**Diabetes mellitus** is the most common of the endocrine disorders. It is a chronic metabolic condition, characterised by hyperglycaemia (due to impaired insulin production and secretion with or without insulin resistance and abnormalities in carbohydrate, fat, and protein metabolism. Diabetes mellitus may be classified according to aetiology, by far the most common types being type 1 and type 2 diabetes

**Type 1 diabetes** is a disease characterised by the destruction of the insulin-producing pancreatic β-cells. In more than 90% of cases, β-cell destruction is associated with autoimmune disease. **Type 1 diabetes** usually develops in children or young adults, although it can develop at any age and is associated with a faster onset of symptoms, leading to dependency on extrinsic insulin for survival.

**Type 2 diabetes** is more common and traditionally occurs in adults older than 40 years, with a peak onset between 60 and 70 years of age in developed countries. Regrettably, it is being increasingly seen in younger people, including adolescents and children.

**T2DM is usually slow and progressive in its development**. **Risk factors for T2DM include:**

• First-degree family history of DM (ie, parents or siblings)

• Overweight or obese

• Habitual physical inactivity

 • Race or ethnicity

• Lifestyle

• A sedentary lifestyle coupled with greater consumption of high-fat, high-carbohydrate foods, and larger portion sizes have resulted in increasing rates of persons being obese.

• Age

• Previously identified IFG, IGT, or A1c between 5.7% and 6.4%

• Hypertension (greater than or equal to 140/90 mm Hg or on therapy for hypertension)

• High-density lipoprotein (HDL) cholesterol less than 35 mg/dL and/or a triglyceride level greater than 250

• History of gestational diabetes or delivery of a baby weighing greater than 4 kg

 • History of cardiovascular disease

 • History of polycystic ovarian syndrome

• Other conditions associated with insulin resistance (eg, acanthosis nigricans)



**Gestational diabetes mellitus**

(GDM) is defined as glucose intolerance in women during pregnancy.

Clinical detection of and therapy for GDM are important because blood sugar control produces significant reductions in adverse maternal, fetal, and neonatal outcomes.

**Drugs** that may cause increased blood glucose include glucocorticoids, pentamidine, nicotinic acid, β-adrenergic agonists, thiazides, phenytoin, clozapine, olanzapine, and γ-interferon.

**Categories of increased risk for diabetes**

 Commonly referred to as prediabetes include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or hemoglobin A1c (A1c) between 5.7% and 6.4%

 **IFG** is defined as having a fasting blood glucose (FBG) level between 100 and 125 mg/dL .

**IGT** is defined by a postprandial blood glucose level between 140 and 199 mg/dL.

The development of IFG, IGT, **or A1c between 5.7% and 6.4%** places the individual at high risk of eventually developing diabetes

**PATHOPHYSIOLOGY**

Impaired Insulin Secretion

In T2DM, more insulin is secreted to maintain normal blood glucose levels until eventually the pancreas can no longer produce sufficient insulin. The resulting hyperglycemia is enhanced by extremely high insulin resistance, pancreatic burnout in which β cells lose functional capacity, or both.

Impaired β-cell function results in a reduced ability to produce a first-phase insulin response sufficient to signal the liver to stop producing glucose after a meal. Over time, patients with T2DM experience progressive β-cell death and many require exogenous insulin to maintain blood glucose control.

 Insulin Resistance

 Insulin resistance is the primary factor that differentiates T2DM from other forms of diabetes. Insulin resistance may be present for several years prior to the diagnosis of DM and can continue to progress throughout the course of the disease.

Resistance to insulin occurs in adipose tissue, skeletal muscle and the liver. Insulin resistance in the liver poses a double threat because the liver becomes nonresponsive to insulin for glucose uptake, and hepatic production of glucose after a meal does not cease, leading to elevated fasting and postmeal blood glucose levels

» Metabolic Syndrome

 Insulin resistance has been associated with a number of other cardiovascular risks, including abdominal obesity, hypertension, dyslipidemia, hypercoagulation, and hyperinsulinemia.

 The clustering of these risk factors has been termed metabolic syndrome. Patients having these additional risk factors have been found to be at much higher cardiovascular risk than would be expected from the individual components of the syndrome.

Incretin Effect

 When nutrients enter the stomach and intestines, incretin hormones are released, which stimulate insulin secretion. This so-called incretin effect is mediated by two hormones, glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), with GLP-1 being studied the most.

 GLP-1 is secreted by the L cells of the ileum and colon primarily, and GIP is secreted by the K cells. GLP-1 secretion is caused by endocrine and neural signals started when nutrients enter the gastrointestinal (GI) tract. Within minutes of food ingestion, GLP-1 levels rise rapidly. A glucose-dependent release of insulin occurs, and the dipeptidyl peptidase-4 (DPP-4) enzyme cleaves GLP-1 rapidly to an inactive metabolite.

**CLINICAL PRESENTATION AND DIAGNOSIS**

**Screening**

* Currently, the American Diabetes Association (ADA) recommends routine screening for T2DM every 3 years in all adults starting at 45 years of age.
* Testing for T2DM should be considered, regardless of age, in adults who have a **BMI greater than or equal to 25** kg/m2 (or BMI greater than or equal to 23 kg/m2 for Asian Americans) and **one or more additional risk factors**.
* The ADA does not currently recommend widespread screening for T1DM.

