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Objectives

- Describe current ADA guideline recommendations for pre-diabetes
- List the available treatment options for pre-diabetes
- Recommend appropriate therapy options based on patient presentation
The Continuum of Diabetes

**Prediabetes Defined**
- A condition in which individuals have blood glucose or A1c levels higher than normal, but not high enough to be classified as diabetes.
- These people have an increased risk of developing type 2 diabetes, heart disease, and stroke.

**Epidemiology**
- Type 1 DM = 5-10% of all diabetes cases
- Type 2 DM = 90-95% of all diabetes cases

**Pathophysiology**
- Types of diabetes
  - Type 1 Diabetes
    - Absolute beta cell deficiency of insulin
  - Type 2 Diabetes
    - Insulin resistance
    - Lack of secretion

**Normal Pancreatic Function**
- Constant basal secretion
- Bursts of bolus secretion
- Preprandial – body using glucose from liver (gluconeogenesis)
- Postprandial – Suppression of hepatic glucose production and glycogen breakdown (glycogenolysis), and stimulates glucose uptake in muscle and liver
**Normal Pancreatic Function**

- After meal, glucose broken down (glycolysis) to form energy (ATP)
- Energy used in brain, liver, GI
  - Goes to muscles next

**Pathophysiology**

- Tissues can’t take up insulin secreted after a meal
- Lack of secretion from pancreas
- Muscles can’t utilize glucose, so it collects in blood
  - Hyperglycemia

**Etiology**

- Genetic predisposition
- Lifestyle

**Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion**

- Normal B-cell function
- Compensatory hyperinsulinemia
- Normoglycemia
- Relative insulin deficiency
- Hypoglycemia
- Type 2 diabetes

**Early Progression**

- Increased visceral fat deposition (from genetics, sedentary lifestyle, obesity???):
  - In liver
  - In muscle
  - In pancreas
- Increased fat in these areas will lead to more lipolysis and generation of free fatty acids

**Early Progression**

- Effects of excessive free fatty acids (FFA):
  - Liver
    - FFA act as precursors to gluconeogenesis
  - Pancreas
    - FFA impair β-cell function
      - Increases apoptosis, reducing β-cell mass
      - Leads to impaired insulin secretion
  - Muscle
    - FFA decrease uptake of glucose
**Early Progression**

- As insulin resistance begins, the pancreas compensates by producing enough extra insulin to provide balance (normoglycemia).
- With time, the β-cells can no longer compensate.
- Hyperglycemia results.

**The Continuum of Diabetes**

- At diagnosis 50% of β-cell function may be lost.

**Natural History of Type 2 Diabetes**

- Electronic monitoring glucose
- Postmeal glucose
- Fasting glucose
- Insulin resistance
- β-cell resistance
- β-cell failure

**The Continuum of Diabetes**

- At diagnosis 50% of β-cell function may be lost.
Diagnosis

- Based on:
  - A1c
  - Fasting Plasma Glucose
  - Random Plasma Glucose
  - 2-h OGTT
- Must have 2 readings above a diagnostic cut point in any combination

Normal Prediabetes Diabetes

FPG (mg/dL) < 100 100-125 ≥ 126

2-h OGTT (mg/dL) < 140 140-199 ≥ 200

Random plasma glucose (mg/dL) ----- ----- ≥ 200

A1c (%) < 5.7 5.7-6.4 ≥ 6.5

Prediabetes Terms

- Impaired Fasting Glucose (IFG)
  - FPG of 100-125 mg/dL
- Impaired Glucose Tolerance (IGT)
  - 2-h OGTT of 140-199 mg/dL

Case

44 YO female with HTN and dyslipidemia presents for a routine follow-up. She is taking HCTZ, lisinopril and atorvastatin. It is time to check some routine labs on a chem 7 for K+ and SCr and lipid panel. Patient is fasting for the lipid panel.

