Chronic complications and management of Diabetes Mellitus

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Microvascular complications — Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy (peripheral and autonomic).

Retinopathy — Diabetes-associated retinopathy is a progressive disorder that affects the microvasculature of the retina. Most patients develop the mildest form of retinopathy (non-proliferative retinopathy). This can progress to an intermediate stage (pre-proliferative) and in some patients progresses to proliferative retinopathy, which carries a high risk of visual loss.

- Screening allows detection of retinopathy in the non-proliferative stage. At this stage, improving glycemic control can reverse nonproliferative changes and prevent progression. In more severe cases, laser therapy can prevent further progression of disease and visual loss.

Diabetic retinopathy (DR) is one of the most important causes of visual loss worldwide, and is the principal cause of impaired vision in patients between 25 and 74 years of age. Visual loss from diabetic retinopathy may be secondary to macular edema (retinal thickening and edema involving the macula), hemorrhage from new vessels, retinal detachment, or neovascular glaucoma.

- Retinopathy — In adults, controlled trials have established increasing risk for diabetic retinopathy with longer duration of diabetes and poorer glycemic control.
- The median duration of diabetes at the time of detection of retinal changes was 16.6 years. Patients with poorer glycemic control developed retinopathy more rapidly than those with good glycemic control: the median disease duration prior to detection of retinopathy was 15.5 years for patients with A1C values ≥ 7.5 percent, as compared with 18.3 years for those with A1C values <7.5 percent.

- Other risk factors associated with retinopathy include hypertension, hyperlipidemia, smoking, and genetic susceptibility . Hypertension with microalbuminuria is associated with accelerated progression of retinopathy .
- The vast majority of patients who develop diabetic retinopathy have no symptoms until the very late stages (by which time it may be too late for effective treatment). Because the rate of progression may be rapid, and therapy can be beneficial for both symptom amelioration and reduction in the rate of disease progression, it is important to screen patients with diabetes regularly for the development of retinal disease.

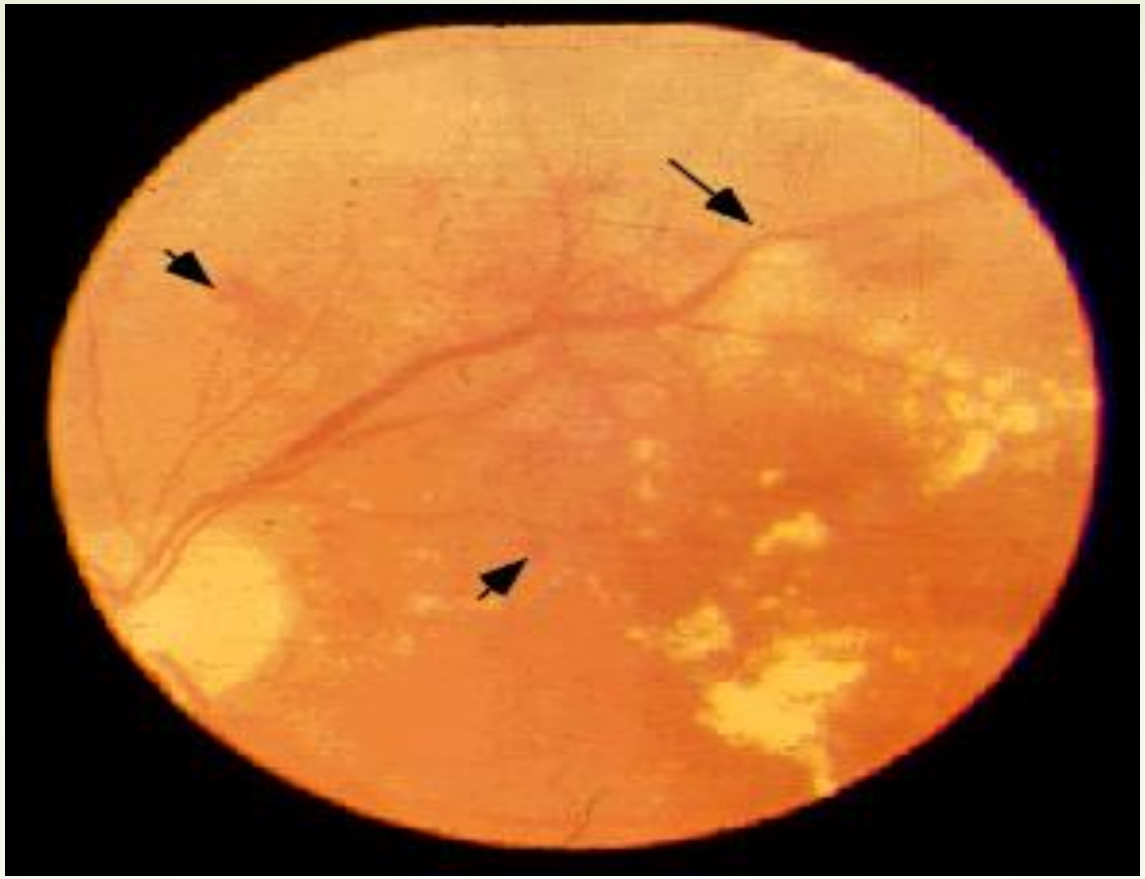
METHOD OF SCREENING —

Ophthalmoscopy is a reasonable screening method when performed by well-trained personnel on dilated fundi.

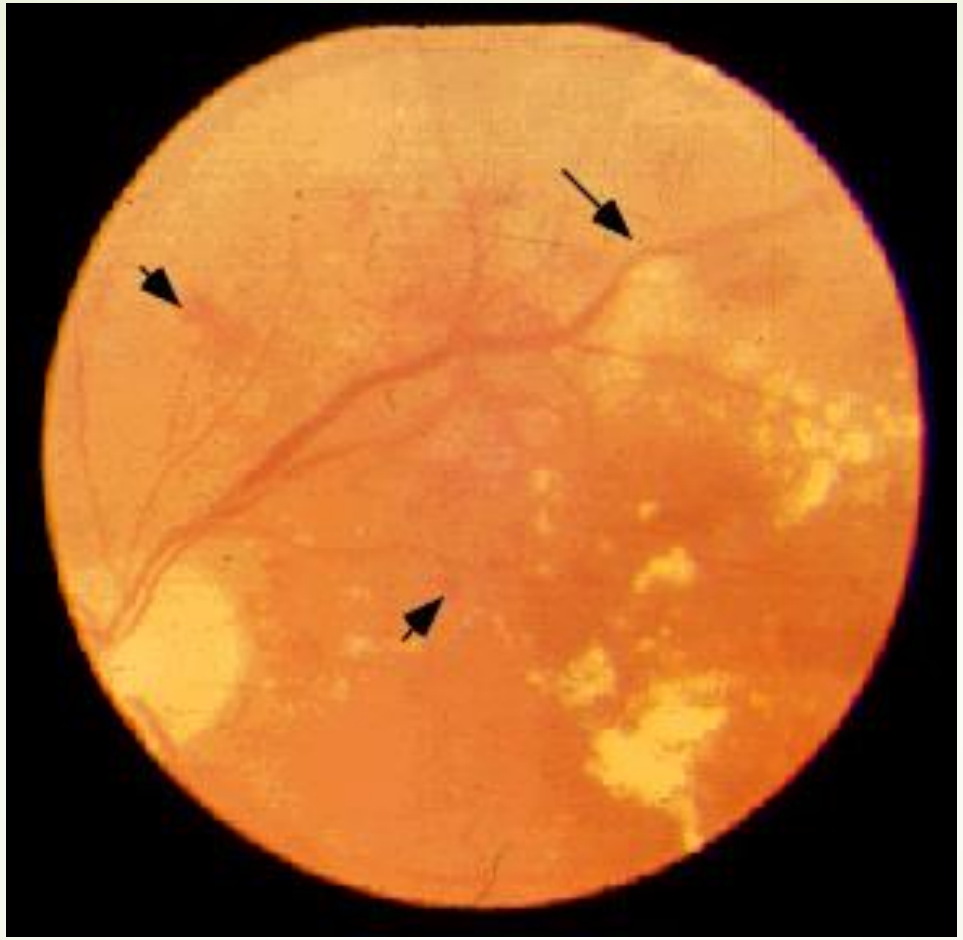
- As an alternative, seven-field stereoscopic fundus photography is another acceptable method, but also requires both a trained photographer and a trained reader. Fundal photography compares favorably with ophthalmoscopy (performed by an experienced ophthalmologist, optometrist, and ophthalmic technician).
- Type 1 diabetesWithin 5 years after diagnosis of diabetes once patient is age 10 years or older-then Yearly.
- Type 2 diabetesAt time of diagnosis of diabetes.then Yearly.