Gestational Diabetes

* All pregnant women who have risk factors for T2DM should be screened for undiagnosed T2DM at their *first prenatal visit* using standard diagnostic criteria.
* Any woman found to have diabetes at that early point in pregnancy is considered to have *T2DM, not GDM.*
* All other pregnant women, not currently known to have DM should be screened *for GDM.*

Two possible strategies exist for GDM screening.

* They are a “**one-step” 2-hour 75-gram** oral glucose tolerance test (OGTT) **and a**
* “**Two-step” process which includes a 1-hour 50-gram** nonfasting screen followed by a **3-hour 100-gram OGTT** for those with **a 1-hour screening glucose of greater than or equal to 140 mg/dL.**



* Any woman diagnosed with GDM should be retested **at 6 to 12 weeks postpartum** using the OGTT with nonpregnant diagnostic criteria

**TREATMENT Goals of Therapy**

DM treatment goals include:

* reducing, controlling, and managing **long-term microvascular, macrovascular, and neuropathic complications**; preserving β-cell function;
* preventing **acute complications** from high blood glucose levels;
* Minimizing **hypoglycemic episodes;** and maintaining the patient’s overall quality of life.

 To achieve the majority of these goals, near-normal blood glucose levels are fundamental; thus, glycemic control remains a primary objective in diabetes management. A near-normal blood glucose level can be achieved with appropriate patient education, lifestyle modification, and medications.

 **Proper care of DM** requires goal setting and assessment for glycemic control, self-monitoring of blood glucose (SMBG), monitoring of blood pressure and lipid levels, regular monitoring for the development of complications, dietary and exercise lifestyle modifications, and proper medication use.

**» Setting and Assessing Glycemic Targets**

Patients and clinicians can evaluate disease state control of the patient’s diabetes by monitoring daily blood glucose values, **A1c** or estimated average glucose (eAG) values, and blood pressure. SMBG enables patients to obtain their current blood glucose level at any time easily and relatively inexpensively. The A1c test provides a weighted-mean blood glucose level from approximately the previous 3 months.

**Self-Monitoring of Blood Glucose**

SMBG is the standard method for routinely checking blood glucose levels. The *ADA* ***premeal*** *plasma glucose goals are* ***80 to 130 mg/dL*** *and peak* ***postprandial plasma*** *glucose goals are less than* ***180 mg/dL*.**

**Hemoglobin A1c**

* Glucose interacts spontaneously with Hgb in red blood cells to form glycated derivatives. The most prevalent derivative is A1c. Greater amounts of glycation occur when blood glucose levels increase.
* Because Hgb has **a life span of approximately 3 months**, levels of A1c provide a marker reflecting the average glucose levels over this timeframe.
* The ADA goal for persons with DM is less **than 7%** , whereas the AACE supports a goal of less than or equal to **6.5% .**
* Testing A1c levels should occur at least twice a year for patients who are meeting treatment goals and four times per year for patients not meeting goals or those who have had recent changes in therapy.

**Ketone Monitoring**

* When there is **a lack of insulin,** peripheral tissues cannot take up and store glucose. This causes the body to think it is starving, and because of **excessive lipolysis, ketones**, primarily **β-hydroxybutyric acid and acetoacetic acid**, are produced as byproducts of **free fatty acid metabolism in the liver**. Glucose and ketones are **osmotically active**, and when an excessive amount of ketones is formed, the body gets rid of them **through urine, leading to dehydration.**
* **Patients with T1DM should test for ketones** during **acute illness or stress** or when blood glucose levels are consistently **elevated above 300 mg/dL. This** commonly occurs when **insulin is omitted or when diabetes is poorly controlled due to nonadherence, illness, or other reasons.**
* The specific treatment of DKA may include rehydration, correction of electrolyte imbalances, and insulin administration



**General Approach to Therapy**

 **»** **Type 1 Diabetes Mellitus**

Treatment of T1DM requires providing exogenous insulin to replace the endogenous loss of insulin from the nonfunctional pancreas. Ideally, insulin therapy mimics normal insulin physiology. The basal-bolus approach attempts to reproduce basal insulin response using intermediate- or long-acting insulin, whereas short- or rapid-acting insulin replicates bolus release of insulin physiologically seen around a meal in nondiabetics.

A number of different regimens have been used through the years to more closely follow natural insulin patterns.

As a rule, basal insulin makes up approximately 50% of the total daily dose. The remaining half is provided with bolus doses around three daily meals. Exact doses are individualized to the patient and the amount of food consumed.

T1DM patients frequently are started on about 0.6 unit/kg/day, and then doses are titrated until glycemic goals are reached. Most people with T1DM use between 0.6 and 1 unit/kg/day

Currently, the most advanced form of insulin delivery is the insulin pump, also referred to as continuous subcutaneous insulin infusion (CSII). Using rapid-acting insulin only, these pumps are programmed to provide a slow release of small amounts of insulin as the basal portion of therapy, and larger boluses of insulin are injected by the patient to account for the consumption of food.

 **Pramlintide,** a synthetic analog of the naturally occurring hormone amylin, is another injectable blood glucose–lowering medication that can be used in people with T1DM or in people with T2DM using insulin for treatment.