On the chem 7 results, you notice her glucose is 115 mg/dL.
- Considering the glucose, define this type of sample.
- Fasting
- Now, you check a FPG and the result is 122 mg/dL.
- This patient is diagnosed with what?
- Prediabetes
Screening Rationale

- Diabetes and prediabetes are prevalent
- Long presymptomatic phase before diagnosis
- Often not diagnosed until complications present
- ~1/4 with diabetes are undiagnosed

Criteria to Screen Asymptomatic Adults

- Consider testing in all adults overweight (BMI ≥ 25 kg/m²) and who have 1 or more of the following risk factors
  - Listed on next slide
- If no criteria present, test at age 45
- If results normal, repeat every 3 years
- Those with prediabetes should be tested yearly

Criteria to Screen Asymptomatic Adults

- Physical inactivity
- 1st degree relative with DM
- High-risk ethnicity
  - African American
  - Latino
  - Native American
  - Asian American
  - Pacific Islander
- Woman delivered a baby > 9lbs
- Woman with GDM
- Woman with PCOS
- HTN or CVD
- HDL <35; TG >250
- Prediabetes criteria
- Conditions of insulin resistance

Treatment of Prediabetes

(Prevent or Delay Type 2 Diabetes)

ADA Recommendations

- Refer patient with Prediabetes to an effective ongoing support program targeting:
  - Weight loss of 7% body weight
  - Increasing physical activity to at least 150 minutes per week of moderate activity

ADA Recommendations

- Follow up counseling is important
- Metformin consideration especially if:
  - BMI > 35 kg/m²
  - Age < 60 years
  - Women with prior GDM
- Annual monitoring
Other Treatment Options

Pharmacologic Options

- Thiazolidinediones (TZDs)
- Alpha glucosidase inhibitors
- Glucagon-like peptide-1 agonists (GLP-1)
- Dipeptidyl peptidase-4 inhibitors (DPP-4)
- Weight loss drugs

Thiazolidinediones (TZDs)

- **Mechanism for prediabetes:**
  - Improves insulin sensitivity with unloading of β-cells, decrease in plasma-free fatty acid concentrations, mobilization of toxic lipid metabolites out of β-cells, direct β-cell effect mediated by the PPAR-γ receptor, and increase in insulin sensitizing adipocytokines with decrease in insulin antagonistic adipocytokines
- **Available medications:**
  - pioglitazone (Actos)
  - rosiglitazone (Avandia)

TZDs Evidence: DPP

- Average age 51 years
- Troglitazone group had a 75% lower incidence of diabetes than the placebo group
- Study did not confirm a sustained effect of troglitazone when the drug was no longer administered

TZDs Evidence: TRIPOD

- Hispanic women with history of GDM age 28-41
- 30-month duration
- Troglitazone arm associated with preservation of β-cells and delay in progression or onset of diabetes
- Troglitazone reduced incidence of diabetes by 50%

TZDs Evidence: DREAM

- Adults age 43-65 with IGT or IFG (impaired fasting glucose)
- 3-year duration
- 50.5% of patients reverted to normal glucose tolerance (p<0.001)
- Rosiglitazone increased the likelihood of regression to normal glucose tolerance by 70-80%
TZDs Evidence: ACT-NOW

- Age 18 and older with IGT
- 2.4-years duration
- Pioglitazone reduced IGT conversion to diabetes by 72% (p<0.001)
- 48% reverted back to normal glucose tolerance (p<0.001)
- Improved insulin sensitivity by 92%


N=602
pioglitazone 45 mg/day (n=308)
5%
diabetes (n=213)

Placebo (n=299)
16.7%
diabetes (n=228)

TZDs Evidence: ADOPT

- Patients age 46-66 recently diagnosed with type 2 diabetes treated
- 4-years duration
- β-cell function and insulin sensitivity showed favorable changes with rosiglitazone


N=4360
rosiglitazone 8mg/day (n=1456)
32%
developed diabetes, n=221

Glyburide 15mg/day (n=1441)
42%
developed diabetes, n=285

Metformin 2g/day (n=1454)
5%
developed diabetes, n=71

TZD Considerations

- Doses:
  - pioglitazone (Actos) 15-45mg once daily
  - rosiglitazone (Avandia) 4-8mg once daily
- A/E: Weight gain, fluid retention, bone fractures
- Other considerations:
  - Small studies have found increasing rosiglitazone to 8mg increased reversion to normal glucose tolerance by an additional 10%
  - May exacerbate heart failure (contraindicated in patients with NYHA Class III/IV heart failure)
- Cost ~$200/month

Alpha Glucosidase Inhibitors

- Mechanism in prediabetes:
  - Improves sensitivity to insulin and decreases postprandial hyperglycemia reducing stress on β-cells
  - Augments incretin secretion
- Available medications:
  - acarbose (Precose)
  - miglitol (Glyset)

Alpha Glucosidase Inhibitors Evidence: STOP-NIDDM

- Patients age 40-70 with risk factors for diabetes
- 3-years duration
- Acarbose decreased progression to diabetes by 25% regardless of age, sex, or body mass index
- Acarbose increased reversion of impaired glucose tolerance (p<0.0001)

STOP-NIDDM: Study to prevent non-insulin dependent diabetes mellitus.