Classification-

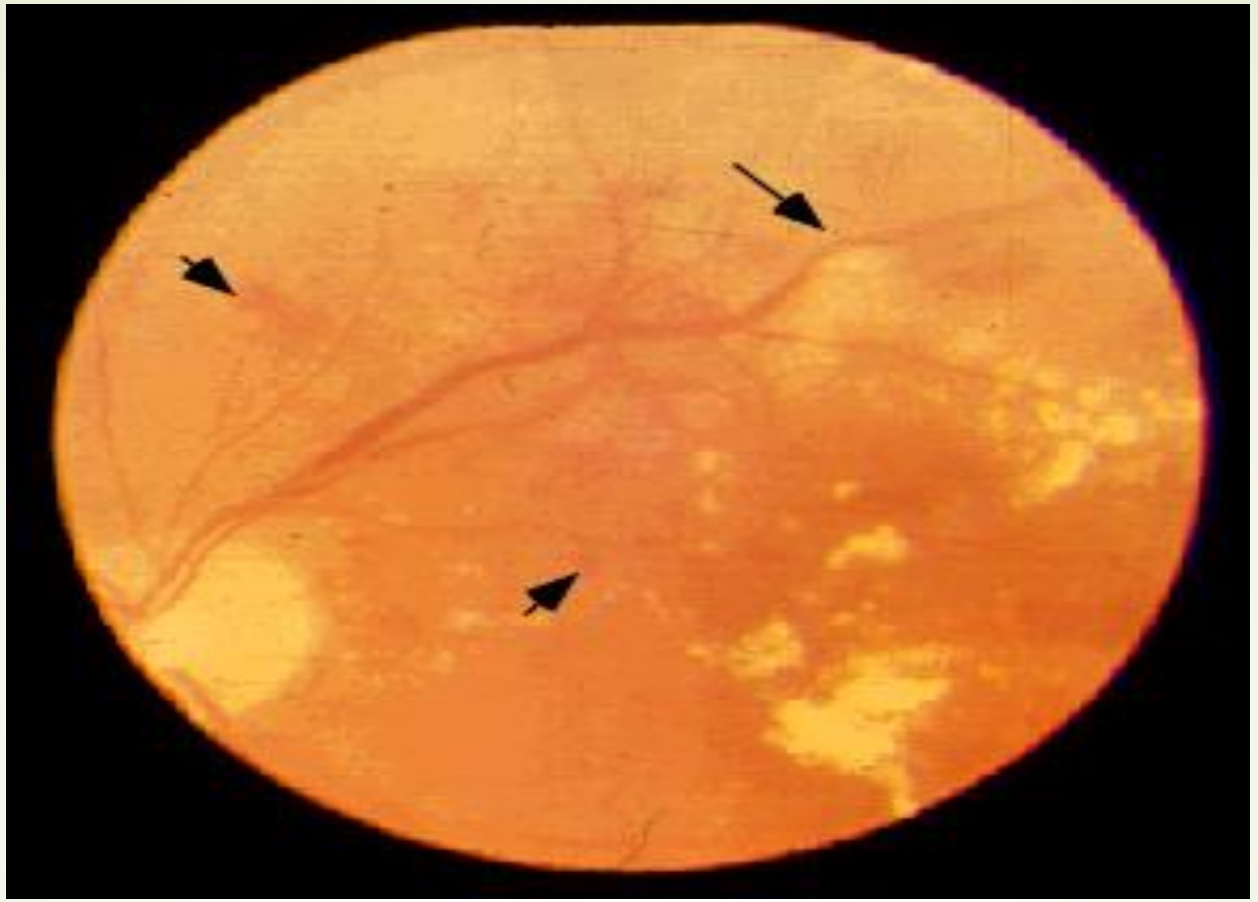
- Background retinopathy describes the earliest retinal changes including dilated retinal venules, microaneurysms, and capillary leakage (picture 1). Loss of visual acuity can occur if these changes are near the macula.
- Preproliferative retinopathy is the second stage of retinopathy with retinal microinfarcts visible as small flame-shaped blot hemorrhages proximal to the occlusion (picture 2) and "cotton wool" or "soft exudates" distal to the occlusion (picture 3).
- Proliferative retinopathy is the most severe form. It includes retinal ischemia, proliferation of new retinal blood vessels (picture 4), further hemorrhage, scarring resulting from contraction of fibrovascular proliferation, and retinal detachment.