**» Type 2 Diabetes Mellitus**

Treatment of patients with T2DM has changed dramatically over the past decade with the addition of a number of new drugs and recommendations to maintain tighter glycemic control. However, lifestyle modifications including education, nutrition, and exercise are paramount to managing the disease successfully.

**» Gestational Diabetes**

* An individualized meal plan consisting of three meals and three snacks per day is commonly recommended in GDM.
* Preventing ketosis, promoting adequate growth of the fetus, maintaining satisfactory blood glucose levels, and preventing nausea and other undesired GI side effects are desired goals in these patients.
* An abundance of glucose causes excessive insulin production by the fetus, which if left uncontrolled, can lead to the development of an abnormally large fetus.
* Infant hypoglycemia at delivery, hyperbilirubinemia, and complications associated with delivery of a large baby also may occur when blood glucose levels are not controlled adequately.
* Insulin should be used when blood glucose levels are not maintained adequately by diet and physical activity. Insulin detemir, insulin aspart, lispro, and regular insulin carry Category B safety ratings.

**Nonpharmacologic Therapy**

 **» Medical Nutrition Therapy**

* MNT is considered an integral component of diabetes management and diabetes self-management education. People with DM should receive individualized MNT, preferably by a registered dietitian.
* The primary focus of MNT for patients with T1DM is matching optimal insulin dosing to carbohydrate consumption.
* In T2DM, the primary focus is portion control and controlling blood glucose, blood pressure, and lipids through individualizing limits of carbohydrates, saturated fats, sodium, and calories. Carbohydrates are the primary contributor to postmeal glucose levels. The percentages of fat, protein, and carbohydrate included in each meal should be individualized based on the specific goals of each patient

**Weight Management**

* **Moderate weight loss** in patients with T2DM has been shown to reduce cardiovascular risk, as well as delay or prevent the onset of DM in those with prediabetes.
* Gastric reduction surgeries, when used as a part of a comprehensive approach to weight loss, are recommended for consideration in patients with T2DM and a BMI that exceeds 35 kg/m .
* Two drug therapy options were recently approved, lorcaserin and phenteremine/topiramate extended release, to aid weight loss in obese patients and in overweight patients with concomitant disease states such as T2DM, hypertension and dyslipidemia.

**Immunizations**

* Influenza and pneumonia are common preventable infectious diseases that increase mortality and morbidity in persons with chronic diseases, including DM.
* **Yearly influenza vaccinations**, commonly called flu shots, are recommended for all patients with DM 6 months of age or older.
* **Pneumococcal vaccination** with the polysaccharide vaccine 23 is also recommended for patients with DM who are 2 years of age or older as a one-time vaccination. Adults aged greater than or equal to 65 years of age who have not previously been vaccinated should receive the pneumococcal conjugate vaccine 13 followed by the polysaccharide vaccine 6 to 12 months later.
* Adults who have received the polysaccharide vaccine should receive the conjugate vaccine after greater than or equal to 12 months.
* **The hepatitis B vaccine series** should also be administered as per the CDC’s recommendations in patients with diabetes

**Sulfonylureas**

* Sulfonylureas enhance insulin secretion by blocking ATP-sensitive potassium channels in the cell membranes of pancreatic β cells.
* These drugs are classified as being either first- or second-generation agents. Both classes of sulfonylureas are equally effective when given at equipotent doses. Today, the vast majority of patients receiving a sulfonylurea are prescribed a second-generation agent.
* All sulfonylureas undergo hepatic biotransformation, with most agents being metabolized by the cytochrome P450 2C9 pathway.
* The first-generation sulfonylureas are more likely to cause drug interactions than second-generation agents. All sulfonylureas, except tolbutamide, require a dosage adjustment or are not recommended in renal impairment. In elderly patients or those with compromised renal or hepatic function, lower starting dosages are necessary.
* Sulfonylureas’ blood glucose–lowering effects can be observed in both fasting and postprandial levels. Monotherapy with these agents generally produces **a 1.5% to 2% decline in A1c concentrations and a 60 to 70 mg/dL reduction in FBG levels.**
* Secondary failure with these drugs occurs as a result of continued pancreatic β-cell destruction.
* One limitation of sulfonylurea therapy is **the inability of these products to stimulate insulin release from β cells at extremely high glucose levels, a phenomenon called glucose toxicity.**
* Common adverse effects include **hypoglycemia and weight gain**. There may be some cross-sensitivity in patients with sulfa allergy.

**Nonsulfonylurea Secretagogues (Glinides)**

* Although producing the same effect as sulfonylureas, nonsulfonylurea secretagogues, also referred to as meglitinides, have a much shorter onset and duration of action. Meglitinides produce a pharmacologic effect by interacting with ATP-sensitive potassium channels on the β cells; however, this binding is to a receptor adjacent to those to which sulfonylureas bind.
* The primary benefit of nonsulfonylurea secretagogues is in reducing postmeal glucose levels.
* These agents have demonstrated a reduction **in A1c levels between 0.8% and 1%**
* Because they have a rapid onset and short duration of action, they are to be taken **15 to 30 minutes before a meal.**

**Biguanides**

The only biguanide approved by (FDA) and currently available in the United States is metformin. This agent is thought to lower blood glucose by decreasing hepatic glucose production and increasing insulin sensitivity in both hepatic and peripheral muscle tissues; however, the exact mechanism of action remains unknown.

