# Therapy of Diabetes Mellitus

# Therapy of Diabetes Mellitus

- **Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia.**
- **It is associated with abnormalities in carbohydrate, fat, and protein metabolism.**
- **It may result in chronic complications including microvascular, macrovascular, and neuropathic disorders.**

# Therapy of Diabetes Mellitus

- **DM is the leading cause of blindness and end-stage renal disease.**
- **It may result in lower extremity amputations, and cardiovascular events.**

## TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

| | TYPE 1 | TYPE 2 |
|---|---|---|
| **Etiology** | Autoimmune destruction of pancreatic β-cells | Insulin resistance, with inadequate β-cell function to compensate |
| **Insulin levels** | Absent or negligible | Typically higher than normal |
| **Insulin action** | Absent or negligible | Decreased |
| **Insulin resistance** | Not part of syndrome but may be present (e.g., in obese patients) | Yes |
| **Age of onset** | Typically <30 years | Typically >40 years |
| **Acute complications** | Ketoacidosis<br>Wasting | Hyperglycemia (can lead to hyperosmotic seizures and coma) |
| **Chronic complications** | Neuropathy<br>Retinopathy<br>Nephropathy<br>Peripheral vascular disease<br>Coronary artery disease | Same as type 1 |
| **Pharmacologic interventions** | Insulin | A number of drug classes are available, including insulin if other therapies fail |

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

# Drug-induced Diabetes Mellitus

1. Pyriminil (vacor) (rodenticide) – loss of pancreatic β-cells.
2. Pentamidine – cytotoxic effect on pancreatic β-cells (type 1).
3. Nicotinic acid – impairment of insulin action.
4. Glucocorticoids – Metabolic effects and insulin antagonism.
5. Thyroid hormones – increase hepatic glucose production.
6. Growth hormone - reduces insulin sensitivity resulting in mild hyperinsulinemia, and increased blood glucose levels
7. Diazoxide: inhibition of insulin secretion.

# Drug-induced Diabetes Mellitus

8. β-adrenergic agonists – glycogenolysis, and gluconeogenesis.
9. Thiazides – hypokalemia-induced inhibition of insulin release.
10. Phenytoin – induces insulin insensitivity.
11. Interferone – β-cell destruction (type 1)
12. Chronic alcohol - insulin resistance and pancreatic β-cell dysfunction.
13. Cyclosporine – suppresses insulin production and release.

# Drug-induced Diabetes Mellitus

14. HIV protease inhibitors - insulin resistance with insulin deficiency relative to hyper-glucagonemia.
15. Atypical antipsychotics (clozapine and olanzapine) – weight gain and insulin resistance.
16. Megestrol acetate – insulin resistance.
1. Others

# Therapy of Diabetes Mellitus

## Desired Outcome:

## The primary goals of DM management are:

1. **To reduce the risk for microvascular and macrovascular disease complications.**
2. **To ameliorate symptoms.**
3. **To reduce mortality.**
4. **To improve quality of life.**
5. **To minimize weight gain and hypoglycemia.**

# Therapy of Diabetes Mellitus

- **Early diagnosis and treatment to near-normal glycemia reduces the risk of developing microvascular (retinopathy, nephropathy, and neuropathy ) disease complications.**

# Therapy of Diabetes Mellitus

- **Aggressive management of cardiovascular risk factors including smoking cessation, treatment of dyslipidemia, intensive blood pressure control, and antiplatelet therapy are needed to reduce the risk of developing macrovascular disease (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease).**

# Therapy of Diabetes Mellitus

- **Hyperglycemia also contributes to poor wound healing by compromising white blood cell function and altering capillary function.**
- **Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are severe manifestations of poor diabetes control, always requiring hospitalization.**

# Nonpharmacologic Therapy

1. **Screening.**
2. **Monitor for:**

- **blood glucose, $HbA_{1c}$, fasting lipid profile, urinary albumin (urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate (eGFR), diabetic neuropathy, and dilated eye examination.**

# Nonpharmacologic Therapy

3. **Glycemic goals:**

- **$HbA_{1c}$ goal for non-pregnant adults of <7%, or of <6.5% without significant hypoglycemia.**
- **Hospital: Critically ill glucose: 140-180 mg/dL, or more stringent guidelines down to 110-140 mg/dL (if without hypoglycemia).**

# Nonpharmacologic Therapy

5. **Medical nutrition therapy:**

- **Weight loss is recommended for all insulin-resistant /overweight or obese individuals.**

a) **Either low-carbohydrate, low-fat, calorie-restricted diets, or Mediterranean diets.**

b) **Healthier eating behaviors leading to sustained weight loss over time is more important than a specific diet.**

# Nonpharmacologic Therapy

- **In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations.**
- **Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia.**
- **Saturated fat should be <7% of total calories.**

# Nonpharmacologic Therapy

- **A Mediterranean-style eating pattern, rich in monounsaturated fatty acids (olive oil), may benefit glycemic control and CVD risk factors and can, therefore, be recommended as an effective alternative to a lower-fat, higher-carbohydrate eating pattern.**
- **Consider financial and cultural food issues.**
- **Discourage bedtime and between-meal snacks, and set realistic goals.**

# Nonpharmacologic Therapy

- **A diet low in fat is recommended for patients with CVD.**
- **Avoid a high-protein diet in patients with nephropathy.**
- **Supplement with all of the essential vitamins and minerals.**

# Nonpharmacologic Therapy

6. **Physical Activity:**

- **Aerobic exercise improves insulin sensitivity, modestly improves glycemic control, reduces cardiovascular risk, contributes to weight loss or maintenance, and improves well-being.**
- **Physical activity goals include at least 150 min/wk of moderate intensity exercise (50%-70% maximal heart rate) spread over at least 3 days a week with no more than 2 days between activities.**