N=1429 with impaired glucose
acarbose 100 mg 3x/day (n=714)
32%
developed diabetes, n=221
p=0.0015

Placebo 3x/day (n=715)
42%
developed diabetes, n=285
p=0.0015

Alpha Glucosidase Inhibitors Considerations

- Doses:
  - acarbose (Precose) 25-100mg three times daily
  - miglitol (Glyset) 25-100mg three times daily
- A/E: Flatulence, diarrhea, abdominal pain
- Other considerations:
  - No hypoglycemia expected
  - Significant gastrointestinal discomfort (contraindicated in patients who have irritable bowel disease)
  - Dosing frequency
  - Cost ~$200/month
Glucagon-like Peptide-1 Agonists (GLP-1)

- **Mechanism in prediabetes:**
  - Restores incretin effects of GLP and GIP and β-cell response to glucose reducing IGT conversion to diabetes
  - Inhibits glucagon secretion, delays gastric emptying, and promotes weight loss
- **Available medications:**
  - liraglutide (Victoza)
  - dulaglutide (Trulicity)
  - albiglutide (Tanzeum)
  - exenatide (Byetta, Bydureon)


GLP-1 Evidence: Exenatide and Metformin

- Patients age 30-75 with type 2 diabetes on metformin randomized to exenatide or glargine insulin
- 3-years duration
- Sustained improvement in 1st phase glucose-stimulated C-peptide secretion 4-weeks after discontinuation of treatment


GLP-1 Evidence: Exenatide and Lifestyle

- Patients age 34-58 with BMI ≥ 30 kg/m² and IGT or IFG
- 24-week duration
- Both groups included lifestyle modifications


GLP-1 Evidence: Liraglutide

- Patients age 18-65 with BMI 30-40 kg/m² over 20-weeks
- 31% had prediabetes and 41% had metabolic syndrome
- Liraglutide decreased conversion of IGT to diabetes by 84-96% (1.8 and 3mg)
- 61% lost >5% body weight
- 28% lost >10% body weight on liraglutide 3mg


GLP-1 Considerations

- **Doses:**
  - liraglutide (Victoza) 0.6-1.2mg once daily
  - dulaglutide (Trulicity) 0.75-1.5mg once weekly
  - albiglutide (Tanzeum) 30-50mg once weekly
  - exenatide (Byetta, Bydureon) 5-10mcg twice daily (immediate release; 2mg once weekly (extended release)
- **AE:** Nausea, vomiting, abdominal distension, diarrhea, constipation, nasopharyngitis, headache, tachycardia
- **Other considerations:**
  - Promotes weight loss
  - Slight risk for hypoglycemia
  - Cost ~$500/month
Dipeptidyl Peptidase-4 Inhibitors (DPP-4)

- **Mechanism in prediabetes:**
  - Prolongs GLP-1 levels which are associated with β-cell preservation
- **Available medications:**
  - sitagliptin (Januvia)
  - alogliptin (Nesina)
  - linagliptin (Trajenta)
  - saxagliptin (Onglyza)

DPP-4 Evidence: Vildagliptin

- Patients aged 18-80 with IGT and BMI 23-45 kg/m²
- 12-weeks duration
- β-cell function increased (p=0.002)
- Increase in postprandial incretin hormone (GLP-1 and GIP) response (p<0.001)

Weight Loss Medications

- **Mechanism in prediabetes:**
  - Lipase inhibitor: Blocks absorption of ~30% of fat from meals contributing to weight loss and less insulin resistance
  - Anorexiant: Reduces appetite contributing to weight loss improving insulin sensitivity and cardiometabolic disease process
- **Available medications:**
  - orlistat (Xenical, Alli)
  - phentermine/topiramate (Qsymia)