 It has been shown to reduce A1c levels by **1.5% to 2% and FPG levels by 60 to 80 mg/dL when** used as monotherapy.

* Unlike the sulfonylureas, metformin retains the ability to reduce fasting glucose levels when they are over 300 mg/dL.
* Metformin does not affect insulin release from β cells of the pancreas, so hypoglycemia is not a common side effect
* Metformi*n significantly reduced all-cause mortality and the risk of stroke in overweight patients with T2DM compared with intensive therapy with sulfonylurea or insulin in the UKPDS.*
* It also *reduced diabetes-related death and myocardial infarction compared with a conventional therapy arm.*
* Given that metformin is the **only oral antihyperglycemic medication proven to reduce mortality** and is available generically, metformin is considered foundational therapy along with lifestyle modification for T2DM and is often used in combination with other antihyperglycemics for synergistic effects.
* metformin **is contraindicated** in patients with abnormal creatinine clearance for any cause and in patients with a serum creatinine level greater than or equal to 1.4 mg/dL in women and 1.5 mg/dL in men.
* It should not be initiated in patients 80 years of age or older unless normal renal function has been established.
* Additionally, therapy with metformin should be withheld in patients undergoing surgery or radiographic procedures in which a nephrotoxic dye is used. Therapy should be withheld the day of the radiographic procedure, and renal function should be assessed 48 hours after the procedure. If renal function is normal, therapy may be resumed.
* **Primary side effects** associated with metformin therapy are GI in nature, including decreased appetite, nausea, and diarrhea. These side effects can be minimized through slow titration of the dose and often subside within 2 weeks.
* Interference with vitamin B12 absorption has also been reported.
* Metformin is thought to inhibit mitochondrial oxidation of lactic acid, thereby increasing the chance of lactic acidosis, a condition which rarely occurs. Patients at greatest risk for developing lactic acidosis include those with renal impairment and those who are of advanced age.
* Metformin should be withheld promptly in cases of hypoxemia, sepsis, or dehydration.
* Patients should avoid consumption of excessive amounts of alcohol while taking metformin, and use of the drug should be avoided in patients with liver disease.

**Selective Sodium-Dependent Glucose Cotransporter-2 (SGLT-2) Inhibitors**

* Canagliflozin, dapagliflozin, and empagliflozin, SGLT-2 inhibitors, are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM.
* The SGLT-2 receptor is responsible for 90% of the ***active glucose reabsorption of the kidney’s proximal tubule. By inhibiting this receptor, glucose reabsorption is decreased***. Glucose passes into the urine, serum glucose is lowered and modest weight loss is promoted.
* Typical A1c reductions are 0.**7% to 1.3%** . Possible adverse reactions include urinary tract infections, genital mycotic infections, increased urination, hypotension, and increased serum creatinine.

**Thiazolidinediones**

* Thiazolidinediones (TZDs) are known to increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma (PPAR-γ) which increases insulin sensitivity and decreases plasma fatty acids.
* As monotherapy, TZDs reduce FPG levels by **around 60 to 70 mg/dL , and the effect on A1c is an up to 1.5% reduction.**
* The onset of action for TZDs is delayed for several weeks and may require up to 12 weeks before maximum effects are observed.
* Both pioglitazone and rosiglitazone minimally increase HDL cholesterol, 2.4 to 5.2 mg/dL on average.Pioglitazone has been shown to decrease serum triglycerides (TG) 51.9 mg/dL on average, but an increase in TG has been observed with rosiglitazone. Low-density lipoprotein (LDL) cholesterol concentrations increase by 12.3 mg/dL and 21.3 mg/dL on average with pioglitazone and rosiglitazone, respectively.
* The TZDs may produce fluid retention and edema. Thus, these drugs are contraindicated in situations in which an increased fluid volume is detrimental such as heart failure. Fluid retention appears to be dose related and increases when combined with insulin therapy.
* A few cases of hepatotoxicity have been reported with rosiglitazone and pioglitazone. Patients with a baseline elevated alanine aminotransferase (ALT) level should be started on TZD therapy with caution. Therapy should be stopped if ALT levels exceed three times the upper limit of normal while on therapy and remain there, especially if the patient’s total bilirubin is also elevated.
* Increased rates of upper and lower limb fractures are known to occur with TZD therapy.
* Premenopausal anovulatory women may begin to ovulate on TZD therapy, and therefore counseling regarding this should be provided to all women capable of becoming pregnant.
* A slight increased risk for bladder cancer has been noted with pioglitazone therapy, especially among men and smokers.
* A 2007 meta-analysis conducted by Nissen and colleagues reported a significantly greater risk of myocardial infarction with rosiglitazone compared with other oral agents.In May 2011, the FDA chose to restrict access and distribution of rosiglitazone

**α-Glucosidase Inhibitors**

* Acarbose and miglitol are α-glucosidase inhibitors which compete with the enzymes of the small intestines that break down complex carbohydrates.
* These drugs delay absorption of carbohydrates and reduce postprandial blood glucose concentrations as much as **40 to 50 mg/dL ; however, A1c reductions range only from 0.3% to 1%**
* High incidences of GI side effects, including flatulence (42%–74%), abdominal discomfort (12%–19%), and diarrhea (29%–31%), have limited their use.
* Low initial doses followed by gradual titration may minimize GI side effects. The α-glucosidase inhibitors are contraindicated in patients with chronic intestinal diseases including inflammatory bowel disease. In addition, neither drug in this class is recommended for patients with a serum creatinine greater than 2 mg/dL.