# Nonpharmacologic Therapy

- **Resistance/Strength training is recommended at least 2 times a week in patients without proliferative diabetic retinopathy.**

# Nonpharmacologic Therapy

7. **Patient Education:**

- **It is not appropriate to give patients with DM brief instructions and a few pamphlets.**
- **Diabetes education, at initial diagnosis and at ongoing intervals over a lifetime, is critical.**
- **Healthy behaviors include healthy eating, being active, monitoring, taking medication, problem solving, reducing risk, and healthy coping.**

# Nonpharmacologic Therapy

- **The patient must be involved in the decision-making process with knowledge of the disease and associated complications.**
- **Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for CVD.**
- **Motivational interviewing techniques to encourage patients to identify barriers that hinder achieving health goals, and then work to solve them, are essential.**

# Other Recommendations

A. **Blood pressure:**

- **Systolic/diastolic blood pressure should be treated to <140 mm / <90 mm Hg.**
- **Lower goals <130 mm Hg / <80 mm Hg may be appropriate for younger patients.**
- **Lifestyle intervention such as weight loss, and diet including reducing sodium and increasing potassium.**
- **Initial drug therapy should be with an ACEi or an angiotensin-receptor blocker (ARB); if intolerant to one, the other should be tried.**

# Other Recommendations

B. **Dyslipidemia:**

- **Lifestyle modification focusing on the reduction of saturated fat, and cholesterol intake; increasing omega-3 fatty acids intake, use of viscous fiber, and plant sterols; weight loss, and increase physical activity should be recommended.**
- **Consider the use of statins according to risks.**

# Other Recommendations

C. **Antiplatelet Therapy:**

- **Use aspirin (75-162 mg daily) for secondary cardioprotection.**

D. **Hospitalized Patients:**

- **Critically ill: IV insulin protocol.**
- **Noncritically ill: scheduled subcutaneous insulin with basal, nutritional, and correction coverage.**

E. **Psychosocial:**

- **Assess the patient's psychological and social situation as an ongoing part of the medical management of diabetes.**

# Prevention of Diabetes Mellitus

A. Efforts to prevent type 1 were all unsuccessful.

B. Prevention of type 2 diabetes:

1. The "4 life-style pillars" for the prevention of type 2 diabetes are to:

a) decrease weight.

b) increase aerobic exercise.

c) increase fiber.

d) decrease fat intake.

# Prevention of Diabetes Mellitus

2. **Drugs:**

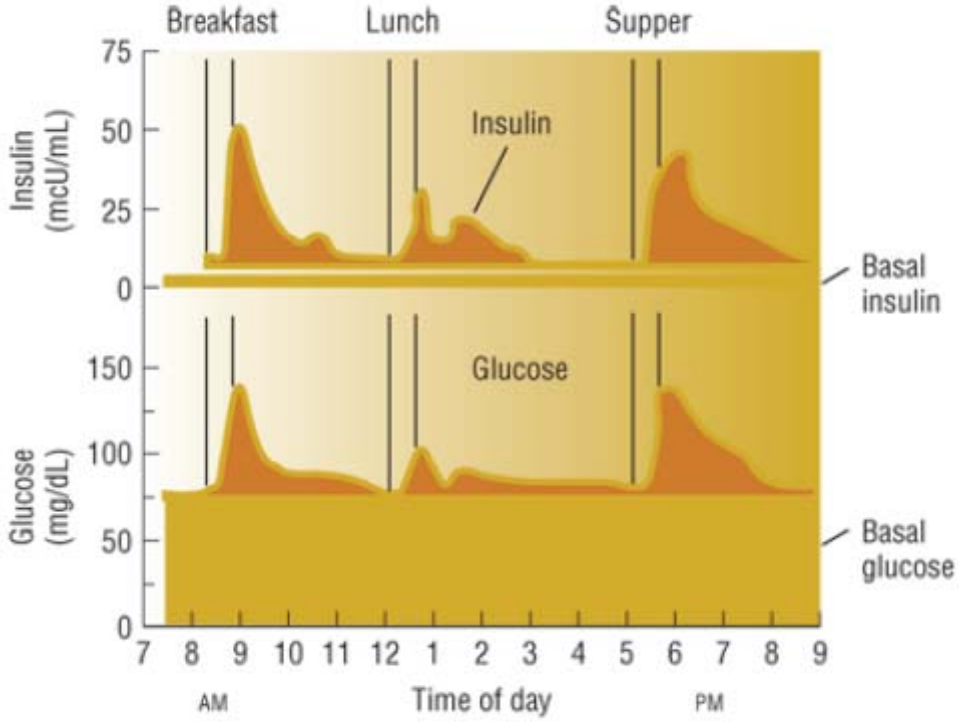
a. **Metformin therapy reduces the risk of developing type 2 DM, especially in obese, <60-year-old patients, and women with prior GDM.**

b. **Rosiglitazone reduces the incidence of type 2 diabetes.**

c. **Acarbose and liraglutide decrease progression to type 2 DM.**

# Pharmacologic Therapy (Type 1 DM)

- **All patients with type 1 DM require insulin.**




**Relationship between insulin and glucose over the course of a day.**

# Pharmacologic Therapy (Type 1 DM)

- **Attempt to mimic normal secretion of insulin.**
- **One or two injections daily of insulin will in NO way mimic normal physiology, and therefore is unacceptable.**
- **The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve adequate blood glucose control throughout the day.**

