Type 2 Diabetes

Jonathon M. Firnhaber, MD
Assistant Professor, Residency Program Director
East Carolina University
Greenville, North Carolina
It is the policy of the AAFP that all individuals in a position to control content disclose any relationships with commercial interests upon nomination/invitation of participation. Disclosure documents are reviewed for potential conflicts of interest. If conflicts are identified, they are resolved prior to confirmation of participation. Only participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in this CME activity.
Pre-Assessment

Please complete your answers on the sheet provided.
Pre-Assessment Question #1

Which of the following metabolic abnormalities predicts the presence of insulin resistance:

a. Microalbuminuria
b. Elevated LDL cholesterol
c. Hepatic steatosis
d. Hypokalemia
Pre-Assessment Question #2

In patients with impaired glucose tolerance, which medication can lower the risk of T2DM by 45%:

a. Metformin
b. Exenatide
c. Glimepiride
d. Sitagliptin
Pre-Assessment Question #3

Sensitivity factor based bolus insulin dosing:

a. Is a new term for sliding scale insulin coverage
b. Takes into account a patient’s degree of insulin sensitivity/resistance
c. Takes into account a patient’s hemoglobin A1C value
d. Should not be combined with sulfonylurea therapy
Learning Objectives

After completing this CME activity, you should be able to:

1. Define the risk factors that predispose patients for type 2 diabetes, and evaluate the current criteria for a diagnosis of prediabetes.

2. Refine medical management skills to ensure treatment choices in patients with type 2 diabetes are appropriate for the disease stage.

3. Evaluate how team-based care and the patient-centered medical home model can be beneficial in the treatment of patients with type 2 diabetes.
Outline

• Briefly discuss screening and diagnosis
• Focus on the pathophysiology of prediabetes and diabetes as it pertains to medication use
• Use of insulin
• A1C targets
• Diabetes from a PCMH standpoint
• What to do when you get home
Sobering diabetes statistics

• Adults with diabetes have *heart disease death* rates and risk for *stroke* about 2 to 4 times higher than adults without diabetes.

• Diabetes is the leading cause of *kidney failure*, accounting for 44% of all new cases of kidney failure in 2008

National Diabetes Statistics, 2011
More sobering diabetes statistics

• Diabetes is the leading cause of new cases of blindness among adults ages 20-74 years

• More than 60% of nontraumatic lower-limb amputations occur in people with diabetes – over 65,000 in 2006

National Diabetes Statistics, 2011
Diagnosed and undiagnosed diabetes

Estimated percentage of people ages 20 years or older with diagnosed and undiagnosed diabetes, by age group, United States, 2005–2008

National Diabetes Statistics, 2011
Diabetes risk factors and prediction

• Multiple diabetes risk models have been developed, but none has been universally accepted
  – Ethnic origin is strongly related to diabetes risk
• Additional risk factors in one or more models:
  – Age, sex, BMI, diet, physical inactivity, smoking
  – Family history of diabetes
  – HTN or antihypertensive treatment, CV disease
  – HDL cholesterol, triglycerides, uric acid
Screening and diagnosis
Screening recommendations

Per 2012 ADA Guidelines, all overweight adults (BMI ≥ 25) with ≥ 1 risk factor:

– Physical inactivity
– First-degree relative with diabetes
– High-risk race/ethnicity
– Woman with baby > 9lb or history of GDM
– HTN (≥ 140/90 or antihypertensive therapy)
– HDL < 35 and/or triglycerides > 250 mg/dL

*Diabetes Care* 2008; 35 Suppl 1, S11-63.
Screening recommendations

Per 2012 ADA Guidelines, all overweight adults (BMI ≥ 25) with ≥ 1 risk factor:

– Women with PCOS
– AIC > 5.7%, IGT or IFG on previous testing
– Other clinical conditions associated with insulin resistance (obesity, acanthosis nigricans)
– History of CVD

Without above criteria, begin screening at 45 y
If normal, re-screen every 3 y at a minimum

*Diabetes Care* 2008; 35 Suppl 1, S11-63.
Diagnosis

Borderline diabetes
Diagnosis

Borderline diabetes
Diagnosis: 2012 ADA Guidelines

Prediabetes

Impaired glucose tolerance:
2 hr glucose in 75 g OGTT 140-199 mg/dL

OR

Impaired fasting glucose:
FPG 100-125 mg/dL

OR

A1C 5.7-6.4%

Diabetes Care 2008; 35 Suppl 1, S11-63.
Prediabetes

• Each year, 5-10% of people with prediabetes become diabetic.
  – Isolated IGT: 4-6%
  – Isolated IFG: 6-9%
  – Both IGT and IFG: 15-19%

• According to an ADA expert panel, up to 70% of individuals with prediabetes will eventually develop diabetes.