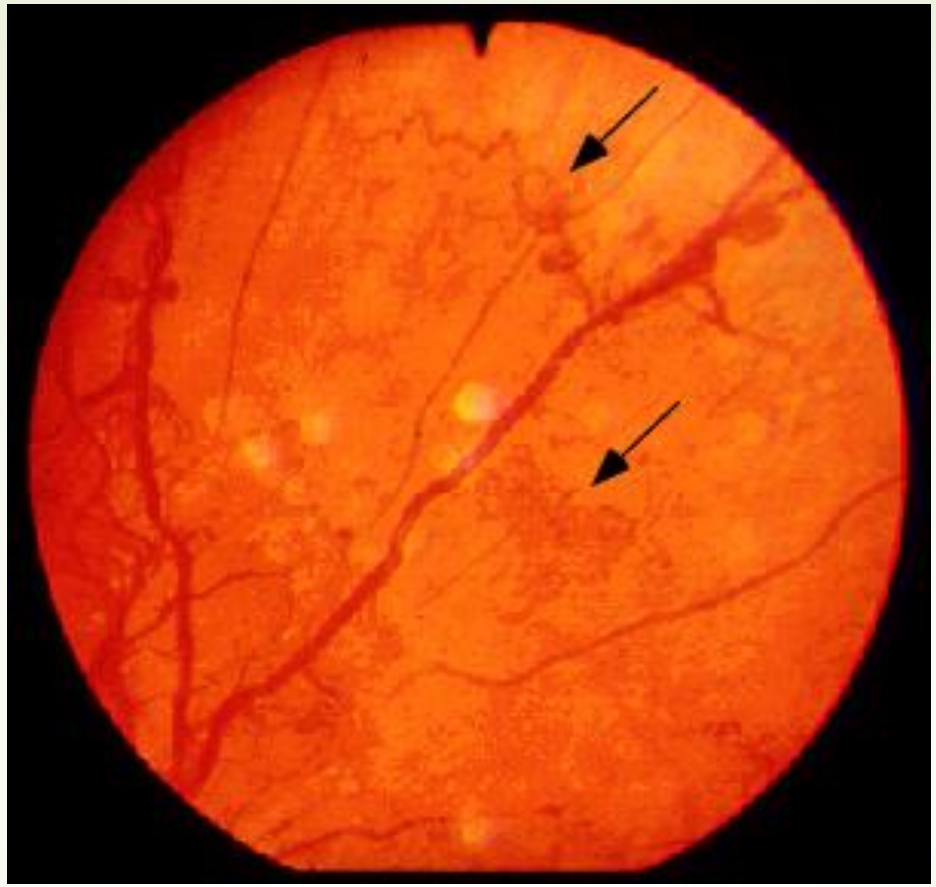
Background diabetic retinopathy showing microaneurysms (small arrows) and hard exudates. The blood vessels can be seen running over the hard exudates (large arrow), indicating that the exudates are due to leakage in the deeper retinal layers (in contrast to soft exudates, which are microinfarcts in the superficial retinal layers with obliterated blood vessels). Many of the hard exudates are clustered around the macula, which is at the periphery at about four o'clock.



Diabetic retinopathy, showing several blot hemorrhages (arrows). These lesions are due to vascular occlusion and rupture.



Cotton wool spots are indicative of retinal ischemia. The differential diagnosis includes diabetes, hypertension, AIDS, and the retinal vascular changes of systemic lupus erythematosus.



Diabetic retinopathy, showing irregular changes in venous caliber, tortuosity of blood vessels, and proliferation of networks of fragile new vessels, arising from both arteries and veins (arrows).

Treatment —

- The following is a brief summary of the treatment of retinopathy in patients with type 1 diabetes.
- Strict glycemic control can prevent, retard, or delay the onset of retinopathy. Background retinopathy can be reversed with better glycemic control, although initial worsening may occur.
- In patients with more advanced disease, laser therapy, if applied in a timely manner, may prevent progression of disease and visual loss.
- If hypertension is present, ACE inhibitors should be started because they retard progression of retinopathy similar to their effect on diabetic nephropathy.

Nephropathy —

Diabetes-associated nephropathy is a progressive disorder of the microvasculature of the kidney.

- Microalbuminuria, defined as persistent albumin excretion between 30 and 300 mg/day (20 to 200 mcg/min), is the earliest stage of nephropathy. In youth with diabetes, microalbuminuria predicts progression of nephropathy to overt proteinuria [albumin excretion >300 mg/day (200 mcg/min)], which can be accompanied by systemic hypertension and impaired glomerular filtration . Some patients with overt proteinuria will progress to end-stage renal disease.
- Microalbuminuria is common among adolescents with type 2 diabetes, occurring in 14 to 22 percent at presentation . The finding of microalbuminuria increased to about 60 percent during the next ten years of follow up; the incidence in adolescents with type 2 diabetes is much higher than that seen in the first ten years of type 1 diabetes.

- All patients with type 2 diabetes are screened annually for microalbuminuria by measuring the microalbumin-to-creatinine ratio in a random urine sample. Upright posture or exercise can yield false-positive results. Therefore, a first morning void should be obtained for testing. Patients with positive results should have repeat screening on at least two occasions during the subsequent three to six months.
- Treatment for microalbuminuria includes optimization of glycemic control and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers. There is some evidence that these interventions can reverse microalbuminuria and delay or prevent the progression of renal disease. Patients with persistent microalbuminuria (measured on three separate days) should usually be treated with an ACE inhibitor

- **Neuropathy —** Involvement of the peripheral and autonomic nervous systems is probably the most common complication of diabetes. Clinical diabetic neuropathy is categorized into distinct syndromes according to the neurologic distribution, although many overlap syndromes occur. In both type 1 and type 2 diabetes, the prevalence varies with both the severity and duration of hyperglycemia.

- **CLASSIFICATION —**
- **Diabetic neuropathy is classified into distinct clinical syndromes. A characteristic set of symptoms and signs exist for each syndrome, depending on the component of the peripheral nervous system that is affected. The most frequently encountered neuropathies include :**
- **Distal symmetric polyneuropathy**
- **Autonomic neuropathy**
- **Thoracic and lumbar nerve root disease, causing polyradiculopathies**
- **Individual cranial and peripheral nerve involvement causing focal mononeuropathies, especially affecting the oculomotor nerve (cranial nerve III) and the median nerve**
- **Asymmetric involvement of multiple peripheral nerves, resulting in a mononeuropathy multiplex**

- Symmetric polyneuropathy — Distal symmetric sensorimotor polyneuropathy is the most common type of diabetic neuropathy and is often considered synonymous with the term diabetic neuropathy. It is characterized by a progressive loss of distal sensation correlating with loss of sensory axons, followed, in severe cases, by motor weakness and motor axonal loss. Classic "stocking-glove" sensory loss is typical in this disorder.
- Autonomic neuropathy — Diabetic autonomic neuropathy is a common complication of diabetes. It is a diagnosis of exclusion and may be unnoticed because of multiorgan involvement and insidious onset. It can, however, cause severe dysfunction of a single organ. Among the problems that can occur are postural hypotension, gastroparesis, and enteropathy with constipation or diarrhea.

- **Polyradiculopathies — The term asymmetric proximal neuropathy was initially used to describe injury to proximal limb and nerve roots. Because of the pleiotropic presentation of this type of diabetic neuropathy, several other terms appeared in the literature, most prominently diabetic amyotrophy and diabetic thoracic polyradiculopathy. These forms of diabetic neuropathy are probably subtypes of diabetic polyradiculopathy .**
- **Diabetic amyotrophy (lumbar polyradiculopathy) —**

  The most common type of diabetic polyradiculopathy is a syndrome frequently called diabetic amyotrophy. The etiology is debated, and several pathophysiologic mechanisms (ischemic, metabolic, and/or inflammatory) have been proposed as the cause. Of these, the most likely cause is ischemic injury from a nonsystemic microvasculitis.