# Insulin

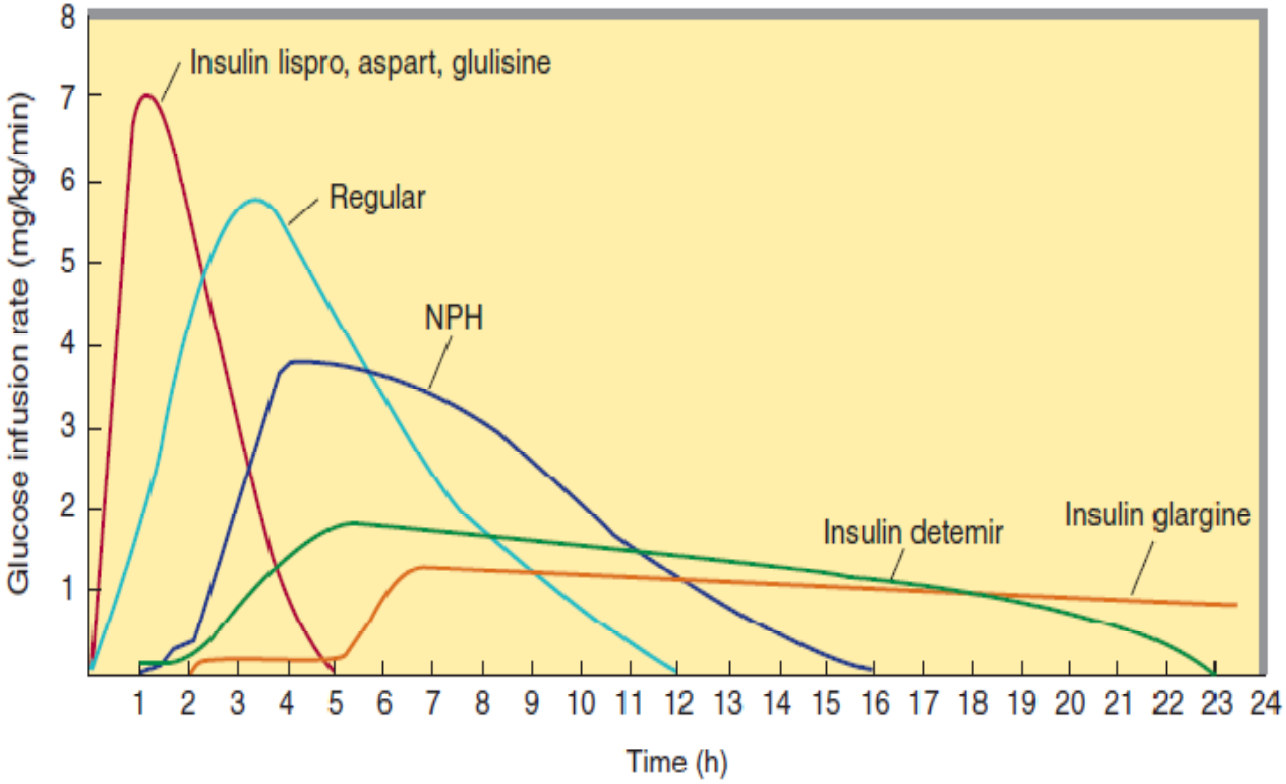



**FIGURE 41–5** Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

**Pharmacokinetics of Select Insulins Administered Subcutaneously**

| Type of Insulin | Onset (Hours) | Peak (Hours) | Duration (Hours) | Maximum Duration (Hours) | Appearance |
|---|---|---|---|---|---|
| ***Rapid acting*** | | | | | |
| Aspart | 15-30 min | 1-2 | 3-5 | 5-6 | Clear |
| Lispro | 15-30 min | 1-2 | 3-4 | 4-6 | Clear |
| Glulisine | 15-30 min | 1-2 | 3-4 | 5-6 | Clear |
| Technosphere[a] | 5-10 min | 0.75-1 | ~3 | ~3 | Powder |
| ***Short-acting*** | | | | | |
| Regular | 0.5-1.0 | 2-3 | 4-6 | 6-8 | Clear |
| ***Intermediate acting*** | | | | | |
| NPH | 2-4 | 4-8 | 8-12 | 14-18 | Cloudy |
| ***Long acting*** | | | | | |
| Detemir | ~2 hours | —[b] | 14-24 | 20-24 | Clear |
| Glargine (U-100) | ~2-3 hours | —[b] | 22-24 | 24 | Clear |
| Degludec | ~2 hours | —[b] | 30-36 | 36 | Clear |
| Glargine (U-300) | ~2 hours | —[b] | 24-30 | 30 | Clear |

[a]Technosphere insulin is inhaled.

[b]Glargine is considered "flat" though there may be a slight peak in effect at 8-12 hours, and with detemir at ~8 hours, but both have exhibited peak effects during comparative testing, and these peak effects may necessitate changing therapy in a minority of type 1 DM patients. Degludec and U-300 insulin glargine appears to have less peak effect compared to U-100 insulin glargine.

# Intensive Insulin Regimen

| | 7 am meal | 11 am meal | 5 pm meal | Bed time |
|---|---|---|---|---|
| 2 doses (R or rapid acting) + N | R, L, A, Glu + N | | R, L, A, Glu + N | |
| 3 doses (R or rapid acting) + N | R, L, A, Glu + N | R, L, A, Glu | R, L, A, Glu + N | |
| 4 doses (R or rapid acting) + N | R, L, A, Glu | R, L, A, Glu | R, L, A, Glu | N |
| 4 doses (R or rapid acting) + N | R, L, A, Glu + N | R, L, A, Glu | R, L, A, Glu | N |
| 4 doses (R or rapid acting) + long acting | R, L, A, Glu | R, L, A, Glu | R, L, A, Glu | G or D |
| CS-II pump | Adjusted basal + Bolus | Adjusted basal + Bolus | Adjusted basal + Bolus | |
| 3 prandial doses | P added to previous regimens | P added to previous regimens | P added to previous regimens | |

A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir or degludec; G, glargine; GLU, glulisine; L, lispro; N, NPH; P, pramlintide; R, regular.