Prediabetes

• Among untreated primary care patients with type 2 diabetes and A1C < 7%, those more likely to have diabetes progression:
  – Younger patients
    • Each decade of increasing age reduced the risk of progression by 15%
  – Those with weight gain
    • Each 1 lb increase in weight was associated with a 2% increased odds of progression

*Diabetes Care* 2008;31: 386-390.
Diagnosis: 2012 ADA Guidelines

A1C > 6.5% (Performed in lab using NGSP certified, DCCT assay-standardized method)*

OR

FPG ≥ 126 mg/dL (Fasting = no caloric intake x 8h)*

OR

2 h glucose ≥ 200 mg/dL during 75g OGTT*

OR

Random glucose ≥ 200 mg/dL (in a patient with classic symptoms of hyperglycemia)
Diagnosis: 2012 ADA Guidelines

A1C > 6.5% (Performed in lab using NGSP certified, DCCT assay-standardized method)*

OR

FPG ≥ 126 mg/dL (Fasting = no caloric intake x 8h)*

OR

2 h glucose ≥ 200 mg/dL during 75g OGTT*

OR

Random glucose ≥ 200 mg/dL (in a patient with classic symptoms of hyperglycemia)

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.
Associated metabolic abnormalities
Associated metabolic abnormalities

- Hyperuricemia
- Dyslipidemia: low HDL/elevated triglycerides
- Urinary microalbuminuria
- Hepatic steatosis
Interrelationship between fatty liver and insulin resistance

• Large prospective study (11,091 patients) found baseline fatty liver associated with higher fasting insulin levels
• Even when insulin level was factored out, those with fatty liver had 2-fold higher OR of developing T2DM over 5 years
• Fatty liver may better predict the presence or severity of insulin resistance than fasting insulin level

Pathophysiology
Glucose dysregulation

• IFG
  – High hepatic insulin resistance
  – Almost normal insulin sensitivity in muscle
  – Impaired early insulin response during OGTT; late phase insulin secretion typically more normal

• IGT
  – Primarily impaired insulin sensitivity in muscle
  – Hepatic sensitivity almost normal
  – Impaired early and late phase insulin secretion

Glucose dysregulation

- Fasting glucose level is determined by endogenous glucose production, which depends mostly on the liver.
- In T2DM, total body glucose disposal is decreased.
  - 85-90% of this impairment is related to muscle insulin resistance.

Long period of insulin resistance

2 h postload glucose (mmol/L)  Insulin sensitivity (HOMA2-%S)
Fasting glucose (mmol/L)  β-cell function (HOMA2-%B)

Long period of insulin resistance

Increase in beta cell mass/function

Increase in beta cell mass/function

Fasting / PP glucose no longer maintained

Decrease in acute insulin secretion as beta cells become unable to compensate for insulin resistance.

Fasting / PP glucose no longer maintained.

Decrease in acute insulin secretion as beta cells become unable to compensate for insulin resistance.

Fasting / PP glucose no longer maintained.

Overt diabetes.

Regulatory/counterregulatory hormones

• Glucagon
  – Released from alpha cells overnight and between meals
  – Triggers glycogenolysis and gluconeogenesis
  – Level normally decreases with increasing glucose
  – Diabetics tend to have paradoxical elevation with meals
Regulatory/counterregulatory hormones

• GIP (glucose-dependent insulinotropic peptide)
  – Incretin hormone; released from gut
  – *Glucose-dependent* decrease in alpha cells’ release of glucagon; increase in beta cells’ secretion of insulin

• GLP-1 (glucagon-like peptide)
  – Same action as GIP
  – Additionally slows gastric emptying and triggers sensation of satiety
Regulatory/counterregulatory hormones

