Learning Objectives

- Create a disease management plan that includes all the components of effective diabetes management.
- Compare pharmacologic interventions for patients with diabetes.
- Optimize management of diabetes to decrease potential microvascular and macrovascular complications.
- Conduct appropriate screening tests for comorbidities in patients with diabetes, including cardiovascular risk factors.

Pharmacological Therapy

- Biguanide: (metformin)
- Thiazolidinedione (TZD): (pioglitazone)
- Sulfonylureas: (glyburide, glipizide, glimepiride)
- Meglitinides: (repaglinide, nateglinide)
- Alpha-glucosidase inhibitors: (acarbose, miglitol)
- Insulin (short and long acting; human and synthetic)
- GLP-1 receptor agonists: (exenatide, liraglutide, pramlintide)
- DPP-4 inhibitors: (sitagliptin, saxagliptin, linagliptin, vildagliptin)
- Bile acid sequestrants: (colesevelam)
- Dopamine-2 agonists: (bromocriptine)

1. Which of the following medications has been shown to reduce the mortality rate in patients with type 2 diabetes?
   - A. Metformin
   - B. Acarbose
   - C. Glipizide
   - D. Pioglitazone

Metformin

- Insulin sensitizer** Decreases glucose production in the liver
- Lowers insulin and lipid levels No hypoglycemia or weight gain
- Improves cardiovascular outcomes in overweight and newly diagnosed type 2 diabetes** decreases mortality**
- Use with caution in the elderly (> 65), renal dysfunction**, cardiopulmonary disorders (OK with stable CHF), and hepatic disease
- Stop prior to IV contrast** and 48 hours after** (angiography/ pyelography)
- Must check creatinine prior to use*
- Rare cases of lactic acidosis* (has been used judiciously to creatinine = 2.5 but recommended to stop at creatinine > 1.5 M, 1.4 W)
- Widely used for polycystic ovary disease*
- Only oral medication for use in children and adolescents*
- Check for B12 deficiency
- Category B in pregnancy

© American Academy of Family Physicians. All Rights Reserved.
Thiazolidinedione

- Pioglitazone (Actos)
  - Insulin sensitizer** (decreases insulin resistance)*
  - ↓ glucoseogenesis
  - Use with caution in the elderly due to declining ventricular function, and in cardiopulmonary disorders (volume overload)*
  - Black Box warning for class III or IV heart failure
  - Monitor LFTs, avoid in hepatic dysfunction including nonalcoholic fatty liver disease
  - Increase ovulation
  - Category C in pregnancy (growth retardation in animals)*
  - Pioglitazone ↓ risk of MI, stroke, and death, ↓ triglycerides, ↑ HDL, ↑ serious heart failure
  - Rosiglitazone: 42% increase risk of MI; restricted
  - Increase in distal limb fractures in women
  - Increased risk of bladder cancer > 1yr use
    - (28/100,000 person/yr)
  - $150/month

2. 55 y/o with newly diagnosed DM and HTN with chronic renal failure and a creatinine of 2.4. Which medication should you start?

A. Acarbose (Precose)
B. Glyburide (DiaBeta)
C. Metformin (Glucophage)
D. Glipizide (Glucotrol)

Sulfonylureas

- Glipizide (Glucotrol), glyburide (Micronase), Glimepiride (Amaryl)
- Stimulate pancreatic beta cells to release insulin
- Weight gain and hypoglycemia
- Can be used in low doses in the elderly
- OK in mild renal dysfunction (except glyburide has an active metabolite eliminated renally)*
- OK in cardiopulmonary comorbidities (sleep apnea, CHF)
- Glyburide as effective as insulin in treating gestational diabetes with fasting sugars ≤ 140 (Category C)
- $4.00

Meglitinides

- Repaglinide (Prandil), Nateglinide (Starlix)
- Rapid acting insulin secretagogues
- Half life < 1 hour
- High cost for moderate decrease in glucose
- May be used in the elderly, renal failure, and cardiopulmonary disorders
- Very helpful for erratic eating schedules

Alpha Glucodiase Inhibitors

- Acarbose (Precose) and Miglitol (Glyset)
- Delay carbohydrate absorption in gut—decrease peak glucose levels, no hypoglycemia as monotherapy*
  - (Treat hypoglycemia in combination Rx with glucose or glucagon)
- Acarbose may delay onset of type 2 diabetes
- Reduce the risk of cardiovascular events* (STOP NIDDM)
- Monitor LFTs; avoid in cirrhosis
- Not for use in renal dysfunction (creatinine > 2)*
- Avoid in GI disease—significant GI side-effects
- Moderate lowering of glucose for cost
- Weight neutral
- Category B in pregnancy

© American Academy of Family Physicians. All Rights Reserved.
3. Which medication is most effective at lowering postprandial blood sugars?