# Pharmacologic Therapy (Type 1 DM)

- **The simplest regimens that can approximate physiologic insulin release use “split-mixed” injections consisting of a morning dose of an intermediate acting insulin such as NPH and a “bolus” rapid-acting insulin or regular insulin prior to the morning and evening meals.**
- **The morning intermediate-acting insulin dose provides basal insulin during the day and provides “prandial” coverage for the midday meal.**

# Pharmacologic Therapy (Type 1 DM)

- **The evening intermediate-acting insulin dose provides basal insulin throughout the evening and overnight.**
- **That is acceptable when patients have fixed timing of meals and carbohydrate intake.**
- **However, That regimen may not achieve good glycemic control overnight without causing nocturnal hypoglycemia.**
- **Moving the evening NPH dose to bedtime may improve glycemic control and reduce the risk of nocturnal hypoglycemia.**

# Pharmacologic Therapy (Type 1 DM)

- **“Basal-bolus” regimens using multiple daily injections (MDIs) may mimic normal insulin physiology, with a combination of intermediate- or long-acting insulin to provide the basal component, and a rapid-acting insulin to provide prandial coverage.**
- **Long-acting insulins include insulin detemir, glargine, or degludec.**

# Pharmacologic Therapy (Type 1 DM)

- **Bolus or prandial insulin can be provided by either regular insulin or rapid-acting insulin analogs: lispro, aspart, or glulisine.**
- **The rapid onset and short duration of action of the rapid-acting insulin analogs more closely replicate normal physiology than does regular insulin.**
- **Remember that regular insulin is soluble or crystalline zink insulin.**

# Pharmacologic Therapy (Type 1 DM)

- **Approximately 50% of total daily insulin replacement should be in the form of basal insulin and the other 50% in the form of bolus insulin, divided between meals.**
- **In new patients, the initial total daily dose is usually between 0.5 and 0.6 units/kg/day.**

# Pharmacologic Therapy (Type 1 DM)

- **Continuous subcutaneous insulin infusion (CS-II) or insulin pumps using a rapid-acting insulin is the most sophisticated and precise method for insulin delivery. In highly motivated patients, it achieves excellent glycemic control more than MDI.**
- **Insulin pump therapy may also be paired to continuous glucose monitoring (CGM), which allows calculation of a correct insulin dose, as well as alert the patient to hypoglycemia and hyperglycemia.**

# Pharmacologic Therapy (Type 1 DM)

- **Insulin pumps require greater attention to detail and more frequent self-monitored blood glucose (SMBG) than does a basal-bolus MDI regimen.**
- **Patients need extensive training on how to use and maintain their pump.**

# Pharmacologic Therapy (Type 1 DM)

- **All patients treated with insulin should be instructed how to recognize and treat hypoglycemia.**
- **At each visit, patients with type 1 DM should be evaluated for hypoglycemia including the frequency and severity of hypoglycemic episodes.**

# Pharmacologic Therapy (Type 1 DM)

- Hypoglycemic unawareness may result from autonomic neuropathy or from frequent episodes of hypoglycemia.
- The loss of warning signs of hypoglycemia is a relative contraindication to continued intensive therapy.

# Pharmacologic Therapy (Type 1 DM)

- **Patients who have erratic postprandial glycemic control despite proper insulin dose may benefit from addition of the amylino-mimetic pramlintide.**
- **Amylin suppresses endogenous production of glucose in the liver.**
- **Pramlintide taken prior to each meal can improve postprandial blood glucose control.**
- **It is NOT a substitute for bolus insulin.**

# Pharmacologic Therapy (Type 1 DM)

- **Pramlintide can NOT be mixed with insulin requiring the patient to take an additional injection at each meal.**
- **When pramlintide is initiated, the dose of prandial insulin should be reduced by 30% to 50%, to prevent hypoglycemia.**

# Pharmacologic Therapy (Type 1 DM)

**Pramlintide:**

1. **Slows gastric emptying – vagally mediated.**
2. **Reduces glucagon secretion.**
3. **Promotes satiety or reduce appetite - centrally.**
4. **Produces moderate weight loss.**

- **Main adverse effects include: Hypoglycemia and GIT disturbances (nausea, vomiting, anorexia).**

# Pharmacologic Therapy (Type 2 DM)

1. Symptomatic patients may initially require treatment with insulin or combination therapy.
2. All patients are treated with therapeutic life-style modification.
3. Patients with $HbA_{1c}$ of 7.5% or less are usually treated with metformin (which is unlikely to cause hypoglycemia).
4. Those with $HbA_{1c}$ more than 7.5% but less than 8.5% could be initially treated with a single agent, or combination therapy.

# Pharmacologic Therapy (Type 2 DM)

5. **Patients with higher initial $HbA_{1c}$ will require two agents or insulin.**
6. **All therapeutic decisions should consider the needs and preferences of the patient, if medically possible.**
7. **Obese patients without contraindications are often started on metformin which is titrated to 2,000 mg/day.**