**Dipeptidyl Peptidase-4 Inhibitors (Gliptins)**

* The dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM.
* They lower blood glucose concentrations by inhibiting DPP-4, the enzyme that degrades endogenous GLP-1, thereby increasing the amount of endogenous GLP-1.
* The blood glucose lowering effect of the gliptins is primarily on postprandial levels.
* Typical A1c reductions **are 0.7% to 1%**
* Common adverse effects include headache and nasopharyngitis.
* Hypoglycemia is not a common adverse effect with these agents because insulin secretion results from GLP-1 activation caused by meal-related glucose detection and not from direct pancreatic β-cell stimulation.
* Acute pancreatitis, including **hemorrhagic and necrotizing pancreatitis, has been reported in patients taking glipitins**

**Central-Acting Dopamine Agonist**

* A quick release formulation of the central-acting dopamine agonist, bromocriptine, is approved for the treatment of T2DM.
* The mechanism of action for how bromocriptine regulates glycemic control is unknown, but data indicate that bromocriptine administered in the morning improves insulin sensitivity, and this is likely a result of its affect on dopamine oscillations.
* When used to treat patients with T2DM, bromocriptine should be taken 2 hours after waking in the morning with food.
* A **modest A1c reduction of 0.3% to 0.6% can** be expected from this drug.
* Main side effects include rhinitis, dizziness, asthenia, headache, sinusitis, constipation, and nausea. Contraindications include syncopal migraine and women who are nursing

**Bile Acid Sequestrants**

* Colesevelam is the only bile acid sequestrant currently approved as an adjunctive therapy to improve glycemic control in conjunction with diet, exercise, and insulin or oral agents for the treatment of T2DM.
* It acts on the intestinal lumen to bind bile acid, but the drug’s exact mechanism that results in plasma glucose lowering is unknown.
* An A1c reduction of approximately **0.4% and a FPG reduction of about 5 to 10 mg/dL** can be expected when colesevelam is added.
* Common adverse effects include constipation and dyspepsia.
* Drug–drug interactions are possible because of absorption and can be particularly important in patients who are taking levothyroxine, glyburide, oral contraceptives, phenytoin, warfarin, and digoxin.
* These medications should not be taken together, and they should be separated by at least 4 hours before dosing colesevelam. Malabsorption of fat-soluble vitamins (A, D, E, and K) is also a concern



**Insulin**

* Insulin is the one agent that can be used in all types of DM and has no specific maximum dose, meaning it can be titrated to suit each individual patient’s needs. Insulin is the primary treatment to lower blood glucose levels for patients with T1DM, and injected amylin can be added to decrease fluctuations in blood glucose levels.
* Insulin can be divided into two main classes, basal and bolus, based on their length of action to mimic endogenous insulin physiology.
* Insulin is typically refrigerated, though most vials are good for 28 days at room temperature.
* The most common route of administration for insulin is subcutaneous injection using a syringe or pen device. Patients should be educated to **rotate their injection** sites to **minimize lipohypertrophy,** a buildup of fat that decreases or prevents proper insulin absorption.
* Additionally, patients should understand that the absorption rate may vary among injection sites (abdomen, thigh, arm, and buttocks) because of differences in blood flow, with absorption occurring fastest in the abdomen and slowest in the buttocks.

**Bolus Insulins**

**Regular Insulin.**

* It is a clear solution that has a relatively short onset and duration of action and is designed to cover insulin response to meals.
* On subcutaneous injection, regular insulin forms small aggregates called hexamers that undergo conversion to dimers followed by monomers before systemic absorption can occur.
* Patients should be counseled to inject regular insulin subcutaneously 30 minutes before consuming a meal. Regular insulin is the only insulin that can be administered intravenously (IV).

**Rapid-Acting Insulin.**

* Three rapid-acting injectable insulins have been approved in the United States: aspart, glulisine, and lispro. Substitution of one or two amino acids in regular insulin results in the unique pharmacokinetic properties characteristic of these agents.
* The onset of action of injectable rapid-acting insulins varies from 15 to 30 minutes, with peak effects occurring one to two hours after administration and is dosed before or with meals.
* An inhaled rapid-acting insulin was also recently approved. Its peak effect is expected to occur around 15 to 20 minutes following a dose with a duration of action of only two to three hours.

**Basal Insulins Intermediate-Duration Insulin**.

* Neutral Protamine Hagedorn, better known as NPH insulin, is prepared by a process in which protamine is conjugated with regular insulin, rendering a product with a delayed onset but extended duration of action, and is designed to cover insulin requirements in between meals and/ or overnight.
* With the advent of the long-acting insulins, NPH insulin use has declined because of
* an inability to predict accurately when peak effects occur and (b) a duration of action of less than 24 hours. Additionally, protamine is a foreign protein that may increase the possibility of an allergic reaction.
* NPH insulin can be mixed with regular insulin and used immediately or stored for future use. NPH insulin can be mixed with either aspart or lispro insulins, but it must be injected immediately after mixing. Whenever mixing insulin products with NPH insulin, the shorter acting insulin should be drawn into the syringe first.

