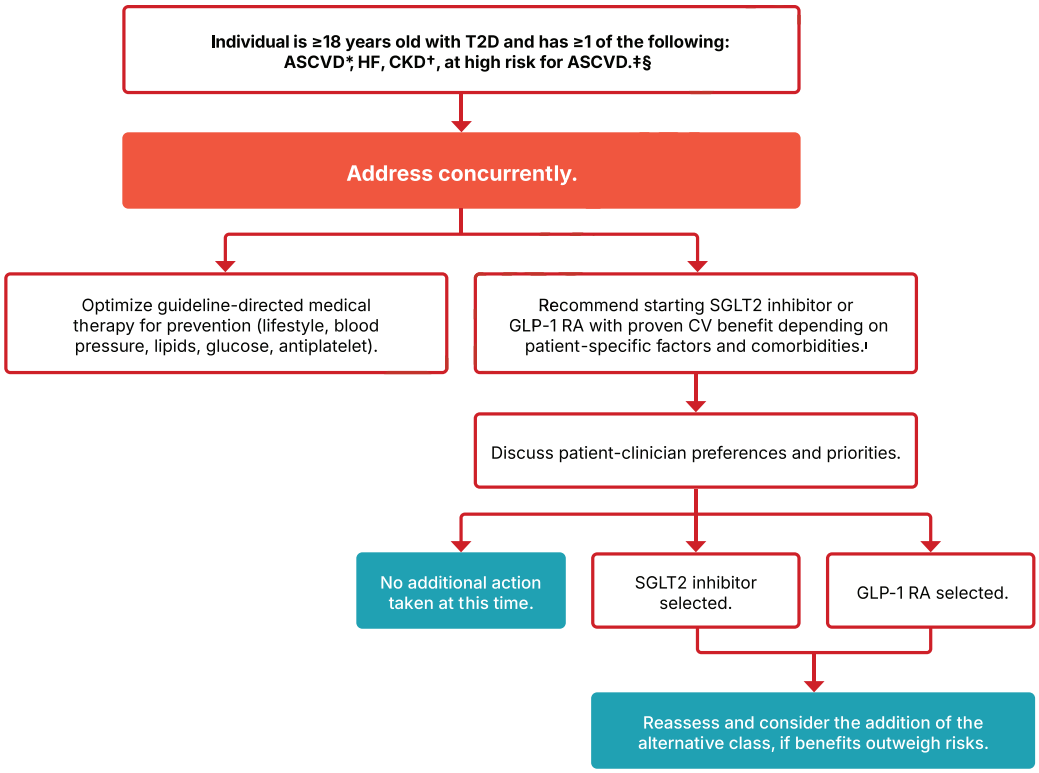


Figure 27.11: Prevention of heart failure

Prevention of the development of symptomatic heart failure in people with diabetes. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; LVEF, left ventricle ejection fraction; SGLT2, sodium–glucose cotransporter 2. Adapted from "Standard of in diabetes mellitus-2025. ADA

Risk reduction of ASCVD:



* ASCVD is defined as a history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† CKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when the individual has established ASCVD, HF, or CKD or is at high risk for ASCVD. Consider a GLP-1 RA when the individual has established ASCVD or is at high risk for ASCVD.

§ Individuals at high risk for ASCVD include those with end-organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, and obesity).

ǁ Most individuals enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Figure 27.12: Prevention ASCVD

Diabetes and secondary prevention of ASCVD,Renal disease

Dual antiplatelet agents:Aspirin,clopidegrol,Ticagrelol,prasugrel:The use and benefit has been studied in recent days.Duration is still matter of interprofessional discussion.The overlooming risk of bleeding is there(TWILIGHT).They are all for secondary prevention

Combination of antiplatelet and anti coagulants:Combination of antiplatelet and low dose rivaroxaban is recommended in established Perivascular disease and/or stable coronary artery disease to avoid major limb or CVS effects(COMPASS).

Statin:For diabetics starting (as primary prevention) moderate intensity statin at 40 years outweigh the adverse effects

SGLT2:Role in heart failure(Dibaetic,non diabetics),(Preserved or reduced heart failure)has been established in recent days

Finerenone:demonstrated delaying CKD and proteinuria with beneficial CVS effect.

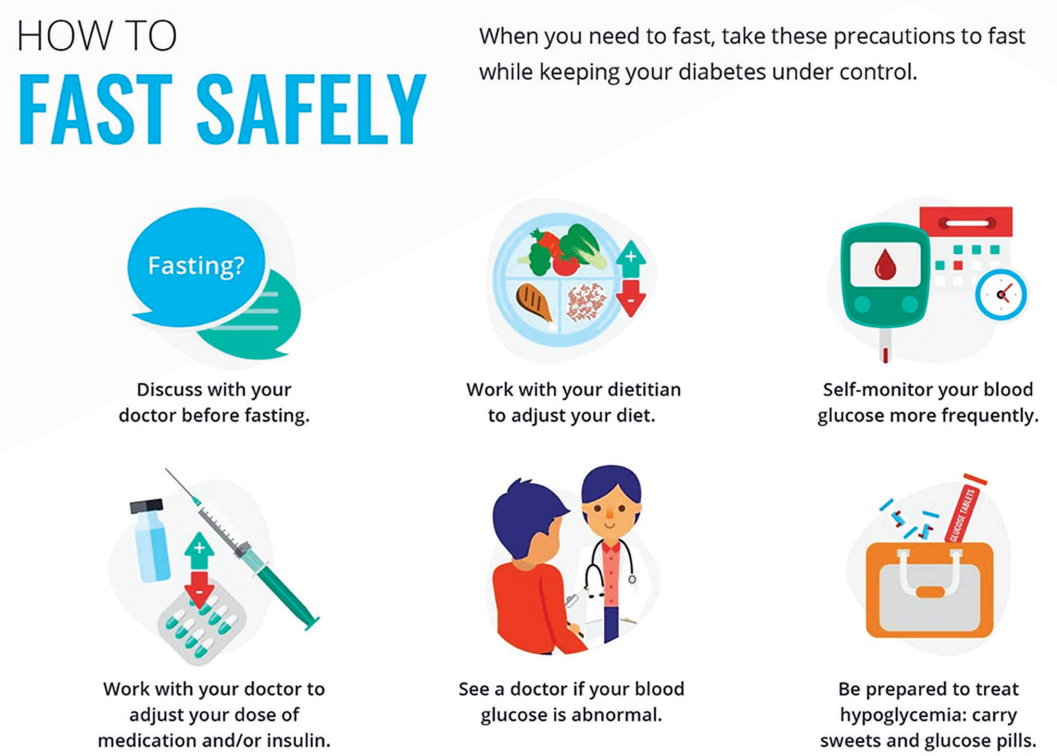


Figure 27.13: Safe fasting

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No diabetic should die unfed unemployed untreated even if he is poor

Professor Dr. Mohammad Ibrahim

Professor Dr. Khwaja Nazimuddin MBBS FCPS(M) FRCP FACP Professor of Medicine and Senior Consultant served in BIRDEM from 1994 to 2023. At present he is in Bangladesh Institute of Health Sciences (BIHS), another institute of Bangladesh Diabetic Samity. His wife Professor Dr. Umme Kulsum BDS DDS MS Professor and Head of Conservative Dentistry just retired from Dhaka Dental College. He has three children. One son two daughters. All are doctors.

Dr. Khwaja Nazimuddin was born in Pabna in 1954. His three other books are Nitta Diner Doctor (Physician in daily life), Face to Face Book (Bangla), Diabetes in Ramadan.

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