# Pharmacologic Therapy (Type 2 DM)

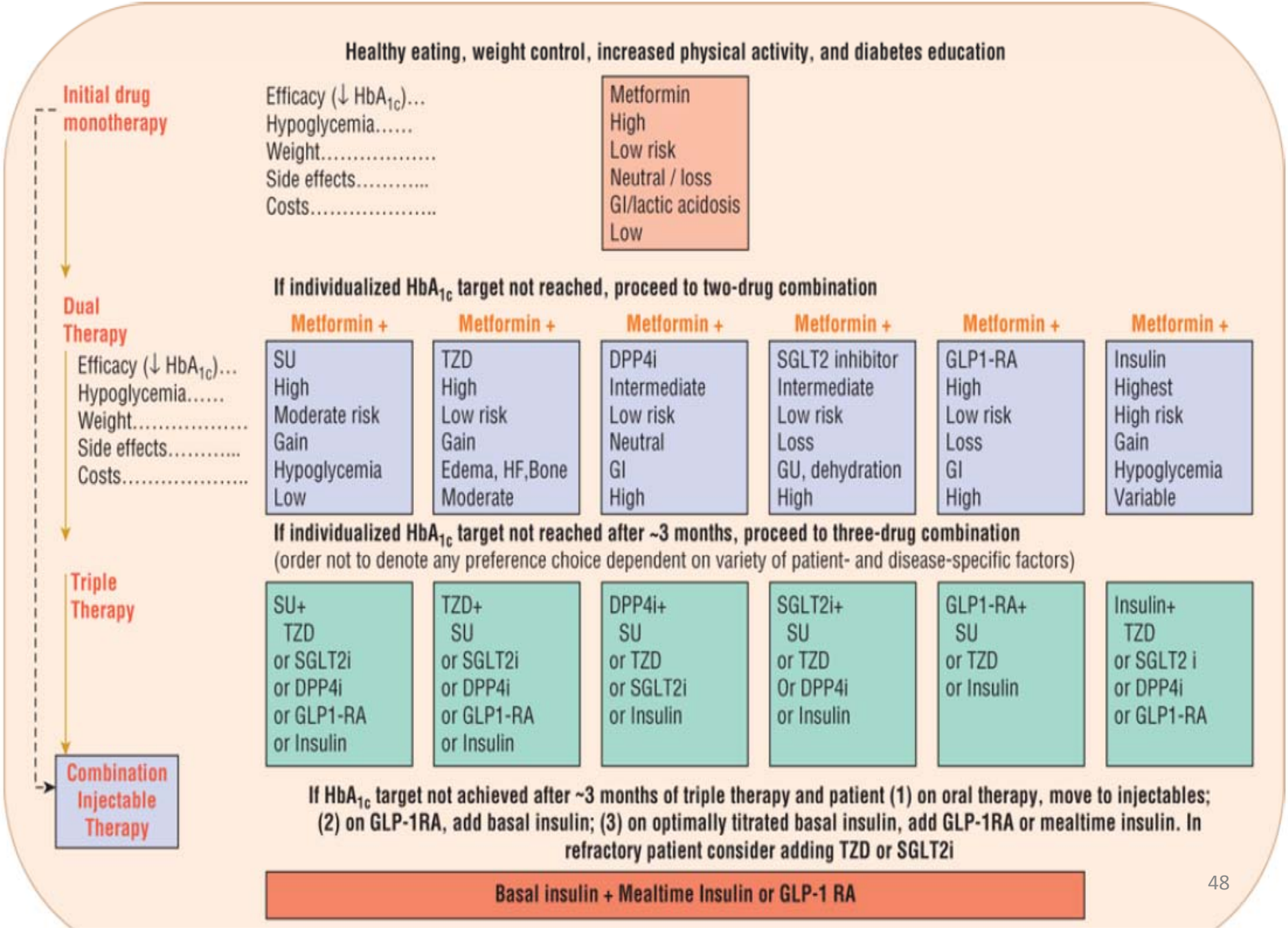
8. Non-obese patients are more likely to be insulinopenic, necessitating medications that may increase insulin secretion.
9. An insulin secretagogue, such as a sulfonylurea, is often added second.

- Sulfonylureas have several potential drawbacks including weight gain and hypoglycemia; they do not produce a durable glycemic response.

# Pharmacologic Therapy (Type 2 DM)

9. Better choices include DPP-4 inhibitors and GLP-1 receptor agonist but they have therapeutic and safety limitations.
10. TZDs produce a more durable glycemic response and are unlikely to cause hypoglycemia, but weight gain, fluid retention and the risk of new onset heart failure have limited their use.

Antihyperglycemic Therapy Recommendations in Type 2 Diabetes. General Recommendations. *(Data from reference 20.)*



| Drug & class | Dose ( mg) | Duration of action (hours) | Drug | Dose ( mg) | Duration of action (hours) |
|---|---|---|---|---|---|
| **Sulfonylureas** | | | | | |
| Glimepiride | 1-8 | 24 | Glipizide | 2.5-40 | 12-24 |
| Glyburide | 1.25-20 | 12-24 | Glipizide extended release | 5-20 | 24 |
| Micronized glyburide | 1-12 | 24 | | | |
| **Non-sulfonyureas secretagogues** | | | | | |
| Rapaglinide | 0.5-4 | 2-3 | Nateglinide | 60-120 | 2-4 |
| **Biguanides** | | | | | |
| Metformin | 500-2500 | 6-12 | Metformin extended release | 1500-2000 | 24 |
| **Thiazolidinediones** | | | | | |
| Rosiglitazone | 4-8 | Poorly correlated with half-life. Max effect ~ 4 weeks | Poiglitazone | 15-45 | Poorly correlated with half-life. Max effect ~ 4 weeks |
| **α-glucosidae inhibitors** | | | | | |
| Acarbose | 25-50 | Affects absorption of carbohydrates in a single meal | Miglitol | 25-100 | Affects absorption of carbohydrates in a single meal |
| **GLP-1 receptor agonists / Incretin mimetics** | | | | | |
| Exenatide | 5-10 mcg | 10 | Liraglutide | 0.6-1.8 | 24 |
| **DPP-4 inhibitors** | | | | | |
| Sitagliptin | 100 | 24 | Saxagliptin | 2.5-5 | 24 |
| Linagliptin | 5 | 24 | | | |
| **Amylin mimetics** | | | | | |
| Pramlintide | 15-60 (type 1 DM) 60 or 120 (type 2 DM) | $C_{max}$ 20 min | | | |
| **Bile acid sequestrants** | | | | | |
| Colesevelam | 3750 | N/A | | | |

# Pharmacologic Therapy (Type 2 DM)

**Treatment selection should be based on multiple factors:**

1. **A patient who has had diabetes for several years, due to progressive failure of β-cell function, is more likely to require insulin therapy.**
2. **If the patient has multiple co-morbidities (CVD, dementia, depression, osteoporosis, heart failure, recurrent genitourinary (GU) infections, some medications may be poor choices based on their potential adverse effects.**

# Pharmacologic Therapy (Type 2 DM)

3. If the patient's postprandial blood glucose readings are the primary reason for poor control, pick a medication that addresses postprandial blood glucose excursions.
4. If the patient's fasting blood glucose readings are consistently elevated, a medication that addresses fasting blood glucose would be a better choice.