• Amylin
  – Secreted with insulin from beta cells
  – Decreases glucagon secretion
  – Slows gastric emptying; increases satiety

• Cortisol
  – Increases muscle/adipose insulin resistance
  – Enhances hepatic glucose production

• Epinephrine
  – Enhances hepatic glycogenolysis
Drugs in prediabetes
Metformin in prediabetes

• Primarily affects FPG by decreasing hepatic glucose output
• In patients with IGT, lowers risk of T2DM by 45%\(^1\)
• Greater effect in prediabetics with higher BMI and higher FPG\(^2\)

TZDs in prediabetes

• Act through peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\))
• Increase hepatic and peripheral insulin sensitivity and preserve insulin secretion
• ACT NOW study with pioglitazone: risk of T2DM decreased by > 70% in obese people with IGT

Other drugs in prediabetes

• Alpha-glucosidase inhibitors in IGT:
  – 25% decrease in relative risk for T2DM
• Nateglinide in IGT
  – No effect on rate of T2DM or CV outcomes
• Fenofibrate in prediabetes + hypertriglyceridemia
  – Higher rate of regression to normoglycemia
• Orlistat
  – 37% decrease in relative risk for T2DM

INSULIN
Initiation of insulin therapy

• ACE/AACE guidelines recommend insulin if:
  – Initial A1C is > 9%, or
  – Diabetes is uncontrolled despite optimal oral hypoglycemic therapy

• Hypoglycemic therapy that includes insulin decreases microvascular complications, but not all-cause mortality.

Insulin secretion

• Insulin has several secretion patterns
  – Continuous, glucose-dependent secretion throughout the day
  – In response to oral carbohydrate loads, a large, first-phase insulin release suppresses hepatic glucose production
  – A slower second-phase insulin release covers ingested carbohydrates

Which regimen is best?

- Basal/bolus therapy offers the most precise and flexible prandial coverage.
- However, the “actual glycemic benefits of these more advanced regimens after basal insulin are generally modest in typical patients.”

*Individualization of therapy is key*

Basal insulin
(generally with continued oral agents)

- Basal insulin + 1 mealtime rapid-acting insulin injection
- Basal insulin + ≥ 2 mealtime rapid-acting insulin injections

Premixed insulin twice daily

Augmentation: basal insulin

- Basal and/or bolus insulin may be used to augment therapy in patients with decreased β-cell function
  - May start with 0.3 units per kg of basal insulin
  - The goal of basal insulin is to suppress hepatic glucose production and improve fasting hyperglycemia
  - Excessively high basal insulin doses may increase risk of between-meal, missed-meal or nocturnal hypoglycemia

Augmentation: bolus insulin

When basal insulin + oral hypoglycemics are not sufficient to control postprandial glucose, bolus insulin can “cover” ingested carbohydrate load

- Fasting glucose has typically normalized when A1C is about 7.5%
- Sensitivity-based correction can be used to refine bolus insulin dosing

Sensitivity factor

• The decrease in glucose (mg/dL) expected per unit of bolus insulin
  – Based on current insulin need:  
    1500/total daily insulin dose
  – Typical range *approximately* 25-50

  – LOW insulin sensitivity (factor) = high resistance
  – HIGH insulin sensitivity (factor) = low resistance
Sensitivity-based correction dose

Measured glucose – target glucose / sensitivity factor = insulin dose

1. Measured glucose – target glucose = glucose excess that needs to be eliminated
2. Excess / sensitivity factor (how much glucose drop is expected per unit given) = units needed
An example

Insulin dosing: 18 U basal + 6 U bolus TID = 36 U/day

Sensitivity factor = $\frac{1500}{36} = 42$

Measured glucose = 288

Target glucose = 120

Excess glucose = 168

Measured – target / sensitivity factor = units needed

$(288 - 120) / 42 = 4 \text{ units supplemental}$
Additional points about insulin

• Insulin therapy may be started with:
  – A set dose of basal insulin (e.g. 10 units daily)
  – Weight-based dosing (e.g. 0.3 units / kg IBW)

• As bolus dosing is incorporated, a typical distribution is 50:50 – bolus:basal

• It is reasonable to allow more astute patients to gently self-titrate insulin
  – Addition of 1-2 units (or 5-10%) to daily dose once or twice weekly if fasting glucose > target