- The traditional features of diabetic amyotrophy include the acute, asymmetric, focal onset of pain followed by weakness involving the proximal leg, with associated autonomic failure and weight loss. Progression occurs over months and is followed by partial recovery in most patients. The same process can occur in the contralateral leg, immediately following (within days) or much later than (months to years) the initial attack. The diagnosis of diabetic amyotrophy is mainly based upon the presence of suggestive clinical features in a patient with known or newly diagnosed diabetes mellitus. Appropriate laboratory investigations, particularly electrodiagnostic studies, and neuroimaging in select patients, are useful to exclude other peripheral and central nervous system etiologies as a cause of the neurologic symptoms and signs.

- No treatments are proven to be effective for diabetic amyotrophy. There is limited and conflicting data regarding the benefit of immunosuppressive therapies including oral prednisone, intravenous methylprednisolone, intravenous immune globulin, cyclophosphamide, and plasma exchange.
- Thoracic polyradiculopathy — Although less common than diabetic lumbar polyradiculopathy, thoracic polyradiculopathy can cause marked symptoms. Affected patients present with severe abdominal pain, sometimes in a band-like pattern, and frequently have undergone extensive gastrointestinal diagnostic studies in attempts to identify the etiology of their pain

- Thoracic and upper limb involvement has also been observed as part of the syndrome of diabetic amyotrophy in a minority of patients. Some have symptoms and signs suggesting a thoracic radiculopathy, a brachial plexopathy, or mononeuropathies of the ulnar and median nerves. Most upper limb symptoms occur in association with lumbosacral plexus involvement.

- Diabetic neuropathic cachexia — Another rare but identifiable syndrome is diffuse diabetic polyradiculopathy superimposed upon severe peripheral neuropathy. This syndrome is associated with unintended severe weight loss and depression and is known as diabetic neuropathic cachexia . It most frequently occurs in men with type 2 diabetes on oral hypoglycemic agents who are middle-aged or older. Most patients improve spontaneously within 12 to 24 months, although some have residual neurologic deficits. There is no specific therapy, and management is supportive.
- Mononeuropathies — There are two types of mononeuropathy associated with diabetes: cranial and peripheral.
- Cranial mononeuropathy — The most common cranial mononeuropathies occur in those nerves which supply the extraocular muscles, especially cranial nerves III (oculomotor), VI (abducens), and IV (trochlear). Patients with diabetic ophthalmoplegia typically present with unilateral pain, ptosis, and diplopia, with sparing of pupillary function .

- Facial mononeuropathy (Bell's palsy) occurs more frequently in diabetic than in nondiabetic patients.

- Peripheral mononeuropathy — The most common peripheral mononeuropathy in diabetic patients is median mononeuropathy at the wrist. While estimates vary, it is likely that at least one-quarter to one-third of patients develop either symptomatic or asymptomatic median mononeuropathy . Ulnar mononeuropathy, either at the elbow or, less commonly, at the wrist can also occur .

- In the lower extremities, peroneal mononeuropathies with compression at the fibula are a well recognized complication of diabetes. Common peroneal palsy, for example, can result in foot drop. It is probable, however, that isolated femoral mononeuropathies are rare in diabetes; many of these patients, after careful clinical and electrodiagnostic examinations, are found to have a high lumbar radiculopathy (diabetic amyotrophy).

- **Mononeuropathy multiplex — Multiple mononeuropathies in the same patient are known as mononeuropathy multiplex (or asymmetric polyneuropathy). The other major disorder that can produce this syndrome is vasculitis, which should also be considered in affected patients .**

Cardiovascular disease

- Heart disease, particularly coronary heart disease (CHD) is a major cause of morbidity and mortality among patients with diabetes mellitus .
- Compared to individuals without diabetes, those with diabetes have a higher prevalence of CHD, a greater extent of coronary ischemia, and are more likely to have a myocardial infarction (MI), and silent myocardial ischemia.

Diabetic autonomic neuropathy –

Diabetic autonomic neuropathy may involve the cardiovascular, genitourinary, and the neuroendocrine system as well as the upper and lower gastrointestinal tract. Abnormalities of gastrointestinal function in diabetics are thought to be related, at least in part, to autonomic neuropathy of the enteric nervous system (ENS).

System	Symptoms
Cardiovascular	Postural hypotension Postprandial hypotension Fixed tachycardia Foot complications Sudden cardiac death
Gastrointestinal	Esophageal motility disorders Gastroparesis Constipation, diarrhea, incontinence
Genitourinary	Bladder dysfunction Sexual dysfunction
Sudomotor	Distal anhidrosis Gustatory sweating
Abnormal pupillary responses	failure in dark adaptation and difficulties in night driving
Neuroendocrine responses to hypoglycemia	Reduced glucagon secretion Delayed epinephrine secretion

Evaluation of the diabetic foot

- Foot problems are an important cause of morbidity in patients with diabetes mellitus. The lifetime risk of a foot ulcer for diabetic patients (type 1 or 2) may be as high as 25 percent .
- A potentially preventable initiating event, most often minor trauma that causes cutaneous injury, can often be identified.
- Foot amputations, many of which are preventable with early recognition and therapy, may be required .
- These observations illustrate the importance of frequent evaluation of the feet in patients with diabetes to identify those at risk for foot ulceration .
- Systematic screening examinations for neuropathic and vascular involvement of the lower extremities and careful inspection of feet may substantially reduce morbidity from foot problems.

- **PHYSICAL EXAMINATION — The physical examination should include an assessment for the presence of existing ulcers, peripheral neuropathy (loss of protective sensation [LOPS]), peripheral artery disease, and foot deformities that may predispose the patient to the development of foot ulcers . Several reports indicate that adequate examinations relevant to foot ulceration are often not performed in diabetic patients.**

Physical signs of peripheral artery disease —

- The feet should be examined for signs of peripheral artery disease such as absence of foot pulses, decrease in skin temperature, thin skin, lack of skin hair, and bluish skin color. However, these signs are neither sensitive nor specific enough to be helpful in an individual patient. Patients with clinical evidence of peripheral vascular disease should have ankle-brachial pressure index (ABI) testing.
- This index is calculated by measuring the systolic blood pressure (by Doppler probe) in the brachial, posterior tibial, and dorsalis pedis arteries .
- The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements.
- The normal index is >1.0, because the pressure is higher in the ankle than in the arm. An index <0.9 has 95 percent sensitivity for detecting angiogram-positive peripheral artery disease .

- **Foot ulceration — Foot ulcers are usually classified into two groups: acute ulcers secondary to dermal abrasion from poorly fitting shoes and chronic plantar ulcers occurring over weight-bearing areas. Chronic ulceration is probably multifactorial, due to a combination of diabetic neuropathy (with decreased pain sensation), autonomic dysfunction, and vascular insufficiency.**
- **Wound evaluation**
- **Signs of infection**

Advice for prophylactic foot care should be given to all patients :

- Avoid going barefoot, even in the home.
- Test water temperature before stepping into a bath.
- Trim toenails to shape of the toe; remove sharp edges with a nail file. Do not cut cuticles.
- Wash and check feet daily.
- Shoes should be snug but not tight and customized if feet are misshapen or have ulcers.
- Socks should fit and be changed daily.