# Pharmacologic Therapy (Type 2 DM)

5. **Adverse effect profile, contraindications, hypoglycemia potential, and tolerability by the patient, should be considered when selecting therapy.**
6. **Motivation, resources, and potential difficulties with adherence should also influence treatment selection.**

# Pharmacologic Therapy (Type 2 DM)

7. If the patient is an older adult, the risk of hypoglycemia and other adverse effects increases and life expectancy diminishes. These factors should influence medication choices and HbA1c goals.
8. Non-glycemic effects (CVD reduction with medications, lipid effects, blood pressure effects, weight, and durability of $HbA_{1c}$ reduction) may all influence the decision.

# Pharmacologic Therapy (Type 2 DM)

- **It is unlikely that any one drug class will arrest β-cell failure, necessitating combination therapy.**
- **The combination of a TZD and GLP-1 receptor agonist is a good one:**

a) **TZDs reduce apoptosis of β-cells.**

b) **GLP-1 receptor agonists augment pancreatic function.**

- **Metformin, pioglitazone, and exenatide are promising.**

# Glucagon-like peptide-1 (GLP-1) from the GIT

1. It enhances insulin release in response to an ingested meal.
2. It suppresses glucagon secretion.
3. It delays gastric emptying.
4. It decreases appetite.
5. It is degraded by dipeptidyl peptidase-4 (DPP-4).

# Pharmacologic Therapy (Type 2 DM)

**Exenatide:**

- **It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.**
- **Used as adjunctive therapy in patients with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.**
- **Delays gastric emptying.**
- **Suppresses postprandial glucagon release.**

# Pharmacologic Therapy (Type 2 DM)

- It increases insulin secretion in a glucose-dependent manner. The increased insulin secretion is speculated to be due in part to an increase in beta-cell mass, from decreased beta-cell apoptosis, increased beta-cell formation, or both. (Noticed in culture)
- Suppresses appetite.
- Associated with weight loss.

# Pharmacologic Therapy (Type 2 DM)

**Adverse effects:**

1. **Nausea, vomiting, diarrhea: major adverse effect is nausea (45%), which is dose-dependent and declines with time.**
2. **Acute pancreatitis.**
3. **Renal impairment and acute renal injury.**
4. **Not associated with hypoglycemia unless used in combination.**

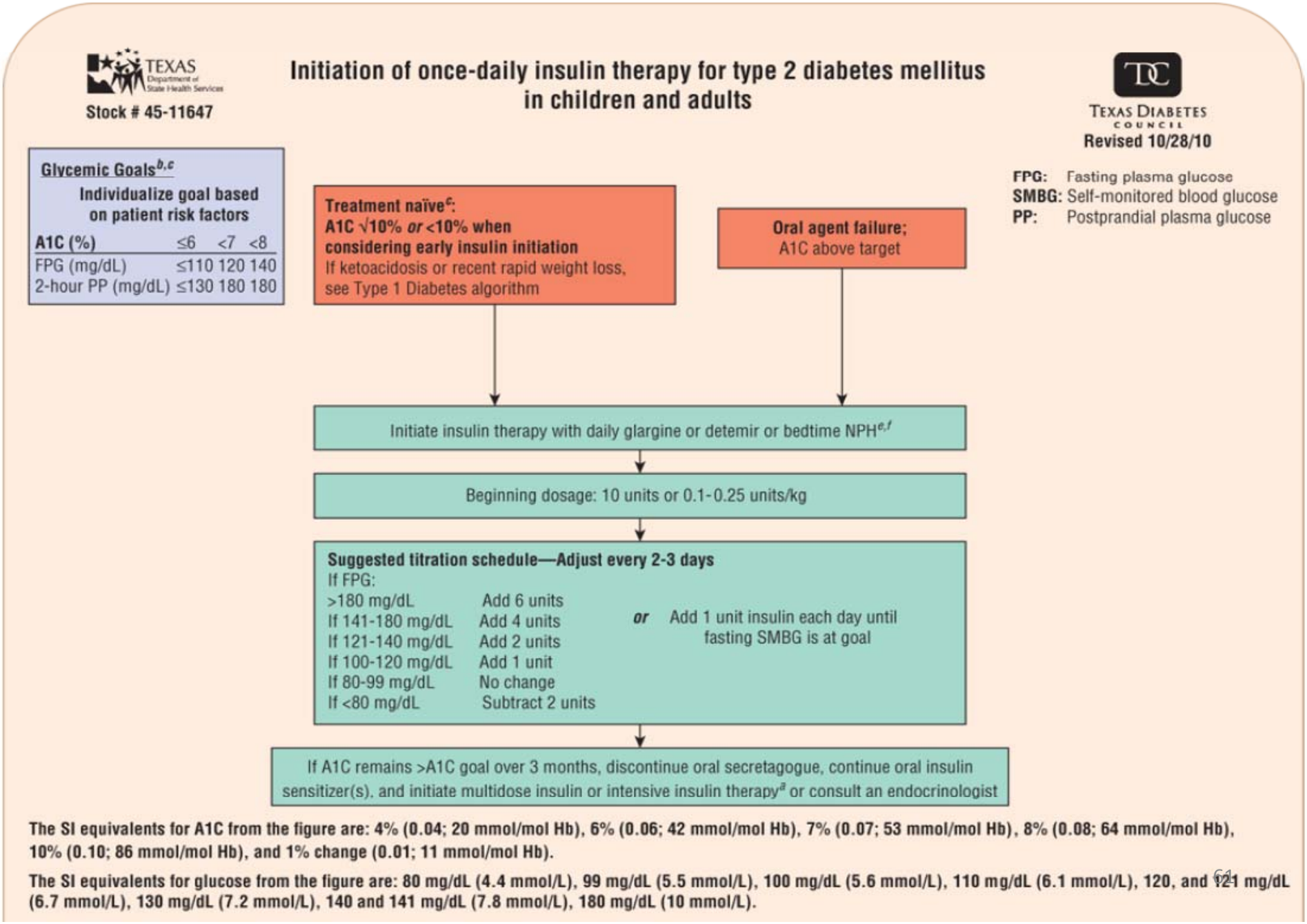
# Pharmacologic Therapy (Type 2 DM)