Orlistat Evidence: XENDOS

- Patients aged 30-60 with BMI ≥ 30 kg/m² with normal or IGT for 4 years
- 37% decrease in risk of progression to diabetes (p=0.0032) overall
- 45% risk reduction in patients with IGT (p=0.0024)
- Average weight loss with orlistat was 5.8kg vs. 3kg with placebo (p<0.001)

Phentermine/Topiramate Evidence: SEQUEL

- Patients aged 40-63 with BMI 27-45 kg/m² with ≥ 2 comorbidities
- 108-weeks duration
- Reduced progression to diabetes by 71% in patients treated with 7.5/46mg and 79% in patients treated with 15/92mg (p<0.05)
**Weight Loss Medication Considerations**

- **Doses**:
  - (1) orlistat (Xenical, Alli) 25-100mg three times daily
  - (2) phentermine/topiramate (Qysmia) 3.75mg/23mg once daily for 14 days, increase to 7.5mg/46mg once daily for 12 weeks (max 15mg/92mg once daily)

- **A/E**: (1) Flatulence, diarrhea, abdominal pain; (2) dry mouth, tachycardia, paresthesia, constipation, nasopharyngitis

- **Other considerations**:
  - Weight loss induced by pharmacologic agents is usually followed by weight regain when drug therapy is discontinued
  - Cost (1) ~$60/month; (2) ~$200/month

**Dual/Triple Treatment**

- Reduce risk progression and reduce adverse effects
  - Low-dose rosiglitazone (2mg/day) plus metformin 1000mg/day
  - Low-dose pioglitazone (15mg/day) plus metformin 850mg/day
  - Low-dose pioglitazone (15mg/day) plus metformin 850mg/day plus exenatide 10mcg twice daily

**To Treat or Not to Treat**

- No pharmacologic agents are ‘FDA approved’ for prediabetes
- With prediabetes, many of the pathophysiologic abnormalities already exist and 10-15% of individuals have signs of microvascular complications
  - 10% incidence of diabetic retinopathy
- Microvascular risk increases curvilinearly as A1c exceeds 6%

**Treatment Considerations**

- Lifestyle changes are recommended first line by the American Diabetes Association
  - Weight regain is common after 2-3 years and 40-50% of prediabetic individuals progress to full diagnosis
- Metformin is recommended second line

- Tailor therapy options to individual patients and their needs taking into consideration
  - Lifestyle changes are not working
  - Strong family history of diabetes
  - Cost
  - Dosage form
  - Monitoring parameters
  - Comorbid conditions
  - Hypoglycemic risk
  - Medication A/E

**...However**

Complex Case 1

- 41 YO Male with past medical history: hypertension, osteoarthritis, chronic knee pain with poor mobility, poor health literacy, poor medication adherence and a desire to lose weight and prevent progression to diabetes because he "wants to be around for his kids"
- **A1c:** 6.3%
- **BMI:** 52 kg/m²
- Medication intolerances: previously tried metformin but could not tolerate due to diarrhea despite proper titration, extended release trial and meal-time dosing
- **Diet:** Received MNT but has not been adherent nor has had success with weight loss
- **Physical activity:** Limited mobility and pain have limited his adherence and success

Which of the following is the best medication to initiate:

A. Biguanide  
B. TZD  
C. Alpha-glucosidase inhibitors  
D. DPP-4 inhibitor

E. GLP-1 agonist  
F. Lipase inhibitor  
G. Sulfonulary  
H. Intensify lifestyle

Complex Case 2

- 56 YO female with past medical history: prediabetes, history of neuropathy, dyslipidemia, CHF NYHA III, anxiety, IBS-D and seizures
- **Current A1c:** 6.3%  
- **BMI:** 38 kg/m²
- **Diet:** She had already changed her diet to low carbohydrate and low fat
- **Physical activity:** Exercises when possible but was limited due to neuropathy pain
- **FSBS:** AM 110-120’s with occasional 140’s
- **Concerns:** She is not satisfied with her FSBS and wants medications but refuses injectables

Which of the following is the best medication to initiate:

A. Biguanide  
B. TZD  
C. Alpha-glucosidase inhibitors  
D. DPP-4 inhibitor

E. GLP-1 agonist  
F. Lipase inhibitor  
G. Sulfonulary  
H. Intensify lifestyle

Pathophysiology of Pre-Diabetes and Early Treatment Considerations