Management of blood glucose in type 2 diabetes mellitus

- Treatment of patients with type 2 diabetes mellitus includes education, evaluation for microvascular and macrovascular complications, normalization of glycemia, minimization of cardiovascular and other long-term risk factors, and avoidance of drugs that can aggravate abnormalities of insulin or lipid metabolism.

TREATMENT GOALS

- Degree of glycemic control — Achieving near normal blood glucose concentrations markedly reduces the risk of microvascular and macrovascular complications in type 1 diabetes.
- Improved glycemic control also improves the risk of microvascular complications in patients with type 2 diabetes .
- Every 1 percent drop in A1C is associated with improved outcomes with no threshold effect.
- Target A1C goals in patients with type 2 diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia.
- Glycemic targets are generally set somewhat higher for older patients and those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy.

- Cardiovascular risk factor management — In addition to glycemic control, vigorous cardiac risk reduction (smoking cessation, aspirin, blood pressure control, reduction in serum lipids, diet, and exercise) should be a top priority for all patients with type 2 diabetes.
- However, in spite of evidence that aggressive risk factor reduction lowers the risk of both micro- and macrovascular complications in patients with diabetes, the vast majority of patients do not achieve recommended goals for A1C, blood pressure control, and management of dyslipidemia.

- **Nonpharmacologic therapy in type 2 diabetes —**
- **There are three major components to nonpharmacologic therapy of blood glucose in type 2 diabetes :**
- **Dietary modification**
- **Exercise**
- **Weight reduction**
- **In addition to improving glycemic control, these changes in lifestyle also slow progression of impaired glucose tolerance to overt diabetes .**
- **Diet and exercise are important components of therapy in patients with type 1 diabetes.**
- **Surgical treatment of obese patients with diabetes results in the largest degree of sustained weight loss and, in parallel, the largest improvements in blood glucose control. Pharmacotherapy for weight loss may also be used for patients with type 2 diabetes, but may not be effectively sustained due to side effects.**

- Pharmacologic therapy for type 2 diabetes — The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a 2006 consensus statement for the management of glycemia in type 2 diabetes, which was updated in 2009 . Because of the difficulty in achieving and sustaining goal glycemia and significant weight loss, the consensus group concluded that metformin therapy should be initiated concurrent with lifestyle intervention at the time of diagnosis.
- The therapeutic options for patients who fail initial therapy with lifestyle intervention and metformin are to add a second oral or injectable agent, including insulin, or to switch to insulin .
- Regardless of the initial response to therapy, the natural history of most patients with type 2 diabetes is for blood glucose concentrations and A1C to rise over time.
- Type 2 diabetic patients often need large daily doses of insulin (>65 units per day, and often much more) to achieve acceptable glycemic control.
- Most patients with type 2 diabetes can be treated with one or two daily injections, in contrast to patients with type 1 diabetes for whom intensive insulin therapy with multiple daily injections is indicated.

- Metformin — In the absence of contraindications, metformin is the first choice for oral treatment of type 2 diabetes. It generally reduces A1C by 1.5 percentage points . In contrast with most other antidiabetic drugs, metformin often leads to modest weight reduction or weight stabilization .
- Gastrointestinal side effects are common, but metformin monotherapy does not usually cause hypoglycemia. Metformin can rarely cause lactic acidosis, and because of the potentially fatal outcome of this side effect, metformin should not be administered when conditions predisposing to lactic acidosis are present. Such conditions include impaired renal function (plasma creatinine above 1.4 mg/dL [124 micromol/L] in women and 1.5 mg/dL [133 micromol/L] in men), decreased tissue perfusion or hemodynamic instability due to infection or other causes, concurrent liver disease or alcohol abuse, and heart failure.

- Patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) or undergo a surgical procedure (with potential compromise of circulation) should have metformin held until renal function and circulation can be established (normal urine output, normal serum creatinine, and no physical exam evidence of fluid overload or circulatory compromise). Serum creatinine is typically assessed two to three days after contrast administration.

- **Sulfonylureas**
- **— Sulfonylureas are the oldest class of oral hypoglycemic agents. They are moderately effective, lowering blood glucose concentrations by 20 percent and A1C by 1 to 2 percent. However, their effectiveness decreases over time.**
- **The sulfonylurea receptor is a component of the ATP-dependent potassium channel in the pancreatic beta cells . Sulfonylurea binding leads to inhibition of these channels, which alters the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion. The net effect is increased responsiveness of beta cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin being released at all blood glucose concentrations.**

- Thus, sulfonylureas are useful only in patients with some beta cell function. Sulfonylureas may also have extrapancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal .
- The major adverse effect of sulfonylureas is hypoglycemia.
- Before beginning a sulfonylurea, the patient should be instructed about the symptoms and treatment of hypoglycemia. Hypoglycemia induced by long-acting sulfonylureas may be severe and is often prolonged in the absence of appropriate therapy.
- Initiation of sulfonylurea therapy is also associated with weight gain.
- The choice of sulfonylurea is primarily dependent upon cost, risk of hypoglycemia, and local availability, since the efficacy of the available drugs is similar.

- Sulfonylureas can be effective when used as monotherapy, or in combination with other oral hypoglycemic drugs or insulin.
- Sulfonylureas usually lower blood glucose concentrations by about 20 percent and A1C by 1 to 2 percent .
- They are most likely to be effective in patients whose weight is normal or slightly increased. In contrast, insulin should be used in patients (regardless of age) who are underweight, are losing weight, or are ketotic despite adequate caloric intake.

- A typical initial sulfonylurea regimen consists of 2.5 mg of glipizide taken 30 minutes before breakfast. If adequate glycemic control is not attained in the next two to four weeks, the dose can be increased to 5 mg and then 10 mg, given before breakfast or before breakfast and the evening meal. The maximum dose of glipizide can be up to 40 mg/day. However, these maximum doses rarely improve glycemic control, and higher doses should generally be avoided .
- Other, infrequent side effects that can occur with all sulfonylureas include nausea, skin reactions (including photosensitivity), and abnormal liver function tests. Chlorpropamide has two unique effects: it can cause an unpleasant flushing reaction after alcohol ingestion by inhibiting the metabolism of acetaldehyde ; and it can cause hyponatremia, primarily by increasing the action of vasopressin

Drug	Duration of biologic effect, h	Usual daily dose, mg	Dosing per day
First-generation sulfonylureas			
Acetohexamide	12 to 18	500 to 750	Once or divided
Chlorpropamide (Diabinese)	24 to 72	250 to 500	Once
Tolbutamide (Orinase)	14 to 16	1000 to 2000	Once or divided
Second-generation sulfonylureas			
Glipizide	14 to 16	2.5 to 10	Once or divided
(Glucotrol)			
(Glucotrol XL)		5 to 10	Once
Gliclazide	24	40 to 240	Once
(Diamicron R)			
(Diamicron MR)			
Glyburide (Glibenclamide)	20 to 24+	2.5 to 10	Once
(Diabeta)			
(Micronase)			
(Glynase)			
Glimepiride (Amaryl)	24+	2 to 4	Once

MEGLITINIDES —

- The meglitinides, repaglinide and nateglinide, are short-acting glucose-lowering drugs for therapy of patients with type 2 diabetes alone or in combination with metformin. They are structurally different than sulfonylureas and exert their effects via different receptors, but act similarly by regulating ATP-dependent potassium channels in pancreatic beta cells, thereby increasing insulin secretion .
- Efficacy — The clinical efficacy of meglitinide monotherapy is similar to that of the sulfonylureas .
- The recommended starting dose of repaglinide is 0.5 mg before each meal for patients who have not previously taken oral hypoglycemic drugs. The maximum dose is 4 mg before each meal; the dose should be skipped if the meal is missed.
- The recommended dose of nateglinide is 120 mg taken immediately before each meal .