A. Exenatide (Byetta)  
B. Pioglitazone (Actos)  
C. Metformin (Glucophage)  
D. Nateglinide (Starlix)

48% **A. Exenatide (Byetta)**  
9% **B. Pioglitazone (Actos)**  
11% **C. Metformin (Glucophage)**  
34% **D. Nateglinide (Starlix)**

GLP-1 Receptor Agonists

- All given by subcutaneous injection
- **Exenatide (Byetta):**
  - GLP-1 agonist
  - Dose 5-10 mcg bid
  - Now OK to give with insulin (not in same syringe)
- **Liraglutide (Victoza):**
  - GLP-1 agonist
  - Dose 0.6, 1.2, 1.8 mg daily
  - Thyroid tumors
- **Pramlintide (Symlin):**
  - Synthetic analogue of human amylin
  - Given with insulin (not in same syringe)
  - Dose 60-120 mcg with meals

GLP-1 Receptor Agonists

- Mechanism of action
  - Potentiate insulin secretion
  - Suppress postprandial glucagon secretion
  - Slow gastric emptying
  - Promote satiety (no weight gain)
- Side effects
  - Nausea, vomiting, diarrhea, weight loss*
  - Pancreatitis*
  - Hypoglycemia (with sulfonylurea)
  - Decrease dose in renal failure (except liraglutide) Avoid if creatinine clearance < 30 mL/min
- Cost ~ $200 / mo
- Category C in pregnancy

DPP-4 Inhibitors

- **Sitagliptin (Januvia) 100 mg daily**
  - 25-50 mg in renal impairment
- **Saxagliptin (Onglyza) 2.5-5 mg daily**
  - 2.5 mg in renal impairment
- **Linagliptin (Tradjenta) 5 mg daily**
- **Block dipeptidyl peptidase 4 (the enzyme that breaks down natural incretins)**
- **Better insulin release and blood sugar control particularly post prandial**
- **Don’t add to sulfonylurea in the elderly**
- **Side effects minimal: URI, sore throat, diarrhea, pancreatitis**
- **Weight neutral**
- **Expensive ~$150-200/mo**

Combination Therapy

- Available combinations
  - Metformin and Glyburide (GlucoVance)
  - Metformin and Glipizide (Metaglip)
  - Metformin and Pioglitazone (Actoplus Met)
  - Metformin and Sitagliptin (Janumet)
  - Metformin and Saxagliptin (Kombiglyze)
  - Metformin and Repaglinide (PrandilMed)
  - Pioglitazone and Glimepiride (Duetact)
- **Best if different mechanisms of action are combined**
- **Metformin can be combined with any other**
- **Usually minimal cost savings because metformin is cheap**
- **As beta cell function declines or inability to gain control, add insulin (all can be used with insulin)**

© American Academy of Family Physicians. All Rights Reserved.
Endocrinologists’ Algorithm for Initiation of Therapy, Based on A1c Levels

- 6.5-7.5%: monotherapy (usually metformin)
- 7.6-9.0%: dual therapy: metformin plus
  - Sulfonylurea or
  - TZD: Pioglitazone or
  - Glime: Repaglinide/nateglinide or
  - DPP4: Sitagliptin/saxagliptin/linagliptin or
  - GLP-1 agonist: Exenatide/pramlintide/liraglutide
- > 9.0%: Insulin or triple therapy:
  - Metformin plus
  - DPP4 or GLP-1 plus/or
  - Sulfonylurea or glinide plus/or
  - TZD

4. Newly diagnosed 53-yr-old Hispanic male was hospitalized with sugars > 500 mg/dL. He was requiring 60 units/day of insulin in the hospital. Which of the following options would NOT be a good option for his insulin administration?