**Long-Duration Insulin.**

* Glargine and detemir are designed as once-daily-dosing basal insulins which provide a relatively constant insulin concentration over 24 hours.
* Insulin glargine differs from regular insulin by three amino acids, resulting in a low solubility at physiologic pH.
* Detemir binds to albumin in the plasma, which gives it sustained action.
* Neither glargine nor detemir can be administered IV or mixed with other insulin products.
* Although detemir is recommended for dosing in the evening if being used as a once-daily dose, it stands to reason that both glargine and detemir could be administered irrespective of meals or time of day.

**Combination Insulin Products.**

A number of combination insulin products are available commercially.

* NPH is available in combinations of 70/30 (70% NPH and 30% regular insulin) and
* 50/50 (50% NPH and 50% regular insulin).
* Two short-acting insulin analog mixtures are also available.
* Humalog mix 75/25 contains 75% insulin lispro protamine suspension and 25% insulin lispro.
* Novolog mix 70/30 contains 70% insulin aspart protamine suspension and 30% insulin aspart.

**Noninsulin Injectable Agents**

* Glucagon-Like Peptide 1 Agonists Exenatide, liraglutide, albiglutide, and dulaglutide are indicated for the treatment of T2DM to improve glycemic control. These agents are part of the group of drugs known as incretins .
* GLP-1 agonists lower blood glucose levels by:

(a) producing glucose-dependent insulin secretion;

 (b) reducing postmeal glucagon secretion, which decreases postmeal glucose output;

 (c) increasing satiety which decreases food intake; and

 (d) regulating gastric emptying, which allows nutrients to be absorbed into the circulation more smoothly.

* Typical A1c reductions vary between GLP-1 agonists. Exenatide immediate release lowers A1c around 0.9%, exenatide extendedrelease lowers A1c around 1.6%, liraglutide reduces A1c around 1.1%, and albiglutide reduces A1c around 0.78%
* GLP-1 agonists typically produce moderate weight loss of around 1 to 3 kg depending on the drug chosen.
* Exenatide is eliminated renally and is not recommended in patients with a creatinine clearance of less than 30 mL/min No specific dose adjustments are recommended for liraglutide or albiglutide in renal impairment.
* An increased risk of hypoglycemia occurs when GLP-1 agonists are used in combination with a sulfonylurea or insulin.
* The main side effects of GLP-1 agonist therapy include nausea, vomiting, and diarrhea. These GI adverse effects tend to lessen over time.
* GLP-1 agonists have been associated with cases of acute pancreatitis. Any patient presenting with symptoms of acute pancreatitis, including abdominal pain, nausea, and vomiting, should have GLP-1 agonist therapy discontinued until pancreatitis can be ruled out.
* **Contain a black-box warning about thyroid C-cell tumors.** They are contraindicated in patients with a personal or family history of medullary thyroid cancer and in those with a history of multiple endocrine tumors.

**Amylin**

* Pramlintide acetate is a synthetic analog of human amylin, which is a naturally occurring neuroendocrine peptide that is cosecreted with insulin by the β cells of the pancreas in response to food.
* Amylin secretion is very low or completely deficient in patients with T1DM and lower than normal in patients with T2DM who require insulin.
* Pramlintide slows gastric emptying, suppresses glucagon secretion, and leads to a reduction in food intake by increasing satiety. By slowing gastric emptying, the normal initial postmeal spike in blood glucose is reduced.
* Pramlintide is given by subcutaneous injection before meals to lower postprandial blood glucose elevations in patients with types 1 or 2 DM.
* Pramlintide generally results in an **additional A1c reduction of 0.4% to 0.5%** and an average weight loss of 1 to 2 kg
* Hypoglycemia, nausea, and vomiting are the most common side effects encountered with pramlintide therapy, although pramlintide itself does not produce hypoglycemia.
* To decrease the risk of hypoglycemia, doses of short-acting, rapid-acting, or premixed insulins should be **reduced by 30% to 50% before pramlintide is initiated.**
* Primarily, the kidneys metabolize pramlintide, but dosage adjustments in liver or kidney impairment are not required.
* Pramlintide has the **potential to delay the absorption of orally administered medications.** When rapid absorption is needed for the efficacy of an agent, pramlintide should be administered 1 hour after or 3 hours before the drug. Pramlintide should not be used in patients receiving medications that alter GI motility.

**Treatment of Concomitant Conditions »**

**1.Cardiovascular Health**

* Cardiovascular disease is the major cause of morbidity and mortality for patients with DM.
* Interventions targeting *smoking cessation, blood pressure control, lipid management, antiplatelet therapy, and lifestyle changes* (including diet and exercise) can reduce the risk of cardiovascular events and should be considered as important as glycemic control in the management of a patient with DM.
* All patients with a history of cardiovascular disease should be prescribed aspirin 75 to 162 mg/day as a secondary prevention strategy. For those with aspirin allergy, another antiplatelet option such as clopidogrel 75 mg/day should be used.
* The ADA currently recommends that antiplatelet therapy should also be considered for patients with DM and no history of heart disease if that patient’s risk of cardiovascular event is calculated to be greater than 10% over 10 years. This includes most men older than 50 years of age and most women older than 60 years of age who have at least one additional cardiovascular risk factor.