- Adverse effects — Hypoglycemia is the most common adverse effect. Nateglinide is hepatically metabolized, with renal excretion of active metabolites. With decreased renal function, the accumulation of active metabolites and hypoglycemia has occurred. This drug must therefore be used cautiously in this setting, if at all. Repaglinide is principally metabolized by the liver, with less than 10 percent renally excreted. Dose adjustments with this agent do not appear to be necessary in patients with renal insufficiency.

Thiazolidinediones

- — The thiazolidinediones, rosiglitazone and pioglitazone, lower blood glucose concentrations by increasing insulin sensitivity.
- The first drug in this class, troglitazone, was removed from the market in the United Kingdom and the United States because of relatively rare, but severe, idiosyncratic hepatic injury that was either fatal or necessitated liver transplantation.
- Hepatotoxicity does not appear to occur with rosiglitazone and pioglitazone. However, some meta-analyses have questioned the safety of rosiglitazone with regard to the risk of myocardial infarction.
- In 2010, the European Medicines Agency suspended sales of rosiglitazone, owing to concern regarding cardiovascular safety and the availability of alternative therapies, including pioglitazone, that do not have the same concerns. At the same time, the US Food and Drug Administration restricted its use to patients with type 2 diabetes who cannot achieve adequate glycemic control with other medications, including pioglitazone. Subsequently, in 2011, the French and German Medicines Agencies suspended the use of pioglitazone because of the potential increased risk of bladder cancer and the concern that the overall risks of pioglitazone exceed its benefits.

- As monotherapy, thiazolidinediones are probably somewhat less effective in lowering glycemia than metformin, lowering A1C by 0.5 to 1.4 percentage points .
- They are also associated with more weight gain and fluid retention than metformin, and are considerably more expensive than generic sulfonylureas and metformin. Drugs in this class are not recommended in patients with symptomatic heart failure and are contraindicated in patients with New York Heart Association class III or IV heart failure.
- If a thiazolidinedione is used, pioglitazone is recommended because of the greater concern about atherogenic lipid profiles and a potential increased risk for cardiovascular events with rosiglitazone.

- **DPP-IV inhibitors —Dipeptidyl peptidase IV (DPP-IV) is a ubiquitous enzyme that deactivates a variety of other bioactive peptides, including glucagon-like peptide-1 and gastric inhibitory peptide; therefore, its inhibition could potentially affect glucose regulation through multiple effects.**

Drugs belonging to this class are:

- Sitagliptin[6] (Januvia)
- Vildagliptin[7] (Galvus)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Gemigliptin (Zemiglo)
- Anagliptin
- Teneligliptin
- Alogliptin
- Trelagliptin
- Omarigliptin (MK-3102) (approved in Japan in 2015,[12] developed by Merck & Co.; research showed that omarigliptin can be used as once-weekly treatment and generally well-tolerated throughout the base and extension studies[13])
- Evogliptin
- Dutogliptin (being developed by Phenomix Corporation), Phase III[15]

- Glucagon-like peptide 1 agonists — Exenatide , liraglutide.Lixisenatide,Albiglutid and Dulaglutide are glucagon-like peptide 1 (GLP-1) analogs that are administered subcutaneously. They are approved in the United States by the FDA for the treatment of type 2 diabetes in patients not sufficiently controlled with diet, exercise, or oral agents.
- 2 studies-LEADER-Liraglutide and SUSTAIN-Semaglutide.
- Exenatide (requires two daily injections or a once weekly injection) or liraglutide (one daily injection) could be considered as add-on drugs for patients with type 2 diabetes who are poorly controlled on maximal doses of one or two oral agents.

- GLP-1 levels are decreased in type 2 diabetes , and GLP-1 regulation may be abnormal in type 1 diabetes .
- GLP-1 exerts many effects
- Pancreas: - by increasing insulin production and secretion.
- - by decreasing Glucagon secretin.
- Liver-by decreasing glucose production.
- GI tract- slow gastric emptying , inhibit inappropriate post-meal glucagon release , and reduce food intake . Owing in part to the effects of GLP-1 on slowed gastric emptying and its well recognized side effects of nausea and vomiting, therapy with GLP-1 and its analogs is associated with weight loss.
- Brain-Steaty.
- Heart-decrease Bp and increased heart rate.
- GLP-1 exhibits a short half-life of one to two minutes due to N-terminal degradation by the enzyme dipeptidyl peptidase IV (DPP-IV) . This necessitates continuous infusion of GLP-1 to achieve steady state levels in pharmacologic studies .

- Alpha-glucosidase inhibitors —The alpha-glucosidase inhibitors (acarbose, miglitol, voglibose) have been studied extensively .
- Taken orally, they inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides in a dose-dependent fashion.
- These drugs slow absorption of glucose; the slower rise in postprandial blood glucose concentrations is potentially beneficial in both type 1 and type 2 diabetes. In older patients with type 2 diabetes, acarbose may also increase insulin sensitivity .
- In patients with type 1 diabetes, acarbose therapy decreases the amplitude of postprandial glycemic excursions and lowers hemoglobin A1C (A1C) values .

- Acarbose and voglibose have also been evaluated for the prevention of type 2 diabetes.
- Because they act by a different mechanism, the alpha-glucosidase inhibitors, acarbose and miglitol, have additive hypoglycemic effects in patients receiving diet, sulfonylurea, metformin, or insulin therapy . This class of drugs is less potent than the sulfonylureas or metformin, lowering A1C by only 0.5 to 0.8 percentage points.
- The main side effects, which may limit their acceptance, are flatulence and diarrhea.

- Pramlintide — Amylin (also known as islet amyloid polypeptide) is a peptide hormone secreted by pancreatic beta cells in conjunction with insulin in response to nutrient stimuli
- Pramlintide is a synthetic analog of human amylin that slows gastric emptying, reduces postprandial rises in blood glucose concentrations, and modestly improves A1C concentrations in patients with type 1 and type 2 diabetes when injected subcutaneously three times per day.
- Pramlintide is only approved for use in patients also taking insulin. It may be considered for patients with type 2 diabetes inadequately controlled on insulin who are overweight or experience weight gain refractory to lifestyle measures.

- SGLT2 inhibitors —
- The SGLT2 is expressed in the proximal tubule and mediates reabsorption of approximately 90 percent of the filtered glucose load. SGLT2 inhibitors promote the renal excretion of glucose and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes. The ability to lower blood glucose and A1C levels is limited by the filtered load of glucose and the osmotic diuresis that is caused by this therapy. The glucose-lowering effect is independent of insulin (beta cell function and insulin sensitivity). Thus, they do not usually cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia. SGLT2 inhibitors decrease blood pressure and weight.