A. 60 units of lantus given in the evening
B. 30 units of NPH insulin given twice daily
C. 40 units of lantus in the evening and 7 units of aspart given with meals
D. 20 units of aspart given with each meal

Insulin

- Weight gain outweighed by glucose control
- Average dose 0.6-0.8 units/kg body weight/day
  - ~ 40-50 units for a 70 kg man
  - Half for basal needs and half with meals
- Bioavailability changes with site of injection*
  - Faster in abdomen
  - Slower in thigh
- Exercise accelerates absorption in thigh*
  - Arm reduces exercise-induced hypoglycemia by 60%
  - Abdomen reduces exercise-induced hypoglycemia by 90%
- Best combination: long-acting basal and rapid-acting synthetic—most closely mimics normal*
- Commonly used in geriatrics when other medications are contraindicated*

Rapid-Acting Analogues

- Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra)
- Analogs of human insulin; all similar (glulisine not studied in pregnancy)
- Onset 15 min, peak 1-3 hr, duration 2-5 hr
- May need to adjust long-acting regimen
- Particularly well-liked by type 1 diabetics (~ 1/3 of daily insulin requirement)
- Available in 75/25 mix with longer acting protamine form

Long-Acting Insulins

- NPH duration 16-24 hr (2/3 in AM, 1/3 in PM)
- Glargine (Lantus) 24 hr (human analog)
  - Cannot mix with other insulins
  - Solution must remain clear
  - May be used in type 1 and 2
  - Initiate dose at 80% of prior total insulin dose
  - Split dose when > 60 units
  - Best approach for geriatric patients in long-term care facilities (predictable control)*
- Detemir (Levemir) similar to glargine
  - Not supposed to increase weight*
  - Length of activity increases as dose increases
**Insulin Pump/Transplant**

- High patient satisfaction
- Improved glucose control
- Uses only short-acting insulin
- Requires motivated patient to do frequent glucose checks
- Pancreatic transplant still primarily experimental
- Early diagnosis of type 1—immunosuppression and hematopoietic stem cell transplant increases beta cell function and prolongs insulin independence.

---

5. 43-yr-old WF has been on metformin, glyburide and pioglitazone for 2 years. A1c consistently 7.5-8.0. Fasting sugars 120-150 mg/dL but postprandial sugars 200-250 mg/dL. What should you do?

A. Change glyburide to nateglinide (Starlix)
B. Stop glyburide and start insulin with meals
C. Stop glyburide and add exenatide (Byetta)
D. Any of the above

---

6. 19 y/o CM with ketoacidosis. K+ 6.8, pH 7.12. What fluid should you use?

A. NS until K+ is 4.0, then add K+
B. ½ NS until K+ is 5.0, then add K+
C. NS until K+ is 5.5, then add K+
D. ½ NS until K+ is 4.0, then add K+
Ketoacidosis

- Insufficient insulin; increased gluconeogenesis and fatty acid oxidation resulting in metabolic acidosis
- Uncommon in type 2 unless African-American or Hispanic
- Glucose > 250, pH < 7.3, bicarb < 18, serum and urine ketones
- Volume replacement (1 L NS/hr until dehydration resolved—then ½ NS at 150-500 ml/hr)* (usually down 5-8 L)
- Insulin drip (1-2 units/hr—0.1 U/kg/h)
- Hourly monitoring of electrolytes, glucose, and pH
- Bicarbonate only for pH < 7.2 or HCO₃ < 10 mEq/L*
- Replace K⁺ as soon as it starts to fall*
- Continue insulin drip until acidosis is resolved*
- Add D5 when glucose is ~ 250 mg/dL*
  - Reduce but do not stop drip if becomes hypoglycemic

Hyperosmolar, Hyperglycemic State*

- Hospitalization (may need ICU)
  - Mortality >>> DKA
- Insulin infusion (oral and SQ are inadequate)*
- IV fluids (normal saline)
- Replace K⁺ as it falls near normal range
- Oral medications and/or subcutaneous insulin is restarted after blood sugars return to the 200 range
- Delirium or altered mental status usually clears with correction of metabolic abnormalities

Fatty Liver

- Usually benign but progresses to cirrhosis in 25% (cryptogenic cirrhosis)
- AST/ALT ratio > 2
- Metformin can improve metabolic problems