A1C targets
Estimated Average Glucose (eAG)

- Hemoglobin A1C – as a concept – may seem arbitrary to some patients
- ADA is recommending the use of eAG, which is expressed in the same units patients are familiar with: mg/dL

The relationship between A1C and eAG is described by the formula:

$$28.7 \times \text{A1C} - 46.7 = \text{eAG}$$

*Diabetes Care* 2008;31: 1473-1478.
# A1C and corresponding eAG

<table>
<thead>
<tr>
<th>Hemoglobin A1C (%)</th>
<th>eAG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>6.5</td>
<td>140</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>7.5</td>
<td>169</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>8.5</td>
<td>197</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>9.5</td>
<td>226</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
</tbody>
</table>
Hemoglobin A1C targets

ACCORD

– 10,251 patients, mean age 62.2, mean A1C at initiation = 8.1%

– Intensive therapy (goal A1C < 6.0%) vs. standard therapy (goal A1C 7.0-7.9%)

– Median A1C achieved: 6.4% vs. 7.5%

Hemoglobin A1C targets

ACCORD

– Primary outcome (nonfatal MI, nonfatal stroke, death from cardiovascular causes):
  352 (intensive) vs. 371 (standard)
  (HR 0.90; 95% CI 0.78 to 1.04)

– Death: 257 vs. 203 (HR 1.22; 95% CI 1.01 to 1.46)

Intensive therapy arm discontinued at 3.5 years

### Factors to consider: general

<table>
<thead>
<tr>
<th></th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient attitude / effort</td>
<td>Motivated, adherent</td>
<td>Less motivated</td>
</tr>
<tr>
<td>Risk of hypoglycemia / other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Severe</td>
</tr>
<tr>
<td>Resources / support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Other factors to consider: Age

• Older adults:
  – Greater atherosclerotic burden
  – Reduced renal function
  – More comorbidities
  – More likely to be compromised by hypoglycemia

_Glycemic targets for older patients, or those with longer-standing, more complicated disease should be less aggressive than for younger, healthier individuals._

Other factors to consider: Chronic kidney disease

*Stage 2 CKD (eGFR <60mL/min) or worse is present in 20-30% of diabetics*

- Most insulin secretagogues are renally cleared
  - Exceptions include repaglinide and nateglinide
  - Glyburide particularly should be avoided because of long duration of action and active metabolites

- Most DPP-4 inhibitors are renally cleared
  - Exception: linagliptin (enterohepatically cleared)

Other factors to consider: Chronic kidney disease

- US guidelines suggest avoiding metformin with creatinine ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women
  - UK guidelines are less restrictive and allow use down to eGFR 30 mL/min with dose reduction recommended at 45 mL/min
- Renal impairment is associated with slower elimination of all insulins

Diabetes lends itself well to the principles of the *Patient-Centered Medical Home* given its robust evidence-based guidelines, high cost, and well-demonstrated quality gap.
Basic components of a PCMH

- Coordination and integration of care
- Quality and safety
- Whole-person orientation
- Personal physician
- Physician-directed medical practice
- Enhanced access
- Payment

Diabetes Care 2011;34:1047-1053.
Basic components of a PCMH

- Coordination and integration of care
- Quality and safety
- Whole-person orientation
- Personal physician
- Physician-directed medical practice
- Enhanced access
- Payment
Basic components of a PCMH

• Coordination and integration of care
  Use of EHR, patient registries and care coordinators
  – Referrals to specialists, diabetes educators or nutritionists can be tracked to ensure appropriate care and follow-up is received
  – Care coordinator/case manager can follow up with high-risk patients between visits to address potential barriers to adherence

Diabetes Care 2011;34:1047-1053.
Basic components of a PCMH

- Coordination and integration of care
- Quality and safety
- Whole-person orientation
- Personal physician
- Physician-directed medical practice
- Enhanced access
- Payment
Basic components of a PCMH

• Quality and safety
  
  Decision support based on updated practice guidelines
  
  – Incorporation of most current care guidelines in daily patient flow
  
  – Use of checklists and worksheets to guarantee consistency
  
  – Use of patient registries to review performance data

*Diabetes Care* 2011;34:1047-1053.
Basic components of a PCMH

• Coordination and integration of care
• Quality and safety
• Whole-person orientation
• Personal physician
• Physician-directed medical practice
• Enhanced access
• Payment
Basic components of a PCMH