- Glycemic efficacy – SGLT2 inhibitors are relatively weak glucose-lowering agents, similar in potency to the DPP-4 inhibitors.
- As examples Drugs in the SGLT2 inhibitors class include empagliflozin, canagliflozin, dapagliflozin, ipragliflozin ertugliflozin
- Cardiovascular effects –.
- Weight loss – SGLT2 inhibitors decrease weight difference -2.36 kg, 95% CI -2.85 to -1.88) Adverse effects
- Genitourinary tract – In clinical trials, side effects of SGLT2 inhibitors include an increased incidence of vulvovaginal candidiasis SGLT2 inhibitors increase the rate of urinary tract infections (. In addition, the US Food and Drug Administration (FDA) has received reports of potentially fatal urosepsis and pyelonephritis requiring hospitalization .
- There are no long-term safety data with regard to the effects of chronic glucosuria on the urinary tract.

- Hypotension – SGLT2 inhibitors cause an osmotic diuresis and intravascular volume contraction•
- Bone fracture – Bone fractures occur more frequently in patients taking canagliflozinTreatment".)
- Dosing – Canagliflozin is taken orally before the first meal of the day . The initial dose is 100 mg once daily, and it can be increased to 300 mg daily
- Dapagliflozin (10 mg once daily) can be taken any time of day, with or without food..
- Empagliflozin is taken orally once daily in the morning, with or without food [. The initial dose is 10 mg daily, and it can be increased to 25 mg once daily to achieve glycemic goals

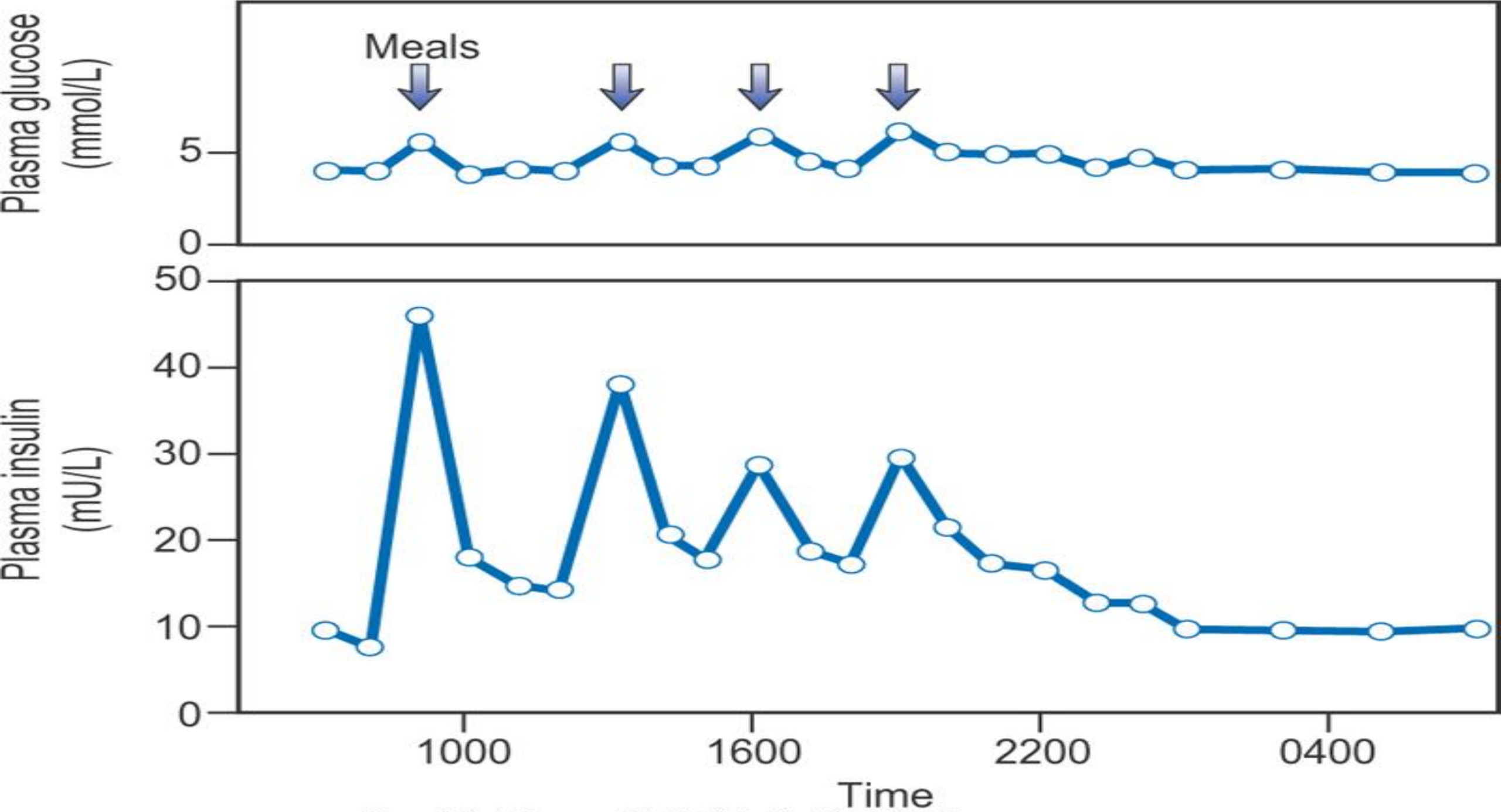
General principles of insulin therapy in diabetes mellitus

- Insulin is used in the treatment of patients with diabetes of all types. The need for insulin depends upon the balance between insulin secretion and insulin resistance.
- All patients with type 1 diabetes need insulin treatment permanently, unless they receive an islet or whole organ pancreas transplant; many patients with type 2 diabetes will require insulin as their beta cell function declines over time.

- In healthy individuals a sharp increase in insulin occurs after meals; this is superimposed on a constant background of secretion.

- Insulin therapy attempts to reproduce this pattern, but ideal control is difficult to achieve for four reasons:

1. In normal subjects, insulin is secreted directly into the portal circulation and reaches the liver in high concentration; about 50% of the insulin produced by the pancreas is cleared by the liver. By contrast, insulin injected subcutaneously passes into the systemic circulation before passage to the liver. Insulin-treated patients therefore have lower portal levels of insulin and higher systemic levels relative to the physiological situation.
2. Subcutaneous soluble insulin takes 60-90 minutes to achieve peak plasma levels, so the onset and offset of action are too slow.
3. The absorption of subcutaneous insulin into the circulation is variable.
4. Basal insulin levels are constant in normal people, but injected insulin invariably peaks and declines in people with diabetes, with resulting swings in metabolic control.