**2» Dyslipidemia**

* Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends statin therapy be considered if a patient falls into one of four statin benefit groups. The groups are:
1. Patients with **clinical atherosclerotic** cardiovascular disease (ASCVD);
2. Patients with no prior history of ASCVD but a LDL level of **190 mg/dL or higher;**
3. Patients with **diabetes and no history of clinical ASCVD who are between the ages of 40 and 75 years with a LDL level between 70 and 189 mg/dL ; and**
4. Patients ages 40 to 75 years with no prior history of ASCVD or diabetes who have a LDL level between 70 and 189 mg/dL and a 10-year estimated ASCVD risk of 7.5% or higher.
* Severe hypertriglyceridemia may warrant therapy **with niacin, a fibrate, and/or fish oil.** Although it was common practice in the past to add niacin or a fibrate onto statin therapy to augment triglyceride and HDL once LDL goals were met, cardiovascular outcome benefit has not been proven when these drugs are added to statin therapy over statin therapy alone.

3**.Hypertension**

* Uncontrolled blood pressure plays a major role in the development of macrovascular events as well as microvascular complications, including retinopathy and nephropathy, in patients with DM.
* The ADA recommends that systolic blood pressure goals for patients with DM be individualized but generally set at less than 140 mm Hg. The diastolic blood pressure goal for patients with DM is less than 90 mm Hg.
* In addition, there are several general principles regarding the treatment of hypertension in diabetes patients. **Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers** are recommended as initial therapy because of their beneficial effects on renal function. It can be expected that most patients will require more than one agent to reach blood pressure goal.
* **Renal function and serum potassium levels** should be monitored closely in all patients taking an ACE inhibitor, angiotensin II receptor blocker, and/or diuretic. ACE inhibitors and angiotensin II receptor blockers are **contraindicated** in patients who are pregnant and in those with bilateral renal artery stenosis.

**Treatment of Acute Complications**

**» Hypoglycemia**

* Hypoglycemia, or low blood sugar, can be defined clinically as a blood glucose level of less than or equal to 70 mg/
* Typical symptoms of hypoglycemia include shakiness, sweating, fatigue, hunger, headaches, and confusion. Common causes of hypoglycemia include delayed or inadequate amounts of food intake, especially carbohydrates, excessive doses of medications (eg, sulfonylureas and insulin), exercising when insulin doses are reaching peak effect.
* Patients experiencing symptoms of hypoglycemia should check their blood glucose level, consume 15 g of carbohydrate, wait 15 minutes for symptom resolution, and retest.
* Examples of acceptable treatments may include a small box of raisins, 4 oz (~120 mL) of orange juice, 8 oz (~240 mL) of skim milk, or three to six glucose tablets.
* In patients receiving an α-glucosidase inhibitor in combination with a sulfonylurea or insulin, hypoglycemia should be treated with glucose tablets or skim milk owing to the mechanism of action of the α-glucosidase inhibitors.
* For patients with hypoglycemia experiencing a loss of consciousness, a glucagon emergency kit should be administered by the intramuscular or subcutaneous route. It is important to contact emergency medical personnel in this particular situation. The patient should be rolled onto his or her side to prevent aspiration because many patients receiving the glucagon injection vomit.

**Hyperosmolar Hyperglycemic State Hyperosmolar hyperglycemic state (HHS**)

* is a life-threatening condition similar to DKA that also arises from inadequate insulin, but HHS occurs primarily in older patients with T2DM.
* DKA and HHS also differ in that HHS lacks the ketonemia and acidosis associated with DKA.
* Infection, silent myocardial infarction, cerebrovascular accident, mesenteric ischemia, acute pancreatitis, and the use of medications that affect carbohydrate metabolism including steroids and thiazide diuretics are known precipitating causes of HHS.
* Two main diagnostic criteria for HHS are a plasma glucose value of greater than 600 mg/dL and a serum osmolality of greater than 320 mOsm/kg
* The extreme hyperglycemia and large fluid deficits resulting from osmotic diuresis are major challenges to overcome with this condition.
* Similar to DKA, the treatment of HHS consists of aggressive rehydration, correction of electrolyte imbalances, and continuous insulin infusion to normalize serum glucose
* Blood glucose levels should be reduced gradually to minimize the risk of cerebral edema

**Diabetic Ketoacidosis**

* Diabetic ketoacidosis is a reversible but potentially life-threatening medical emergency that results from a relative or absolute deficiency in insulin.
* Without insulin, the body cannot use glucose as an energy source and must obtain energy via lipolysis. This process produces ketones and leads to acidosis.
* Often, precipitating factors such as infection, omission, or inadequate administration of insulin can cause DKA.
* Signs and symptoms develop rapidly within 1 day or so and commonly include fruity or acetone breath; nausea; vomiting; dehydration; polydipsia; polyuria; and deep, rapid breathing.
* Hallmark diagnostic criteria for DKA include hyperglycemia (greater than 250 mg/dL, ketosis (anion gap greater than 12 mEq/L), and acidosis (arterial pH less than or equal to 7.3).Typical fluid deficit is 5 to 7 L or more, and major deficits of serum sodium and potassium are common.
* The severity of DKA depends on the magnitude of the decrease in arterial pH, serum bicarbonate levels, and the mental state rather than the magnitude of the hyperglycemia.
* Treatment goals of DKA consist of reversing the underlying metabolic abnormalities, rehydrating the patient, and normalizing the serum glucose.
* Fluid replacement with normal saline at 1 to 1.5 L/hour for the first hour is recommended to rehydrate the patient and to ensure the kidneys are perfused.
* Potassium and other electrolytes are supplemented as indicated by laboratory assessment.
* The use of sodium bicarbonate in DKA is controversial and generally only recommended when the pH is less than 7.
* Regular insulin at 0.1 unit/kg/hour by continuous IV infusion is the preferred treatment in DKA to regain metabolic control rapidly.
* When plasma glucose values drop below 250 mg/dL , dextrose 5% should be added to the IV fluids.
* During the recovery period, it is recommended to continue administering insulin and to allow patients to eat as soon as possible. Dietary carbohydrates combined with insulin assist in the clearance of ketones.