- **With time some patients with type 2 DM become relatively insulinopenic necessitating insulin therapy.**
- **In these patients use insulin injections at bedtime (intermediate- or long-acting basal insulin) while continuing to use oral agents or GLP-1 receptor agonists for control during the day.**

# Pharmacologic Therapy (Type 2 DM)

- **This strategy is associated with less weight gain, equal efficacy, and lower risk of hypoglycemia when compared to starting prandial insulin or split-mix twice daily insulin regimens.**
- **Any modification of this strategy should depend on fasting and posprandial glucose monitoring, $HbA_{1c}$ monitoring, and time of development of hypoglycemia.**

Simplified Insulin algorithm for type 2 DM in children and adults. See: *www.texasdiabetescouncil.org* for current algorithms. *(Reprinted from the Texas Diabetes Council.)*




**The SI equivalents for A1C from the figure are: 4% (0.04; 20 mmol/mol Hb), 6% (0.06; 42 mmol/mol Hb), 7% (0.07; 53 mmol/mol Hb), 8% (0.08; 64 mmol/mol Hb), 10% (0.10; 86 mmol/mol Hb), and 1% change (0.01; 11 mmol/mol Hb).**

**The SI equivalents for glucose from the figure are: 80 mg/dL (4.4 mmol/L), 99 mg/dL (5.5 mmol/L), 100 mg/dL (5.6 mmol/L), 110 mg/dL (6.1 mmol/L), 120, and 121 mg/dL (6.7 mmol/L), 130 mg/dL (7.2 mmol/L), 140 and 141 mg/dL (7.8 mmol/L), 180 mg/dL (10 mmol/L).**

## Comparative Pharmacology of Antidiabetic Agents

| Agent/Generic Name (Brand Name)/Mechanism | FDA Indications | A1C Efficacy[a] | Adverse Effects | Comments |
|---|---|---|---|---|
| **Insulin**<br>Replaces or augments endogenous insulin | Monotherapy; combined with any oral agent | ↓ A1C[b] ↓FPG[b]<br>↓ PPG[b]<br>↓ TG | Hypoglycemia, weight gain, lipodystrophy, local skin reactions | Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents. |
| **Insulin-Augmenting Agents** | | | | |
| **Nonsulfonylurea secretagogues (glinides)**<br>Repaglinide (Prandin)<br>Nateglinide (Starlix)<br>Stimulates insulin secretion | Monotherapy; combined with metformin or TZD | Monotherapy:<br>↓ A1C ~1% (repaglinide)<br>↓ A1C ~0.5% (nateglinide)<br>Combination: additional 1% ↓ A1C | Hypoglycemia, weight gain | Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG. |
| **Sulfonylureas**<br>Various; see Table 53-28. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization. | Monotherapy; combined with metformin; combined with insulin (glimepiride) | Monotherapy:<br>↓ A1C ~1%<br>Combination: additional 1% ↓ in A1C | Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare | Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week). |

| Incretin-Based Therapies | | | | |
|---|---|---|---|---|
| **Glucagonlike peptide-1 receptor agonists/incretin mimetic**<br>Exenatide (Byetta)<br>Liraglutide (Victoza)<br>Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety | Monotherapy (exenatide only)<br>Combined with metformin, SFU, or TZD, combined with metformin + SFU; combined with metformin + TZD | Monotherapy:<br>↓ A1C 0.8%–0.9%<br>Combination: additional 1% ↓ in A1C | GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis | Weight loss.<br>Exenatide: take within 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart).<br>Liraglutide: Do not use if personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.<br>Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis with both drugs. |
| **DPP-4 inhibitors**<br>Sitagliptin (Januvia)<br>Saxagliptin (Onglyza)<br>Linagliptin (Tradjenta)<br>Stimulates insulin secretion and reduces postprandial glucagon levels | Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin only) | Monotherapy:<br>↓ A1C 0.5%–0.8%<br>Combination:<br>↓ A1C 0.5%–0.9% | Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare) | Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin and sazagliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis. |

| Amylin Receptor Agonists | | | | |
|---|---|---|---|---|
| **Amylin mimetic**<br>Pramlintide (Symlin) | Type 1: Adjunct to mealtime insulin | T1: ↓ A1C 0.33%<br>T2: ↓ A1C 0.40% | GI: nausea, decreased appetite | Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis. |
| Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety | Type 2: Adjunct to mealtime insulin; ± SFU and metformin | | Headache; hypoglycemia; weight loss (mild) | |
| **Insulin Sensitizers** | | | | |

| Insulin Sensitizers | | | | |
|---|---|---|---|---|
| **Biguanides**<br>Metformin (Glucophage)<br>↓ Hepatic glucose output;<br>↑ peripheral glucose uptake | Monotherapy; combined with SFU or TZD; or with insulin | Monotherapy: ↓ A1C ~1%<br>Combination: additional 1% ↓ in A1C | GI: nausea, cramping, diarrhea; lactic acidosis (rare) | Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction. |
| **Thiazolidinediones**<br>Rosiglitazone (Avandia)<br>Pioglitazone (Actos)<br>Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output | Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD | Monotherapy: ↓ A1C ~1%<br>Combination: additional 1% ↓ in A1C | Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in women) | Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older women. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks). |