• Physician-directed medical practice
  Aspects of care that do not require in-depth medical training can be delegated to nonphysician team members
  – Medication reconciliation
  – Ordering routine lab tests, including point-of-care
  – Foot examination
  – Downloading / summarizing glucometer data

Diabetes Care 2011;34:1047-1053.
What do do when you get back home

1. Wish you hadn’t left when you see all the things that accumulated in your absence
2. Have a glass of wine and let the dirty clothes wait a few more days
3. Wonder if your coworkers will believe you really are sick and need to stay out one more day
4. Change how you approach your diabetic patients
What do do when you get back home

1. Wish you hadn’t left when you see all the things that accumulated in your absence
2. Have a glass of wine and let the dirty clothes wait a few more days
3. Wonder if your coworkers will believe you *really are* sick and need to stay out one more day
4. Change how you approach your diabetic patients
Take Aways

What changes you will incorporate into your practice as a result of completing this activity? Take some of the knowledge you've learned here and incorporate it into your practice. Ideally, you will make a change that is individualized to your situation. However, based on some of the key points of this presentation, as a starting point you might want to consider a change based on the following:

- Identify prediabetics
- Everyone gets the checklist
- Use insulin appropriately
1. Identify prediabetics

Impaired glucose tolerance:
2 hr glucose in 75 g OGTT 140-199 mg/dL

OR

Impaired fasting glucose:
FPG 100-125 mg/dL

OR

A1C 5.7-6.4%
1. Identify prediabetics

1. Chart review:
   - Prospective
   - Retrospective

2. Paper charts:
   - Sticker on chart or on individual notes
   - Add diagnosis to list with red pen

3. EMR:
   - Add new diagnosis
   - Move diagnosis to top of list
1. Identify prediabetics

4. Tell your prediabetics that they have prediabetes
5. Discuss interventions to delay or prevent progression to diabetes
6. Continue to address prediabetes at follow-up visits
2. Everyone gets the checklist

THE CHECKLIST MANIFESTO
How to get things right

Atul Gawande
2. Everyone gets the checklist

Diabetes Summary

Name: ____________________________ Date: ____________________________

Hemoglobin A1C / date:
  Goal: ____________________________
  Comments: ______________________

Blood pressure:
  Goal < 130/80
  Comments: ______________________

Eye exam: ________________________ Foot exam: ________________________

Urinary microalbumin:
  Comments: ______________________

Lipids: Total: LDL: HDL:
  Triglycerides:
    Goal: < 100 > 40 < 150
    Comments: ______________________

Creatinine: ______________________

Medication changes: ______________________
3. Use insulin appropriately

- ACE/AACE guidelines recommend insulin if:
  - Initial A1C is > 9%, or
  - Diabetes is uncontrolled despite optimal oral hypoglycemic therapy
3. Use insulin appropriately

- Basal and/or bolus insulin may be used to augment therapy in patients with decreased β-cell function
  - Fasting glucose has typically normalized when A1C is around 7.5%
  - Sensitivity-based correction can be used to refine bolus insulin dosing
Post-Assessment

Please complete your answers on the sheet provided.

The questions have been scrambled and are **not** in the same order as the pre-assessment.
Pre-Assessment Question #1

In patients with impaired glucose tolerance, which medication can lower the risk of T2DM by 45%:

a. Metformin  
b. Exenatide  
c. Glimepiride  
d. Sitagliptin
Pre-Assessment Question #2

Sensitivity factor based bolus insulin dosing:

a. Is a new term for sliding scale insulin coverage
b. Takes into account a patient’s degree of insulin sensitivity/resistance
c. Takes into account a patient’s hemoglobin A1C value
d. Should not be combined with sulfonylurea therapy
Pre-Assessment Question #3

Which of the following metabolic abnormalities predicts the presence of insulin resistance:

a. Ingested carbohydrates
b. The liver
c. Peripheral lipolysis
d. Breakdown of muscle glycogen stores
Please complete the session/speaker evaluation located on the back of your pre/post-assessment sheet and return to Chapter Staff as you exit.
Questions?