Microvascular Complications

- Nephropathy, Retinopathy, Neuropathy
- All treated with:
  - Glycemic control
  - BP control
  - Lipid control
  - Smoking cessation
- No evidence that ASA is helpful*

7. 60-yr-old AAF with pain and loss of sensation in her feet bilaterally. Would like something for pain. What would be a first-line choice?
   A. Tramdol
   B. Pregabalin
   C. Hydrocodone
   D. Depakote
   E. Capsaicin cream
Treatment

• Retinopathy
  – Refer to ophthalmologist for any retinopathy
  – Laser photocoagulation
  – ASA not harmful in presence of retinopathy

• Neuropathy
  • 1st: amitriptyline, nortriptyline, gabapentin, pregabalin, duloxetine, venlafaxine, 5% lidocaine patch
  • 2nd: opioids, tramadol
  • 3rd: topiramate, lamotrigine, carbamazepine, capsaicin cream
  • Also try: L carnitine, acupuncture
  • Symptomatic only

Treatment

• Nephropathy
  • Avoid NSAIDS: they acutely reduce renal blood flow and may cause interstitial nephritis*
  • Treat with increased doses of ACE inhibitors or switch to ARB if creatinine is increasing despite ACE therapy
  • Continue albumin measurement to assess response to therapy and progression
  • When hypoglycemia occurs in previously well controlled type 2, most likely cause is progressing renal failure*
  • Refer: rapid decline, difficulty managing, advanced disease

Treatment of Hypertension

• Blood pressure goal < 130/80mmHg*
• Life-style change: DASH diet, weight loss, aerobic exercise, smoking cessation, ↓Na, ↑K+ and Ca++
• ACE inhibitor or ARB delay nephropathy, reduce microalbuminuria, decrease insulin resistance, no adverse effect on lipids, minimal side effects, CV risk reduction
  – With ACEI, ARB, diuretic monitor creatinine and K+
  – Hyperkalemia may be counteracted with laxis
• HCTZ (synergistic with ACE/ARB) if GFR ≥ 30
  – Furosemide if GFR < 30
  – Avoid HCTZ in CHF as it increases uric acid and glucose
• β-blocker history of MI, heart failure, CAD or stable angina
  – Avoid β-blockers in asthma and impotence
  – In systolic heart failure ACE inhibitors, ARBs, and β-blockers all improve survival* (digoxin does not)

Treatment of Hyperlipidemia

• Diabetic dyslipidemia (elevated triglycerides, decreased HDL, increased LDL) – check yearly
• Check TSH as hypothyroidism can contribute to dyslipidemia*
• Aggressive lifestyle changes
• Statins are drug of choice—reduce risk of sudden death, MI, and stroke* even with normal lipids
• All diabetes patients with CVD or > age 40 should receive statin therapy regardless of baseline LDL cholesterol
• Fibrates or fish oil* may be added to help control triglycerides
• Consider niacin if HDL is low
• Goal is Chol < 200, Trig < 150, LDL < 100 (< 70 with heart disease) or at least 30-40% reduction in LDL

8. 57 y/o CM with diabetic foot ulcer. What is the best indicator of its ability to heal?

A. Size of ulcer
B. Patient’s pulse
C. Signs of infection
D. Patient’s blood sugar
E. Patient’s blood pressure
Diabetic Foot

- Leading cause of non-traumatic foot amputation
- Neuropathy, altered foot structure, vasculopathy
- Best test for sensation is a monofilament*
- Best treatment is aggressive prevention
- Diabetic foot ulcer: remove pressure; good wound care and debridement; no antibiotics if not infected.
- Osteomyelitis usually occurs in the foot**: best test is MRI**
- Best indicator for successful healing: intact vascular supply (pulses)*
- Assess decreased pulse with noninvasive vascular studies (ankle-brachial index)*
- Etiology:
  - Untreated: aerobic Gm+ staph and β-hemolytic strep
  - Treated: polymicrobial
  - Cover MRSA and Strept (dicloxacillin, cephraxin, augmentin, doxycycline, trimethoprim/sulfamethoxazole)

References


Answers

1. A  
2. D  
3. A  
4. D  
5. D  
6. C  
7. B  
8. B