## Delayers of Carbohydrate Absorption

| | | | | |
|---|---|---|---|---|
| **α-Glucosidase inhibitors**<br>Acarbose (Precose)<br>Miglitol (Glyset)<br>Slow absorption of complex carbohydrates | Monotherapy; combined with SFUs, metformin, or insulin | Monotherapy: ↓ A1C ~0.5%<br>Combination: additional ~0.5% ↓ A1C | GI: flatulence, diarrhea. Elevations in LFTs seen in doses >50 mg TID of acarbose | Useful for PPG control (↓ PPG 25–50 mg/dL).<br>LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose. |
| **Bile acid sequestrant**<br>Colesevelam (Welchol) | Combined with metformin, SFU, or insulin | ↓ A1C 0.3%–0.4% | Constipation, dyspepsia, and nausea; ↑ TG | Added benefit of ↓ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid. |

[a]Comparative effectiveness data provided for SFUs, glinides, TZDs, and α-glucosidase inhibitors.[307]
[b]Theoretically, unlimited glucose lowering with insulin therapy.
A1C, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; TG, triglycerides; TID, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

# Effect of Some Antidiabetics on Body Weight

| Drug | Effect on body weight |
|---|---|
| Insulin | Weight gain |
| Sulfonylureas | Weight gain |
| Meglitinides | Weight gain |
| Metformin | No change or reduce |
| Thiazolidinediones | Weight gain + fluid retention |
| Amylin Analogues -pramlintide | Moderate weight loss |
| GLP-1 analogues (exenatide) | Weight loss |
| DPP-4 inhibitors (sitagliptin) | Weight neutral |

# Special Populations (Children and Adolescents with Type 2 DM)

- **Type 2 DM is increasing in adolescence probably caused by obesity and physical inactivity.**
- **Need extraordinary efforts on life-style modification measures.**
- **If failed, use metformin, sulfonylureas (or TZDs) or any combination of these may improve glycemic control.**

# Special Populations (Children and Adolescents with Type 2 DM)

- **Insulin therapy is the standard of care when glycemic goals cannot be achieved or maintained with metformin and sulfonylurea.**

# Special Populations (Elderly patients with Type 2 DM)

- Consideration of the risks of hypoglycemia, the extent of co-morbidities, self-care, nutritional status, social support, falls risk, mental status, and life expectancy should all influence glycemic goals and treatment selection.
- Avoidance of both hypo- and hyperglycemia is extremely important.

# Special Populations (Elderly patients with Type 2 DM)

- **Elderly patients may have an altered presentation of hypoglycemia because of loss of autonomic nerve function with age.**
- **DPP-4 inhibitors (Sitagliptin), shorter-acting insulin secretagogues, low-dose sulfonylureas, or α-glucosidase inhibitors may be used.**

# Special Populations (Elderly patients with Type 2 DM)

- DPP-4 inhibitors or α-glucosidase have low risk of hypoglycemia.
- Metformin may be used at low doses if $Cl_{cr}$ is > 30 mL/min/1.73 $m^2$.
- Simple insulin regimens with daily basal insulin may be appropriate.

# Dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin)

- Inhibit DPP-4, the enzyme that degrades incretin hormones.
- Prolong the half-life of endogenous GLP-1.
- Decrease postprandial glucose levels.
- Decrease glucagon concentration.
- Increase circulating GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose-dependent manner.

# Sitagliptin

- Most commonly used in combination with a TZD or metformin, or sulfonylureas.
- May be used as monotherapy.
- Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.
- Dosage should be reduced in patients with impaired renal function
- Weight neutral.

# Sitagliptin

**Adverse effects:**

1. **Nasopharyngitis, upper respiratory infections, headaches**
2. **Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.**
3. **Acute pancreatitis which may be fatal.**
4. **Allergic reactions.**

# Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

- These are true emergencies.
- Insulin given by continuous IV infusion (regular insulin = soluble insulin) to restore the patient's metabolic status is the cornerstone of therapy.
- Pay attention to volume deficits, electrolyte disturbances, and acidosis.
- Treat the precipitating problem.

# Hospitalization for Intercurrent Medical Illness

- **Patients on oral agents may need transient therapy with insulin to achieve adequate glycemic control during a hospitalization.**
- **It is important to stop metformin in all patients who arrive in acute care settings as contraindications to metformin are prevalent in hospitalized patients (renal dysfunction, hypoxia..).**

# Perioperative Management

- **Patients who require surgery may experience worsening of glycemia similar to those admitted to hospital for a medical illness.**
- **Acute stress increases counter-regulatory hormones.**
- **Therapy should be individualized based on the type of DM, nature of the surgical procedure, previous therapy, and metabolic control prior to the procedure.**

# Perioperative Management

- **Patients on oral agents may need to be transiently switched to insulin to control blood glucose, preferably as continuous insulin infusions.**
- **Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.**

# Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- **SGLT2 is the main transporter for glucose re-absorption in the proximal tubules (90%).**
- **Inhibitors include canagliflozin which increases urinary glucose loss.**
- **Not very effective in chronic renal dysfunction and are even contraindicated.**

# (SGLT2) Inhibitors

**Adverse effects:**

1. **Increased incidence of genital and urinary tract infections.**
2. **Intravascular volume contraction and hypotension ← osmotic diuresis.**
3. **Increase LDL cholesterol.**
4. **Higher rates of breast cancer and bladder cancer.**

*** this class is a bad idea.**