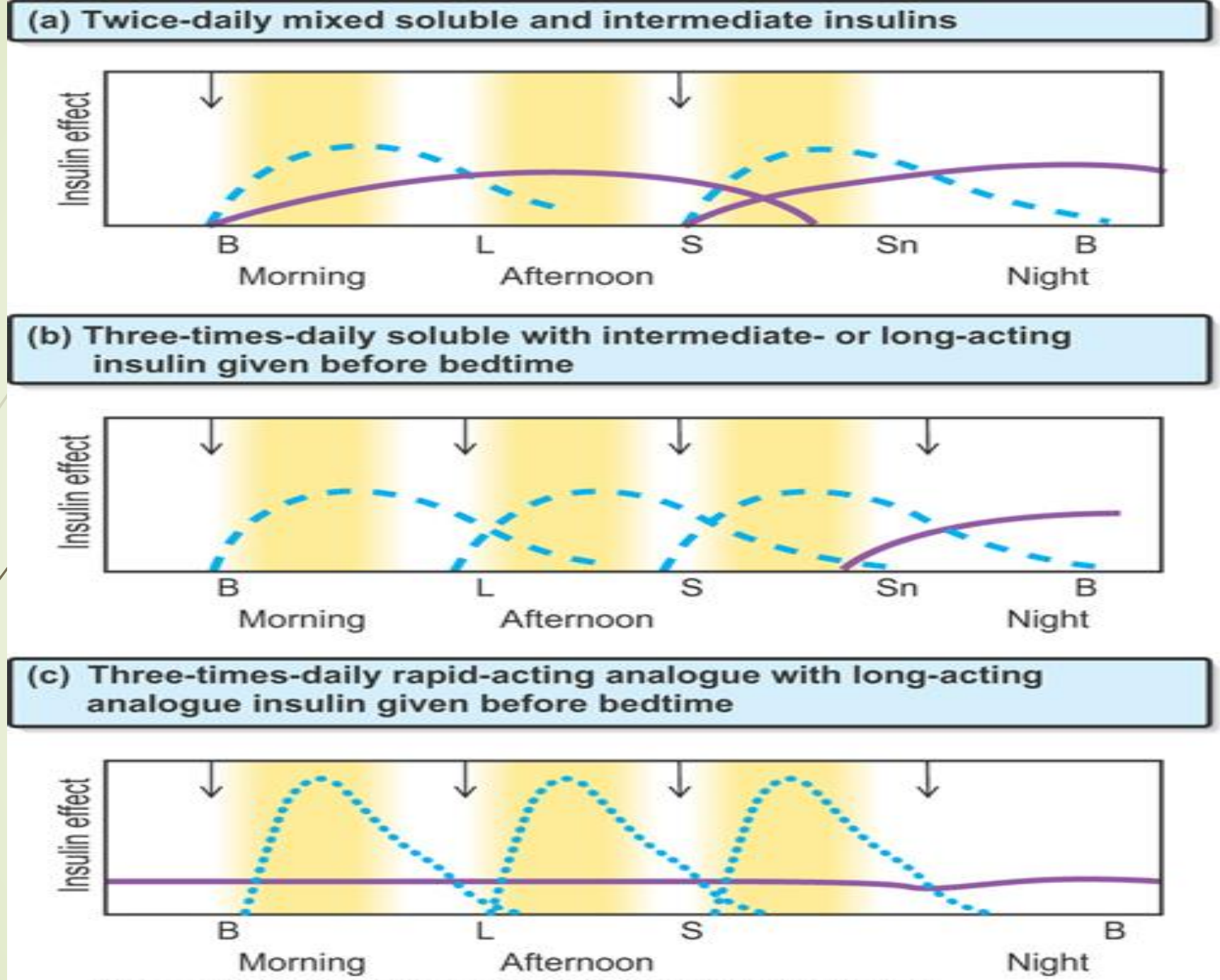


Insulin Preparations

Class	Agents
Human insulins	Regular, NPH, lente, ultralente
Insulin analogues	Aspart, glulisine, lispro, glargine,detemir,degludec
Premixed insulins	Human 70/30, 50/50 Humalog mix 75/25 Novolog mix 70/30

- A multiple injection regimen with short-acting insulin and a longer-acting insulin at night is appropriate for most younger patients.

- The advantages of multiple injection regimens are that the insulin and the food go in at roughly the same time so that meal times and sizes can vary, without greatly disturbing metabolic control.



Duration of Action of Standard Insulins and Insulin Analogues

Insulin	Onset of Action	Peak of Action	Effective Duration
Standard			
Regular	30-60 min	2-3 h	8-10 h
NPH	2-4 h	4-10 h	12-18 h
Zinc Insulin(Lente)	2-4 h	4-12 h	12-20 h
Extended Zinc Insulin(Ultralente)	6-10 h	10-16 h	18-24 h
Analogues			
glulisine,Aspart,Lispro	5-15 min	30-90 min	4-6 h
Glargine	2-4 h	None	20-24 h
Insulin detemir	About two hours	Three to nine hours	6 to 24 hours
Insulin degludec	About two hours	No peak	>40 hours

The Basal-Bolus Insulin Concept

- Basal insulin
  - Controls glucose production between meals and overnight
  - Nearly constant levels
  - 50% of daily needs
- Bolus insulin (mealtime or prandial)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour postmeal
  - 10% to 20% of total daily insulin requirement at each meal
- For ideal insulin replacement therapy,
- each component should come from a
- different insulin with a specific profile.

Barriers to Using Insulin

- Patient resistance
  - Perceived significance of needing insulin
  - Fear of injections
  - Complexity of regimens
  - Pain, lipohypertrophy
- Physician resistance
  - Perceived cardiovascular risks
  - Lack of time and resources to supervise treatment
- Medical limitations of insulin treatment
  - Hypoglycemia
  - Weight gain

Insulin Injection Devices

- Insulin pens
- Faster and easier than syringes
  - Improve patient attitude and adherence
  - Have accurate dosing mechanisms, but inadequate mixing may be a problem

Insulin Pumps

- Continuous subcutaneous insulin infusion (CSII)
  - External, programmable pump connected to an indwelling subcutaneous catheter to deliver rapid-acting insulin

- Intraperitoneal insulin infusion
  - Implanted, programmable pump with intraperitoneal catheter. Not available in the United States

D.Dx of Early Morning Hyperglycemia

Somogi Effect :

High sugar in early morning due to rebound response to hypoglycemia at 2-3 AM, treatment is by decreasing evening NPH dose.

Down phenomenon :

High sugar in early morning due to physiologic release of GH and ACTH at early morning hours.

Guide to adjusting insulin dosage according to blood glucose test results

	Blood glucose persistently too high	Blood glucose persistently too low
Before breakfast	Increase evening long-acting insulin	Reduce evening long-acting insulin
Before lunch	Increase morning short-acting insulin	Reduce morning short-acting insulin or increase mid-morning snack
Before evening meal	Increase morning long-acting insulin or lunch short-acting insulin	Reduce morning long-acting insulin or lunch short-acting insulin or increase mid-afternoon snack
Before bed	Increase evening short-acting insulin	Reduce evening short-acting insulin

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[a]	or GLP-1-RA	or Insulin[a]	or GLP-1-RA
or Insulin[a]	or Insulin[a]		or Insulin[a]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).