**Treatment of Long-Term Complications**

**» Retinopathy**

* Diabetic retinopathy occurs when the microvasculature that supplies blood to the retina becomes damaged. This damage permits leakage of blood components through the vessel walls. Diabetic retinopathy is the leading cause of blindness in adults 20 to 74 years of age in the United States.
* The risk of retinopathy is increased in patients with long-standing DM, chronic hyperglycemia, hypertension, and nephropathy.
* Other eye disorders, including glaucoma and cataracts, are more likely to occur in patients with diabetes as well.
* The ADA recommends that patients with T2DM receive a dilated eye examination at the time of diagnosis by an ophthalmologist or optometrist.
* Examinations should begin within 5 years of diagnosis of T1DM. Once one or more normal examinations occur, the dilated eye exam is recommended to be repeated at least every two years. But, in patients with documented retinopathy, an annual dilated eye exam is recommended.
* Glucose and blood pressure control are the best strategies for decreasing the risk and slowing the progression of retinopathy

**2» Neuropathy**

* Peripheral neuropathy is a possible complication of diabetes. The most common types of peripheral neuropathy include chronic sensorimotor distal peripheral neuropathy, which can cause pain, tingling, and numbness in the feet and hands, and autonomic neuropathy, which can lead to hypotension, gastroparesis, sexual dysfunction, and autonomic failure in response to hypoglycemia.
* Two drugs, pregabalin and duloxetine, have been approved for the relief of distal peripheral neuropathy pain. A number of other drugs are also sometimes used including venlafaxine, amitriptyline, valproate, and opioids.

**3Microalbuminuria and Nephropathy**

* DM is a leading contributor to end-stage renal disease. Early evidence of nephropathy is the presence of albumin in the urine. Therefore, as the disease progresses, larger amounts of protein spill into the urine.
* The ADA recommends urine protein tests annually in T2DM patients. The most common form of screening for protein in the urine is a random collection for measurement of the urine albumin-to-creatinine ratio. The desirable value is less than 30 mcg of albumin per milligram of creatinine.
* The terms microalbuminuria and macroalbuminuria are being replaced by the term “persistent albuminuria,” with the level of albuminuria further defined as either being between 30 and less than 299 mcg of albumin per milligram of creatinine previously referred to as microalbuminuria or greater than or equal to 300 mcg of albumin per milligram of creatinine previously known as macroalbuminuria.
* Glycemic control and blood pressure control are primary measures for the prevention of progression of nephropathy. ACE inhibitors and angiotensin II receptor blockers prevent the progression of renal disease in patients with T2DM.

**4.Foot Ulcers**

* Lower extremity amputations are one of the most feared and disabling sequelae of long-term uncontrolled DM.
* A foot ulcer is an open sore that develops and penetrates to the subcutaneous tissues.
* Complications of the feet develop primarily as a result of peripheral vascular disease, neuropathies, and foot deformations.
* Peripheral arterial disease causes ischemia to the lower limbs. This decreased blood flow deprives the tissues of oxygen and nutrients and impairs the ability of the immune system to function adequately.
* Symptoms of peripheral arterial disease include intermittent claudication, cold feet, pain at rest, and loss of hair on the feet and toes.
* Smoking cessation is the single most important treatment for peripheral arterial disease. In addition, exercising by walking to the point of pain and then resting and resuming can be a vital therapy to maintain or improve the symptoms of peripheral arterial disease.
* Pharmacologic intervention with antiplatelet therapy (aspirin 160–325 mg/day or clopidogrel 75 mg/day) is indicated in patients with peripheral arterial disease. For those that remain symptomatic, cilostazol 100 mg twice daily may be useful to improve blood flow and reduce the symptoms of peripheral vascular disease.
* **Neuropathies** play a large part in the development of foot ulcers. Loss of sensation in the feet allows trauma to go unnoticed. **Autonomic neuropathy** can cause changes in blood flow, perspiration, skin hydration, and possibly, bone composition of the foot. **Motor neuropathy** can lead to muscle atrophy, resulting in weakness and changes in the shape of the foot.
* To prevent foot complications, the ADA recommends daily visual examination of the feet and a foot check performed at every physician visit.
* Treatment consists of glycemic control, preventing infection, debriding dead tissues, applying dressings, treating edema, and limiting ambulation. Additionally, diabetics should wear properly fitted, cushioned footwear and padded socks



